Cancer and Obesity

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researched on the cancer and the obesity.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Abrahamson, P. E., M. D. Gammon, et al. (2006). "General and abdominal obesity and survival among young women with breast cancer." Cancer Epidemiol Biomarkers Prev **15**(10): 1871-7.

Among postmenopausal women, obesity is linked to increased risk of breast cancer and poorer subsequent survival. For premenopausal women, obesity may reduce incidence, but less is known about its effect on prognosis, particularly for abdominal obesity. This study investigated whether general or abdominal obesity at diagnosis influenced survival in a cohort of young women with breast cancer. A population-based follow-up study was conducted among 1,254 women ages 20 to 54 who were diagnosed with invasive breast cancer between 1990 and 1992 in Atlanta or New Jersey. Women were interviewed within several months of diagnosis and asked about their weight and height at age 20 and in the year before diagnosis. Study personnel did anthropometric measures at the interview. With 8 to 10 years of follow-up, all-cause mortality status was determined using the National Death Index (n = 290 deaths). Increased mortality was observed for women who were obese [body mass index (BMI), > or =30] at the time of interview compared with women of ideal weight [BMI, 18.5-24.9; stage- and income-adjusted hazard ratio (HR), 1.48; 95% confidence interval (95% CI), 1.09-2.01]. A similar result was seen for the highest versus lowest quartile of waist-to-hip ratio (HR, 1.52; 95% CI, 1.05-2.19). Strong associations with mortality were found for women who were obese at age 20 (HR, 2.49; 95% CI, 1.15-5.37) or who were overweight/obese (BMI, > or =25) at both age 20 and the time of interview (HR, 2.22; 95% CI, 1.45-3.40). This study provides evidence that breast cancer survival is reduced among younger women with general or abdominal obesity.

Adams, T. D. and S. C. Hunt (2009). "Cancer and obesity: effect of bariatric surgery." World J Surg **33**(10): 2028-33.

Recent international cancer prevention guidelines recommend weight loss, where appropriate, for the purpose of cancer risk reduction. However, limited research associates voluntary weight loss to subsequent cancer incidence because of the difficulty of achieving long-term weight loss maintenance among large participant groups. Bariatric surgery has demonstrated long-term sustained weight loss, and as a result, patients after bariatric surgery represent an ideal population to explore the relationship between long-term, voluntary weight loss and cancer incidence. This paper briefly reviews cancers that have shown to be associated with overweight and obesity and looks at studies that demonstrate reduced total mortality after bariatric surgery. Reduced cancer mortality and incidence as well as reduced cancer-related physician visits after bariatric surgery are presented. Study limitations and future research questions related to cancer and bariatric surgery are briefly discussed.

Aitken, R. J., M. A. Allman-Farinelli, et al. (2009). "Current and future costs of cancer, heart disease and stroke attributable to obesity in Australia - a comparison of two birth cohorts." Asia Pac J Clin Nutr **18**(1): 63-70.

The obesity epidemic appears set to worsen the morbidity and mortality from leading causes of death in Australia - ischaemic heart disease, stroke and obesity-related cancers. The aim of this study was to compare hospital separations, deaths and direct health costs for middle-aged adults (45 to 54 years) in 2004/05 with those attaining age 45 to 54 years in 2024/25 who were born into an obesogenic environment. Using data from National Health Surveys, prevalence of obesity in 2004/05 was calculated for those born in 1950/51-59/60 and four scenarios were considered to project rates in 2024/25 for those born in 1970/71-79/80: an age-cohort model; a linear trend model; a steady state where rates increase to equal those of the older birth cohort at the same age; and a best case where rates remain at 2004/05 levels. Population attributable fractions were calculated by gender and disease using relative risks of disease from the literature, and applied to hospital separations, deaths, and direct health system costs data to estimate the proportion of each attributable to obesity. In 2024/25 the projected number of hospitalizations of 45 to 54 year olds due to the diseases of interest could be more than halved, over 200 lives rescued and $51.5 million (in 2004/05 dollars) saved if further gains in obesity in the younger birth cohort are halted. Instead, if the worst case scenario is realized there will be a more than doubling in costs (in 2004/05 dollars) compared with those born in 1950/51-59/60.

Alokail, M. S., N. M. Al-Daghri, et al. (2009). "Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women." Cardiovasc Diabetol **8**: 33.

BACKGROUND: Both obesity and type 2 diabetes are among the risk factors for breast cancer development. Combined effect of these metabolic abnormalities on breast cancer risk however, has not been examined in premenopausal women. We tested this association in type 2 diabetic women, categorized as obese, overweight and normal body weight groups based on BMI. DESIGN AND METHODS: A total of 101 subjects were included in this study. Serum levels of IL-6, TNF-alpha, C reactive protein, leptin, TGF-alpha, adiponectin and insulin were measured by ELISA. Data were logarithmically transformed for variables not normally distributed. Analysis of variance with post-hoc Bonferroni was applied to compare the data between the groups. Simple and partial correlation coefficients between the variables were determined and a stepwise multiple linear regression analysis was performed to determine the relationships between the variables of interest. RESULTS: Significantly increased levels of IL-6, C reactive protein, leptin and significantly decreased levels of adiponectin were found in obese group, while the levels of TNF-alpha and TGF-alpha were unaltered. A positive correlation between waist circumference and IL-6 was found in obese group. Similarly, C reactive protein, waist and hip circumferences were linearly correlated with BMI in obese group. Stepwise multiple linear regression analysis revealed several significant predictors for breast cancer risk. CONCLUSION: Obesity and type 2 diabetes, owing to their effects on adipocytokines and inflammatory mediators, contribute to increased breast cancer risk in premenopausal women. This study emphasizes healthy life style and better management of these metabolic disorders to avoid the pathogenesis of breast cancer and of other chronic diseases.

Amling, C. L. (2005). "Relationship between obesity and prostate cancer." Curr Opin Urol **15**(3): 167-71.

PURPOSE OF REVIEW: This review examines the relationship between obesity and prostate cancer, with an update of recent research in this field. RECENT FINDINGS: A recent report of the Cancer Prevention Study II showed a direct relationship between increasing body mass index and prostate cancer mortality. However, the US Health Professionals Followup Study reported an inverse association between obesity and the risk of developing prostate cancer in men under 60 years of age or in those with a family history of prostate cancer. These studies illustrate the contradictory evidence linking obesity to prostate cancer risk and mortality. Body mass does not appear to affect the performance of prostate-specific antigen as a diagnostic test, and on prostate biopsy a lower body mass is associated with a higher cancer detection rate and a higher cancer volume as measured by core length involvement. In two recent radical prostatectomy series, obesity was associated with worse pathological features and higher biochemical recurrence rates. The higher risk of recurrence persisted in patients with organ-confined disease and negative surgical margins, implying that this risk is not related to surgical technique. Several potential biological mechanisms have been proposed to explain this link including hormonal alterations, hyperinsulinemia, glucose intolerance, and elevated insulin-like growth factor and leptin levels. SUMMARY: Recent literature provides evidence that obesity may promote the development of a more aggressive form of prostate cancer, resulting in higher recurrence rates after primary therapy and higher cancer mortality rates overall. The mechanism to explain the association between obesity and prostate cancer is unclear.

Anderson, A. S. and S. Caswell (2009). "Obesity management--an opportunity for cancer prevention." Surgeon **7**(5): 282-5.

There is increasing evidence of an association between obesity and the development, morbidity and mortality of cancers of the colorectum, (post menopausal) breast, endometrium, kidney, pancreas and oesophagus. In addition to obesity per se, waist circumference is now emerging as a clear indicator of disease risk. Weight gain during adult life also appears to increase risk for breast and colon cancers. Major causative factors which are influenced by excess energy storage include hormones involved in metabolic control (insulin and leptin), cell growth (IGF-I and IGF-binding proteins) and reproduction (steroids and leptin). In addition, raised oestrogens are likely to contribute to the greater risk of breast and endometrial cancers. In cancer survivors, there are also strong indications that being overweight increases the risk for recurrence and reduces the likelihood of survival. Whilst there are no robust data testing the effect of weight loss on recurrence, current guidance highlights that normal weight, overweight and obese patients should avoid weight gain and that a modest weight loss of 5-10% is likely to have significant health benefits. Two studies have now reported long-term effects of obesity surgery on cancer risk (in addition to reducing metabolic disorders and type 2 diabetes). It is becoming increasingly clear that multi-disciplinary groups (including surgeons) are needed to identify, monitor and evaluate programmes for both obesity prevention and management.

Arditi, J. D., M. Venihaki, et al. (2007). "Antiproliferative effect of adiponectin on MCF7 breast cancer cells: a potential hormonal link between obesity and cancer." Horm Metab Res **39**(1): 9-13.

Adiponectin, a hormone secreted by adipose tissue, circulates at high concentrations in human plasma. Paradoxically, plasma levels of adiponectin are approximately 50% lower in obese than in lean subjects. An association between low plasma levels of adiponectin and higher risk of developing breast and other cancers was recently reported. Obesity and overweight have also been associated with increased mortality from cancer. To test the hypothesis that adiponectin exerts direct antiproliferative and/or pro-apoptotic effects on cancer cells, we used the MCF7 human breast adenocarcinoma cell line. The proliferation rate of the MCF7 cells was measured using the MTT method, while apoptosis was examined by quantifying the DNA fragmentation using an ELISA assay. In addition, adiponectin receptor 1 (AdipoR1) and AdipoR2 mRNA expression was detected using RT-PCR. Adiponectin diminished the proliferation rate of MCF7 cells; this effect was significant after 48-96 hours of treatment. The presence of receptor expression suggested that the effect of adiponectin on cell proliferation was most likely specific and adiponectin receptor-mediated. Adiponectin induced no apoptosis of MCF7 cells over 48 hours. We conclude that adiponectin inhibits proliferation but causes no apoptosis of MCF7 breast cancer cells. These data suggest that adiponectin may represent a direct hormonal link between obesity and cancer.

Arnold, L. D., A. V. Patel, et al. (2009). "Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity?" Cancer Epidemiol Biomarkers Prev **18**(9): 2397-405.

Between 2001 and 2005, Blacks from the United States experienced a 32% higher pancreatic cancer death rate than Whites. Smoking, diabetes, and family history might explain some of this disparity, but prospective analyses are warranted. From 1984 to 2004, there were 6,243 pancreatic cancer deaths among Blacks (n = 48,525) and Whites (n = 1,011,864) in the Cancer Prevention Study II cohort. Multivariate Cox proportional hazards models yielded hazards ratios (HR) for known and suspected risk factors. Population attributable risks were computed and their effect on age-standardized mortality rates were evaluated. Blacks in this cohort had a 42% increased risk of pancreatic cancer mortality compared with Whites (HR, 1.42; 95% confidence intervals (CI), 1.28-1.58). Current smoking increased risk by >60% in both races; although Blacks smoked less intensely, risks were similar to Whites (HR(Black), 1.67; 95% CI, 1.28-2.18; HR(White), 1.82; 95% CI, 1.7-1.95). Obesity was significantly associated with pancreatic cancer mortality in Black men (HR, 1.66; 95% CI, 1.05-2.63), White men (HR, 1.42; 95% CI, 1.25-1.60), and White women (HR, 1.37; 95% CI, 1.22-1.54); results were null in Black women. The population attributable risk due to smoking, family history, diabetes, cholecystectomy, and overweight/obesity was 24.3% in Whites and 21.8% in Blacks. Smoking and overweight/obesity play a substantial a role in pancreatic cancer. Variation in the effect of these factors underscores the need to evaluate disease on the race-sex level. The inability to attribute excess disease in Blacks to currently known risk factors, even when combined with suspected risks, points to yet undetermined factors that play a role in the disease process.

Baillargeon, J., E. A. Platz, et al. (2006). "Obesity, adipokines, and prostate cancer in a prospective population-based study." Cancer Epidemiol Biomarkers Prev **15**(7): 1331-5.

BACKGROUND: The purpose of this investigation was to examine the association of obesity and the adipokines leptin, adiponectin, and interleukin-6 (IL-6) with prostate cancer risk and aggressiveness. METHODS: One hundred twenty-five incident prostate cancer cases and 125 age-matched controls were sampled from among participants in the original San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort study. The odds ratios (OR) of prostate cancer and high-grade disease (Gleason sum >7) associated with the WHO categories of body mass index (kg/m(2)) and with tertiles of serum concentrations of adiponectin, leptin, and IL-6 were estimated using multivariable conditional logistic regression models. RESULTS: Body mass index was not associated with either incident prostate cancer [obese versus normal; OR, 0.75; 95% confidence interval (95% CI), 0.38-1.48; P(trend) = 0.27] or high-grade versus low-grade disease (OR, 1.17; 95% CI, 0.39-3.52; P(trend) = 0.62). Moreover, none of the three adipokines was statistically significant associated with prostate cancer risk or high-grade disease, respectively: leptin (highest versus lowest tertile; OR, 0.77; 95% CI, 0.28-1.37; P(trend) = 0.57; OR, 1.20; 95% CI, 0.48-3.01; P(trend) = 0.85); adiponectin (OR, 0.87; 95% CI, 0.46-1.65; P(trend) = 0.24; OR, 1.93; 95% CI, 0.74-5.10; P(trend) = 0.85); IL-6 (OR, 0.84; 95% CI, 0.46-1.53; P(trend) = 0.98; OR, 0.84; 95% CI, 0.30-2.33; P(trend) = 0.17). CONCLUSIONS: Findings from this nested case-control study of men routinely screened for prostate cancer and who had a high prevalence of overweight and obesity do not provide evidence to support that prediagnostic obesity or factors elaborated by fat cells strongly influence prostate cancer risk or aggressiveness. However, due to the small sample population, a small or modest effect of obesity and adipokines on these outcomes cannot be excluded.

Baillargeon, J. and D. P. Rose (2006). "Obesity, adipokines, and prostate cancer (review)." Int J Oncol **28**(3): 737-45.

Prostate cancer, the third most common cancer in men worldwide, varies substantially according to geographic region and race/ethnicity. Obesity and associated endocrine variation are foremost among the risk factors that may underlie these regional and ethnic differences. The association between obesity and prostate cancer incidence is complex and has yielded inconsistent results. Studies that have linked obesity with prostate cancer mortality, advanced stage disease, and higher grade Gleason score, however, have produced more consistent findings, indicating that obesity may not necessarily increase the risk of prostate cancer, but may promote it once established. Additionally, metabolic syndrome, which includes disturbed glucose metabolism and insulin bioactivity, may also be associated with prostate carcinogenesis. Adipokines, defined as biologically active polypeptides produced by adipose tissue, have been linked with a number of carcinogenic mechanisms, including angiogenesis, cell proliferation, metastasis, and alterations in sex-steroid hormone levels. A number of emerging studies have implicated the role of adipokines in prostate carcinogenesis. This review explores the specific roles of several adipokines as putative mediating factors between obesity and prostate cancer with particular attention to leptin, interleukin-6 (IL-6), heparin-binding epidermal growth factor-like growth factor (HB-EGF), vascular endothelial growth factor (VEGF) and adiponectin.

Banez, L. L., R. J. Hamilton, et al. (2007). "Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer." Jama **298**(19): 2275-80.

CONTEXT: Recent studies have suggested that obese men have lower serum prostate-specific antigen (PSA) concentrations than nonobese men. Because men with higher body mass index (BMI) have greater circulating plasma volumes, lower PSA concentrations among obese men may be due to hemodilution. OBJECTIVE: To determine the association between hemodilution and PSA concentration in obese men with prostate cancer. DESIGN, SETTING, AND PARTICIPANTS: Retrospective study of men who underwent radical prostatectomy for prostate adenocarcinoma from 1988 to 2006, using data from the databases of the Shared Equal Access Regional Cancer Hospital (n = 1373), Duke Prostate Center (n = 1974), and Johns Hopkins Hospital (n = 10 287). Multivariate linear regression models adjusting for clinicopathological characteristics were used to analyze the main outcome measures. MAIN OUTCOME MEASURES: Associations between BMI and mean adjusted PSA concentrations, mean plasma volume, and mean adjusted PSA mass (total circulating PSA protein, calculated as PSA concentration multiplied by plasma volume), assessed by determining P values for trend. RESULTS: After controlling for clinicopathological characteristics, higher BMI was significantly associated with higher plasma volume ($P < .001$ for trend) and lower PSA concentrations ($P <$ or $= .02$ for trend) in all cohorts. In 2 of the 3 cohorts, PSA mass did not change significantly with increasing BMI. In the third cohort, higher BMI was associated with increased PSA mass ($P < .001$ for trend), but only between BMI category less than 25 and the other categories. CONCLUSIONS: In men undergoing radical prostatectomy, higher BMI was associated

with higher plasma volume; hemodilution may therefore be responsible for the lower serum PSA concentrations among obese men with prostate cancer. Prospective studies are needed to evaluate this association in screened populations.

Barb, D., K. Pazaitou-Panayiotou, et al. (2006). "Adiponectin: a link between obesity and cancer." Expert Opin Investig Drugs **15**(8): 917-31.

Adiponectin, an insulin-sensitising hormone produced by adipocytes, has direct antidiabetic, antiatherogenic, anti-inflammatory and antiangiogenic properties. Circulating adiponectin levels are lower in obesity, a disease state that is associated with certain malignancies. Recently, accumulating evidence suggests that adiponectin may have an important protective role in carcinogenesis. There is also evidence that at least some, if not most, cancer cell types express adiponectin receptors; thus adiponectin may act on tumour cells directly by binding and activating adiponectin receptors and downstream signalling pathways. Through its antiangiogenic properties, and also possibly through other mechanisms regulating cell proliferation discussed in this review, adiponectin may prove to be an effective novel anticancer agent. Large association and prospective studies to assess adiponectin levels in relation to risk from cancer, as well as mechanistic studies to prove adiponectin's role in the development of malignancies, and interventional trials to address potential roles of adiponectin in cancer pathogenesis and therapeutics are needed.

Basen-Engquist, K., S. Scruggs, et al. (2009). "Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning." Am J Obstet Gynecol **200**(3): 288 e1-8.

OBJECTIVE: This study aims to determine the prevalence of physical activity and obesity and their relationship to physical functioning (PF), fatigue, and pain in endometrial cancer survivors. STUDY DESIGN: Surveys were mailed to 200 survivors of endometrial cancer diagnosed within the last 5 years; 61% were returned. Surveys assessed physical activity, height and weight, comorbid health problems, PF, fatigue, and pain. RESULTS: In all, 22% exercised in the past month at the level of current public health recommendations, 41% reported no physical activity, and 38% reported some activity. A total of 16% were overweight and 50% were obese. Both lower body mass index (BMI) and higher physical activity were related to better PF. Higher physical activity was related to less fatigue, primarily for patients of normal BMI. CONCLUSION: Results suggest endometrial cancer survivors' obesity and inactivity contributes to poorer quality of life. This population could benefit from quality-of-life interventions incorporating physical activity.

Bassett, W. W., M. R. Cooperberg, et al. (2005). "Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE." Urology **66**(5): 1060-5.

OBJECTIVES: To determine the association between obesity and prostate cancer recurrence after primary treatment with radical prostatectomy. METHODS: Data were abstracted from CaPSURE, a disease registry of 10,018 men with prostate cancer. We included 2131 men who had undergone radical prostatectomy between 1989 and 2003 and had body mass index (BMI) information available. Recurrence was defined as two consecutive prostate-specific antigen (PSA) levels of 0.2 ng/mL or greater or any second treatment. Patients were risk stratified using the PSA level, Gleason grade, and clinical T stage. RESULTS: Patients were followed up for a median of 23 months. Of the 2131 patients, 251 (12%) developed recurrence at a median of 13 months (range 1 to 107); 183 (9%) of these men had PSA failure and 68 (3%) received a second treatment. After adjusting for risk group, ethnicity, age, and comorbidities, a significant association was found between an increasing BMI and disease recurrence (P = 0.028). Very obese patients (BMI 35 kg/m2 or more) were 1.69 times more likely to have recurrence relative to men of normal weight (BMI less than 25.0 kg/m2; 95% confidence interval [CI] 1.01 to 2.84). An increasing PSA level (P <0.0001) and Gleason grade (P <0.0001) were also associated with recurrence. Ethnicity was not significantly associated with either BMI or PSA recurrence (P = 0.685 and P = 0.068, respectively). CONCLUSIONS: The results of our study have shown that obesity is an independent predictor of prostate cancer recurrence. Because of the increased comorbidities and greater rates of recurrence, obese individuals undergoing radical prostatectomy need vigilant follow-up care.

Batty, G. D., F. Barzi, et al. (2009). "Obesity and liver cancer mortality in Asia: The Asia Pacific Cohort Studies Collaboration." Cancer Epidemiol **33**(6): 469-72.

While obesity is associated with liver cancer in studies from western societies, the paucity of data from Asia limits insights into its aetiological role in this population. We examined the relationship between body mass index (BMI) and liver cancer mortality using data from the Asia Pacific Cohort Studies Collaboration. In 309,203 Asian study members, 4 years of follow-up gave rise to 11,135 deaths from all causes, 420 of which were ascribed to liver cancer. BMI, whether categorised according to

current guidelines for Asian groups or World Health Organisation recommendations, was not associated with liver cancer in any of our analyses.

Batty, G. D., M. J. Shipley, et al. (2005). "Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study." Int J Obes (Lond) **29**(10): 1267-74.

OBJECTIVE: To examine the relation of obesity and overweight with organ-specific cancer mortality. METHODS: In the Whitehall prospective cohort study of London-based government employees, 18 403 middle-age men participated in a medical examination between 1967 and 1970. Subjects were followed up for cause-specific mortality for up to 35 y (median: interquartile range (25th-75th centile); 28.1 y: 18.6-33.8). RESULTS: There were over 3000 cancer deaths in this cohort. There was a raised risk of mortality from carcinoma of the rectum, bladder, colon, and liver, and for lymphoma in obese or overweight men following adjustment for range of covariates, which included socioeconomic position and physical activity. These relationships held after exclusion of deaths occurring in the first 20 y of follow-up. CONCLUSION: Avoidance of obesity and overweight in adult life may reduce the risk of developing some cancers.

Becker, S., L. Dossus, et al. (2009). "Obesity related hyperinsulinaemia and hyperglycaemia and cancer development." Arch Physiol Biochem **115**(2): 86-96.

Excess body weight in combination with physical inactivity is a major determinant for the development of insulin resistance with associated hyperglycaemia and hyperinsulinaemia and further leads to tumour development. Several prospective epidemiological studies have shown a direct association between excess weight and common malignancies, such as colon, breast (post-menopausal), endometrial, gallbladder, pancreatic, kidney and oesophageal cancers, but also less frequent malignancies, such as leukaemia, multiple myeloma and non-Hodgkin lymphoma. Insulin resistance and hyperinsulinaemia are certainly key biological mechanisms underlying the relationship between adiposity and tumour development. The anti-diabetic drug, metformin, in addition to reduction of insulin resistance has also shown anti-tumour properties, and is increasingly being considered as a drug to prevent and treat obesity-related cancers. Several biological pathways have been involved in the association between excess body weight, insulin resistance and cancer, such as chronic low-grade inflammation, glucose toxicity, AGE product metabolism and the adenosine monophosphate kinase pathway.

Bege, T., B. Lelong, et al. (2009). "Impact of obesity on short-term results of laparoscopic rectal cancer resection." Surg Endosc **23**(7): 1460-4.

INTRODUCTION: The influence of obesity [body mass index (BMI) >or= 30 kg/m(2)] on the outcome of laparoscopic colorectal surgery remains controversial. The complexity of rectal laparoscopic resections requires a specific assessment of the impact of obesity on the feasibility and short-term results of the surgery. METHODS: Between February 2002 and May 2007, 210 laparoscopic mesorectal excisions were performed. Demographic, oncologic and perioperative data were entered in a prospective database. Twenty-four patients (11.4%) with BMI over 30 kg/m(2) formed the obese group (OG). The outcomes in the OG and the nonobese group (NOG) were compared. RESULTS: There were significantly more American Society of Anesthesiologists (ASA) score 3 patients (26% in OG versus 9% in NOG; $p = 0.03$) in the obese group. Obese patients experienced longer operative times (513 min in OG vs. 421 min in NOG; $p < 0.01$) and more frequent conversion to laparotomy (46% in OG vs. 12% in NOG; $p < 0.001$). Morbidity grade 1 was higher in the obese group (29.2% vs. 9.7% in NOG; $p = 0.01$), but there was no difference in regards to morbidity grade 2 or more (33.3% in OG vs. 32.3% in NOG). In addition, conversion to laparotomy among the obese did not increase significantly morbidity grade 2 or higher (5 of 11 for OG converted vs. 3 of 13 for OG nonconverted; $p = 0.39$). Regarding the oncological parameters (e.g. number of lymph nodes removed, distal and lateral margins) there was no difference between groups. CONCLUSION: Obesity increases operative duration and conversion rate of rectal laparoscopic resection for cancer. Although obesity is associated with a worse preoperative evaluation, there is no increase in relevant morbidity and no impairment of oncological safety.

Begum, P., C. E. Richardson, et al. (2009). "Obesity in post menopausal women with a family history of breast cancer: prevalence and risk awareness." Int Semin Surg Oncol **6**: 1.

BACKGROUND: Obesity and physical activity are modifiable risk factors in the development of post-menopausal breast cancer. The aim of this study was to assess the level of awareness and prevalence of these factors in women attending family history clinics. METHODS: Women attending the breast cancer family history clinic from 2004 to 2006 completed a questionnaire (SP15 format) about their knowledge of and exposure to various diet and lifestyle factors. All women had been counselled by a Consultant Cancer Geneticist and were given verbal and written information on the effect of life style on

breast cancer risk. Responses were analysed using SPSStrade mark software. RESULTS: The response rate was 70% and two thirds of women were post-menopausal. The prevalence of obesity in post-menopausal women was 37% with 40% being overweight. The majority of women consumed a healthy balanced diet. Only 15% of post-menopausal women exercised for more than 4 hours per week. Two-thirds of women correctly stated that obesity increases their breast cancer risk and 73% of these were overweight or obese. Over 87% were correctly aware of the role of family history, 68% of a high fat diet, and 57% of hormone replacement therapy in the development of breast cancer. CONCLUSION: Women attending family history clinics lead a high risk lifestyle for the development of breast cancer with high prevalence of obesity and low levels of physical activity. A campaign of patient education is needed to promote healthy lifestyle choices, especially physical activity, in these high-risk women.

Bender, R., H. Zeeb, et al. (2006). "Causes of death in obesity: relevant increase in cardiovascular but not in all-cancer mortality." J Clin Epidemiol **59**(10): 1064-71.

BACKGROUND AND OBJECTIVE: To assess the relation between body mass index (BMI) and the risk of death from various causes in a prospective cohort study. METHODS: In 6,192 obese patients (BMI > or =25 kg/m(2)) with mean BMI 36.6 kg/m(2) (SD 6.1) and mean age 40.4 years (SD 12.9) who had been referred to the obesity clinic of the Heinrich-Heine-University Dusseldorf, Germany, between 1961 and 1994, there were 1,058 deaths from all causes during a median follow-up time of 14.8 years. We calculated standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) for death from predefined groups of diseases by using Germany as reference population. RESULTS: In both sexes, risk of death from cardiovascular diseases (men: SMR = 2.2, CI 1.9-2.5; women: SMR = 1.6, CI 1.5-1.8), from diabetes (men: SMR = 5.4, CI 3.2-8.7; women: SMR = 3.5, CI 2.6-4.8), and in men from digestive diseases (SMR = 1.6, CI 1.01-2.3) was significantly increased. In contrast to other studies, an association between obesity and all-cancer mortality could not be found. Only in morbidly obese women (BMI > or =40 kg/m(2)), all-cancer mortality was significantly increased (SMR = 1.5, CI 1.1-1.9). CONCLUSION: Obesity is associated with increased risk of death from cardiovascular diseases and diabetes in both sexes, and from diseases of the digestive system in men.

Birmingham, J. M., J. V. Busik, et al. (2009). "Novel mechanism for obesity-induced colon cancer progression." Carcinogenesis **30**(4): 690-7.

Adipose tissue secretes factors linked to colon cancer risk including leptin. A hallmark of cancer is sustained angiogenesis. While leptin promotes angiogenesis in adipose tissue, it is unknown whether leptin can induce epithelial cells to produce factors that may drive angiogenesis, vascular development and therefore cancer progression. The purpose of this study was to compare the effects of leptin-stimulated colon epithelial cells differing in adenomatous polyposis coli (Apc) genotype (gatekeeper tumor suppressor gene for colon cancer) on angiogenesis. We employed novel colonic epithelial cell lines derived from the Immorto mouse [young adult mouse colon (YAMC)] and the Immorto-Min mouse [Immorto-Min colonic epithelial cell (IMCE)], which carries the Apc Min mutation, to study the effects of leptin-stimulated colon epithelial cells on angiogenesis. We utilized ex vivo rat mesenteric capillary bioassay and human umbilical vein endothelial cell (HUVEC) models to study angiogenesis. IMCE cells stimulated with leptin produced significantly more vascular endothelial growth factor (VEGF) than YAMC (268 +/- 18 versus 124 +/- 8 pg/ml; $P < 0.01$) cells. Leptin treatment induced dose-dependent increases in VEGF only in IMCE cells. Conditioned media from leptin (50 ng/ml)-treated IMCE cells induced significant capillary formation compared with control, which was blocked by the addition of a neutralizing antibody against VEGF. Conditioned media from leptin-treated IMCE cells also induced HUVEC cell proliferation, chemotaxis, upregulation of adhesion proteins and cell-signaling activation resulting in nuclear factor kappa B nuclear translocation and DNA binding due to VEGF. This is the first study demonstrating that leptin can induce preneoplastic colon epithelial cells to orchestrate VEGF-driven angiogenesis and vascular development, thus providing a specific mechanism and potential target for obesity-associated cancer.

Bradbury, B. D., J. B. Wilk, et al. (2005). "Obesity and the risk of prostate cancer (United States)." Cancer Causes Control **16**(6): 637-41.

The role of obesity in prostate cancer etiology remains controversial. A recent report suggested that obese men younger than age 60 may have a lower risk of developing prostate cancer than men the same age who are not obese. The current study used a nested, matched case-control study design and data collected in the General Practice Research Database between January 1991 and December 2001 to assess the association between body mass index (BMI) and the risk of incident prostate cancer. Seven hundred and thirty cases of prostate cancer with adequate information on BMI were identified and matched to 2740 controls on age,

sex, general practice, and index date. Obese men (BMI > or = 30.0 kilograms [kg]/square of height in meters [m(2)]) were at lower risk of developing prostate cancer (AOR=0.78, 95% CI: 0.56, 1.09) compared to normal weight men (BMI=23.0-24.9 kg/m(2)), and the data best fit an inverse quadratic model for the relation between BMI and the risk of prostate cancer. This study provides modest support for a protective association between obesity and the risk of incident prostate cancer.

Brawer, R., N. Brisbon, et al. (2009). "Obesity and cancer." Prim Care **36**(3): 509-31.

Obesity has become the second leading preventable cause of disease and death in the United States, trailing only tobacco use. Weight control, dietary choices, and levels of physical activity are important modifiable determinants of cancer risk. Physicians have a key role in integrating multifactorial approaches to prevention and management into clinical care and advocating for systemic prevention efforts. This article provides an introduction to the epidemiology and magnitude of childhood and adult obesity; the relationship between obesity and cancer and other chronic diseases; potential mechanisms postulated to explain these relationships; a review of recommended obesity treatment and assessment guidelines for adults, adolescents, and children; multilevel prevention strategies; and an approach to obesity management in adults using the Chronic Care Model.

Brennan, P., J. McKay, et al. (2009). "Obesity and cancer: Mendelian randomization approach utilizing the FTO genotype." Int J Epidemiol **38**(4): 971-5.

BACKGROUND: Obesity is a risk factor for several cancers although appears to have an inverse association with cancers strongly related to tobacco. Studying obesity is difficult due to numerous biases and confounding. METHODS: To avoid these biases we used a Mendelian randomization approach incorporating an analysis of variants in the FTO gene that are strongly associated with BMI levels among 7000 subjects from a study of lung, kidney and upper-aerodigestive cancer. RESULTS: The FTO A allele which is linked with increased BMI was associated with a decreased risk of lung cancer (allelic odds ratio (OR) = 0.92, 95% confidence interval (CI) 0.84-1.00). It was also associated with a weak increased risk of kidney cancer, which was more apparent before the age of 50 (OR = 1.44, CI 1.09-1.90). CONCLUSION: Our results highlight the potential for genetic variation to act as an unconfounded marker of environmentally modifiable factors, and offer the potential to obtain estimates of the causal effect of obesity. However, far larger sample sizes than studied here will be required to undertake this with precision.

Briganti, A., P. I. Karakiewicz, et al. (2009). "Obesity does not increase the risk of lymph node metastases in patients with clinically localized prostate cancer undergoing radical prostatectomy and extended pelvic lymph node dissection." Int J Urol **16**(8): 676-81.

OBJECTIVES: Several studies have shown that obesity is associated with more aggressive prostate cancer (PCa) variants. We hypothesized that obesity, quantified as body mass index (BMI), is associated with a higher risk of lymph node invasion (LNI) in patients undergoing extended pelvic lymph node dissection (ePLND). METHODS: Clinical and pathological data were available for 994 consecutive men with PCa treated with radical prostatectomy (RP) and ePLND at a single European tertiary academic centre. Univariable and multivariable logistic regression analyses addressed the rate of LNI. Covariates consisted of pre-treatment prostate specific antigen (PSA), biopsy Gleason sum, clinical stage history of diabetes mellitus as well as BMI coded as either continuous or categorized (<25, 25.0-29.9, 30 kg/m(2) or more) variable. Predictive accuracy was assessed with area under curve estimates. RESULTS: Overall LNI was diagnosed in 105 patients (10.6%). Mean number of removed lymph nodes was 18.3 (range 7-60). Of all 994 patients, 372 (37.4%) were normal weight, 518 (52.1%) overweight, and 104 (10.5%) were clinically obese. Prevalence of LNI did not significantly differ across different BMI categories (<25, 25.0-29.9 and 30 kg/m(2) or more; 9.9, 10.6 and 12.5%, respectively; P = 0.75). In logistic regression models, neither continuously coded nor categorized BMI was a significant predictor of LNI at univariable or multivariable analyses (all P-values >or=0.1). Moreover, inclusion of BMI with PSA, clinical stage, biopsy Gleason sum and presence of DM did not increase the ability of these variables to predict LNI (82.2% without BMI vs 82.5% and 82.9% with BMI coded as continuous and categorized variable, respectively; all P >or= 0.4). CONCLUSIONS: In men undergoing RP and ePLND, increased BMI was not associated with increased risk of lymph node metastases. Therefore, routinely considering patient BMI in risk stratification schemes or prognostic LNI models may not be warranted.

Brown, K. A., K. J. McInnes, et al. (2009). "Subcellular localization of cyclic AMP-responsive element binding protein-regulated transcription coactivator 2 provides a link between obesity and breast cancer in postmenopausal women." Cancer Res **69**(13): 5392-9.

Epidemiologic evidence supports a correlation between obesity and breast cancer in women. AMP-activated protein kinase plays an important role in energy homeostasis and inhibits the actions of cyclic AMP-responsive element binding protein-regulated transcription coactivator 2 (CRTC2). In postmenopausal women, the cyclic AMP-responsive element binding protein-dependent regulation of aromatase is a determinant of breast tumor formation through local production of estrogens. The present work aimed to examine the effect of adipokines on aromatase expression and identify additional mechanisms by which prostaglandin E(2) causes increased aromatase expression in human breast adipose stromal cells. Treatment of human adipose stromal cells with forskolin and phorbol 12-myristate 13-acetate (PMA), to mimic prostaglandin E(2), resulted in nuclear translocation of CRTC2. Aromatase promoter II (PII) activity assays showed that CRTC2 in addition to forskolin/PMA treatment significantly increased PII-induced activity. CRTC2 binding to PII was examined by chromatin immunoprecipitation, and forskolin/PMA treatment was associated with increased binding to PII. Treatment of human adipose stromal cells with leptin significantly up-regulated aromatase expression associated with nuclear translocation of CRTC2 and increased binding of CRTC2 to PII. Adiponectin treatment significantly decreased forskolin/PMA-stimulated aromatase expression, consistent with the decreased nuclear translocation of CRTC2 and the decreased binding of CRTC2 to PII. The expression and activity of the AMP-activated protein kinase LKB1 was examined and found to be significantly decreased following either forskolin/PMA or leptin treatment. In contrast, adiponectin significantly increased LKB1 expression and activity. In conclusion, the regulation of aromatase by CRTC2, in response to the altered hormonal milieu associated with menopause and obesity, provides a critical link between obesity and breast cancer.

Buist, D. S., L. Ichikawa, et al. (2007). "Receipt of appropriate primary breast cancer therapy and adjuvant therapy are not associated with obesity in older women with access to health care." J Clin Oncol **25**(23): 3428-36.

PURPOSE: Many studies have reported body mass index (BMI) increases the risk of breast cancer recurrence and breast cancer-specific mortality. Few studies have reported or examined whether breast cancer treatment differs by BMI. The purpose of this study was to examine the association between BMI at breast cancer diagnosis and receipt of appropriate primary tumor therapy and adjuvant therapy. METHODS: We identified 897 women age >or= 65 years diagnosed with stage I or II breast cancer from 1990 to 1999 at five health care organizations. We used medical records to confirm demographics, tumor characteristics, treatment, comorbid conditions, and to calculate BMI at diagnosis (< 25 kg/m(2), n = 328; 25 to < 30 kg/m(2), n = 305; 30 to < 35 kg/m(2), n = 188; >or= 35 kg/m(2), n = 76). We defined primary therapy based on National Guidelines as receiving breast-conserving surgery with radiation therapy and axillary node dissection, simple mastectomy with axillary node dissection, or modified radical mastectomy (73% overall); adjuvant therapy was defined as receipt of hormonal therapy, chemotherapy, or both (60% overall). RESULTS: The median BMI was 26.7 kg/m(2) (range, 14.6 to 61.2). The proportion of women receiving primary therapy and adjuvant therapy was lowest for women less than 25 kg/m(2) (69% and 56%, respectively) and greatest for obese I (78% and 64%, respectively). There were no differences in receipt of primary or adjuvant treatment across BMI in univariate or multivariable models (after adjusting for age, stage, comorbidity, diagnosis year, and hormone receptor positivity). CONCLUSION: Receipt of appropriate primary therapy and adjuvant therapy is not associated with BMI in older women with access to health care. Additional research in larger samples and more diverse settings is needed.

Buschemeyer, W. C., 3rd and S. J. Freedland (2007). "Obesity and prostate cancer: epidemiology and clinical implications." Eur Urol **52**(2): 331-43.

OBJECTIVES: Both obesity and prostate cancer (PCa) are epidemic in Western society. Although initial epidemiological data appeared conflicting, recent studies have clarified the association between obesity and PCa. Therefore, we sought to review the epidemiological data linking obesity and PCa with an emphasis on the clinical implications and how to improve outcomes among obese men. METHODS: A PubMed search using the keywords "prostate cancer" and "obesity" was performed. Relevant articles and references were reviewed for data on the association between obesity and PCa. RESULTS: Recent data suggest obesity is associated with reduced risk of nonaggressive disease but increased risk of aggressive disease. This observation may be explained in part by an inherent bias in our ability to detect PCa in obese men (lower PSA values and larger sized prostates, making biopsy less accurate for finding an existent cancer), which ultimately leads to increased risk of cancer recurrence after primary therapy and increased PCa mortality. Despite this detection bias potentially contributing to more aggressive cancers, multiple biological links also

exist between obesity and PCa including higher estradiol, insulin, free IGF-1, and leptin levels, and lower free testosterone and adiponectin levels, all of which may promote more aggressive cancers. CONCLUSIONS: The association between obesity and PCa is complex. Emerging data suggest obesity increases the risk of aggressive cancer, while simultaneously decreasing the risk of more indolent disease. This is likely driven by both "biological" and "nonbiological" causes. Simple changes in clinical practice patterns can reduce the impact of nonbiological causes and may help improve PCa outcomes among obese men.

Carmichael, A. R. (2006). "Obesity and prognosis of breast cancer." Obes Rev **7**(4): 333-40.

Obesity has a complicated relationship to both breast cancer risk and the clinical behaviour of the established disease. It is suggested that obesity is associated with both an increased risk of developing breast cancer risk and worse prognosis after disease onset. In post-menopausal women, various measures of obesity such as body mass index, weight, weight gain and waist : hip ratio have all been positively associated with risk of developing breast cancer. In most but not all case-control and prospective cohort studies, an inverse relationship has been found between weight and breast cancer among pre-menopausal women. Some data suggest that adult weight gain and central obesity increase the risk of pre-menopausal breast cancer. Obesity at the time of diagnosis is thought to be significant as a poor prognostic factor. Obesity is associated with adverse outcomes in both pre- and post-menopausal women with breast cancer. Many cancer survivors seek ways to minimize the risk of recurrence and death because of breast cancer. Despite complex and at times controversial data, enough evidence is available at present to suggest that weight management should be a part of the strategy to prevent the occurrence, recurrence and death because of breast cancer. In this review the effect of obesity on the prognosis of breast cancer is examined in detail.

Carmichael, A. R. (2006). "Obesity as a risk factor for development and poor prognosis of breast cancer." Bjog **113**(10): 1160-6.

The evidence that obesity adversely affects women's health is overwhelming and indisputable. The risk of postmenopausal breast cancer increases with obesity; measured as weight gain, body mass index, waist-hip ratio or percent body fat. It is also established that obesity is associated with poor prognosis of breast cancer. This review examines in detail the possible mechanisms by which obesity causes poor prognosis of breast cancer such as estrogenic activity, advanced or more aggressive disease at diagnosis and high likelihood of both local and systemic treatment failure. After careful consideration of the available evidence, the author concludes that obesity contributes towards development and poor prognosis of breast cancer; therefore, weight management should be an integral part of any strategy to prevent and improve the outcome of breast cancer.

Carter, J. C. and F. C. Church (2009). "Obesity and breast cancer: the roles of peroxisome proliferator-activated receptor-gamma and plasminogen activator inhibitor-1." PPAR Res **2009**: 345320.

Breast cancer is the most prominent cancer among females in the United States. There are a number of risk factors associated with development of breast cancer, including consumption of a high-fat diet and obesity. Plasminogen activator inhibitor-1 (PAI-1) is a cytokine upregulated in obesity whose expression is correlated with a poor prognosis in breast cancer. As a key mediator of adipogenesis and regulator of adipokine production, peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is involved in PAI-1 expression from adipose tissue. We summarize the current knowledge linking PPAR-gamma and PAI-1 expression to high-fat diet and obesity in the risk of breast cancer.

Ceschi, M., F. Gutzwiller, et al. (2007). "Epidemiology and pathophysiology of obesity as cause of cancer." Swiss Med Wkly **137**(3-4): 50-6.

According to World Health Organisation estimates 1.1 billion people were overweight or obese worldwide in the year 2000 with the prevalence rapidly increasing. Compelling evidence suggests that excess body weight is a risk factor for several cancer types including cancer of the colon, breast, endometrium, kidney, oesophagus, as well as possibly additional sites. According to previous meta-analyses and systematic literature reviews, an important proportion of cancer has been estimated to be attributable to excess body weight. The extrapolation of a European meta-analysis [1] to the Swiss situation broadly estimates that around 700 cancers could be prevented in the absence of overweight and obesity in this country. The data presented highlights the public health relevance of preventing excess body weight. Several interacting metabolic and hormonal pathways seem to underlie the association between being overweight and cancer with insulin-resistance playing a central role. Since evidence is mounting that excess body weight can also adversely affect cancer prognosis, obesity is a primary target for cancer control programs.

Chak, A., G. Falk, et al. (2009). "Assessment of familiality, obesity, and other risk factors for early age of cancer diagnosis in adenocarcinomas of the esophagus and gastroesophageal junction." Am J Gastroenterol **104**(8): 1913-21.

OBJECTIVES: Adenocarcinomas of the esophagus and adenocarcinomas of the gastroesophageal junction are postulated to be complex genetic diseases. Combined influences of environmental factors and genetic susceptibility likely influence the age at which these cancers develop. The aim of this study was to determine whether familiality and other recognized risk factors are associated with the development of these cancers at an earlier age. METHODS: A structured validated questionnaire was utilized to collect self-reported data on gastro-esophageal reflux symptoms, risk factors for Barrett's esophagus (BE) and family history, including age of cancer diagnosis in affected relatives from probands with BE, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction, at five tertiary care academic hospitals. Medical records of all relatives reported to be affected were requested from hospitals providing this cancer care to confirm family histories. Familiality of BE/cancer, obesity (defined as body mass index >30), gastroesophageal reflux symptoms, and other risk factors were assessed for association with a young age of cancer diagnosis. RESULTS: A total of 356, 216 non-familial and 140 familial, cancers were studied. The study population consisted of 292 (82%) men and 64 (18%) women. Mean age of cancer diagnosis was no different in a comparison of familial and non-familial cancers, 62.6 vs. 61.9 years, P=0.70. There were also no significant differences in symptoms of gastroesophageal reflux, body mass index, race, gender, and smoking history between familial and non-familial cancers. Mean age of cancer diagnosis was significantly younger in those who were obese 1 year before diagnosis as compared to those who were non-obese, mean age 58.99 vs. 63.6 years, P=0.008. Multivariable modeling of age at cancer diagnosis showed that obesity 1 year before diagnosis was associated with a younger age of cancer diagnosis (P=0.005) after adjustment for heartburn and regurgitation duration. CONCLUSIONS: Obesity is associated with the development of esophageal and gastroesophageal junctional adenocarcinomas at an earlier age. Familial cancers arise at the same age as non-familial cancers and have a similar risk factor profile.

Chang, S., L. C. Masse, et al. (2008). "State ranks of incident cancer burden due to overweight and obesity in the United States, 2003." Obesity (Silver Spring) **16**(7): 1636-50.

OBJECTIVE: Given links between obesity and cancer, we estimated incident cancer burden due to overweight and obesity at the state level in the United States. METHODS AND PROCEDURES: Using state rankings by per capita burden of incident cancer cases diagnosed in 2003 that were related to overweight and obesity, we examined the frequency with which states ranked in the highest and lowest quintiles of weight-related burden for cancers of the postmenopausal breast, endometrium, kidney, colon, and prostate. In this study, data from the Behavioral Risk Factor Surveillance System (BRFSS), US Census, US Mortality Public Use Data Tapes, and National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program were used. RESULTS: Western states had the lowest weight-related cancer burden for both sexes. Iowa, South Dakota, and West Virginia had the highest burden for all three types of male cancers. West Virginia is the only state that ranked in the quintile of highest weight-related burden for all four cancers considered in women. DISCUSSION: For certain cancers, including endometrial, postmenopausal breast, and colon cancers, states with high burdens clustered in geographic regions, warranting further inquiry. Although state ranks for the total cancer burden and the prevalence of overweight and obesity correlated with state ranks for weight-related incident cancer burden, they often served poorly as its proxy. Such a finding cautions against simply targeting states with high overweight and obesity or high total burdens of cancers for which overweight and obesity are risk factors, as this approach may not reach areas of unrecognized burden.

Chia, V. M., P. A. Newcomb, et al. (2007). "Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis." Int J Gynecol Cancer **17**(2): 441-6.

Endogenous and exogenous sources of estrogen and characteristics altering these hormone levels have been related to endometrial cancer risk; however, their relationship to survival following diagnosis is less clear. In a population-based study, we examined whether mortality after endometrial cancer diagnosis was affected by prediagnosis obesity, diabetes, smoking, oral contraceptive use, parity, or postmenopausal hormone (PMH) use. Eligible women, aged 40-79 years, diagnosed from 1991-1994 with incident invasive endometrial cancer and identified through the Wisconsin statewide mandatory cancer registry were invited to participate. Of 745 eligible cases, 166 women were deceased after 9.3 years of follow-up, with 43 attributable to endometrial cancer, based upon vital records linkage. Hazard rate ratios (HRR) and 95% confidence intervals were

adjusted for age at diagnosis, menopausal status, stage of disease, and other exposures of interest. Obese women (body mass index [BMI] >or=30 kg/m(2)) prior to endometrial cancer diagnosis had an increased risk of both all-cause (HRR=1.6, 95% CI 1.0-2.5) and endometrial cancer (HRR=2.0, 95% CI 0.8-5.1) mortality, compared with nonoverweight women (BMI<25 kg/m(2)). Endometrial cancer cases with diabetes also had an increased risk of all-cause mortality compared with nondiabetic women (HRR=1.7, 95% CI 1.1-2.5), although there was no association with endometrial cancer mortality. There were no associations between PMH use, oral contraceptive use, parity, or smoking and mortality from any cause. The results suggest that history of obesity and diabetes may increase risk of mortality after endometrial cancer diagnosis; modification of these characteristics may improve survival after endometrial cancer diagnosis.

Chung, Y. W., D. S. Han, et al. (2006). "Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case-control study in Korea." Dig Liver Dis **38**(9): 668-72.

BACKGROUND: Previous studies on colorectal cancer risk suggest that obesity, serum lipids and glucose might be related to colorectal carcinogenesis. This case-control study was conducted to investigate the association between obesity, serum lipids and glucose, and the risk of advanced colorectal adenoma and cancer. METHODS: Patients with histologically confirmed colorectal cancers (n=105), same number of patients with advanced colorectal adenomas matched by age and sex, and the same number of controls matched by age and sex were selected in Hanyang University Guri Hospital between January 2002 and June 2004. RESULTS: Adenoma and cancer group showed significantly higher levels of mean body mass index and serum glucose. Cancer group also showed significantly lower mean serum lipids levels than controls. We used an unordered polytomous logistic model to calculate multivariate odds ratios for advanced adenoma and cancer relative to controls. Higher serum glucose level was more strongly associated with increased risk of cancer relative to controls (odds ratio, 3.0; 95% confidence interval, 0.9-9.8) than with increased risk of advanced adenoma (odds ratio, 2.1; 95% confidence interval, 0.9-5.4). Higher body mass index was strongly associated with increased risk of advanced adenoma (odds ratio, 10.8; 95% confidence interval, 4.6-25.3), but associated with attenuated risk of cancer (odds ratio, 2.3; 95% confidence interval, 0.9-5.8). Serum triglycerides and cholesterol levels were strongly associated with reduced risk of cancer (odds ratio, 0.3; 95% confidence interval, 0.1-0.8 and odds ratio, 0.2; 95% confidence interval, 0.1-0.6, respectively). CONCLUSIONS: Obesity and hyperglycaemia are positively related to advanced colorectal adenoma formation. Furthermore, hyperglycaemia plays an important role in progression to cancer. Findings on an inverse relationship between serum triglyceride and cholesterol levels and the risk of colorectal cancer may be the secondary results from metabolic or nutritional changes in advanced colorectal cancer patients and should be clarified in further studies.

Cleary, M. P. and M. E. Grossmann (2009). "Minireview: Obesity and breast cancer: the estrogen connection." Endocrinology **150**(6): 2537-42.

There is now substantial evidence that overweight and/or obesity and/or weight gain are risk factors for the development of postmenopausal breast cancer. In addition, obesity and/or elevated body mass index at breast cancer diagnosis has a negative impact on prognosis for both premenopausal and postmenopausal women. Therefore, understanding the mechanism of how obesity affects the mammary tumorigenesis process is an important health issue. Elevated serum estrogen levels as well as enhanced local production of estrogen have been considered primary mediators of how increased body weight promotes breast cancer development in postmenopausal women. Here, we provide an overview of estrogen's relationship with both obesity and breast cancer as separate entities. Human and relevant preclinical studies are cited. In addition, other growth factors that may be involved in this relationship are considered.

Clegg, D. J. and S. C. Heffelfinger (2006). "Obesity: its influence on breast cancer susceptibility." Womens Health (Lond Engl) **2**(4): 577-85.

Obesity is an increasing worldwide epidemic. With an increased prevalence of obesity there is an increase in obesity-related cancers, such as breast cancer. Although reproductive and lifestyle choices are among the best-recognized risk factors for breast cancer, few of these can be modified readily by the individual. Obesity is unlike these other risk factors since it can be modified and controlled. Breast cancer prognosis is worse in patients who are obese, and epidemiological data suggests that obesity is a significant risk factor for postmenopausal breast cancer. Addressing the obesity epidemic, at both an individual and public health level, is expected to have a significant impact on breast cancer incidence and mortality.

Cohen, S. S., R. T. Palmieri, et al. (2008). "Obesity and screening for breast, cervical, and colorectal

cancer in women: a review." Cancer **112**(9): 1892-904.

The literature examining obesity as a barrier to screening for breast, cervical, and colorectal cancer has not been evaluated systematically. With the increasing prevalence of obesity and its impact on cancer incidence and mortality, it is important to determine whether obesity is a barrier to screening so that cancers among women at increased risk because of their body size can be detected early or prevented entirely. On the basis of 32 relevant published studies (10 breast cancer studies, 14 cervical cancer studies, and 8 colorectal cancer studies), the authors reviewed the literature regarding associations between obesity and recommended screening tests for these cancer sites among women in the U.S. The most consistent associations between obesity and screening behavior were observed for cervical cancer. Most studies reported an inverse relation between decreased cervical cancer screening and increasing body size, and several studies reported that the association was more consistent among white women than among black women. For breast cancer, obesity was associated with decreased screening behavior among white women but not among black women. The literature regarding obesity and colorectal cancer screening adherence was mixed, with some studies reporting an inverse effect of body size on screening behavior and others reporting no effect. Overall, the results indicated that obesity most likely is a barrier to screening for breast and cervical cancers, particularly among white women; the evidence for colorectal cancer screening was inconclusive. Thus, efforts to identify barriers and increase screening for breast and cervical cancers may be targeted toward obese women, whereas outreach to all women should remain the objective for colorectal cancer screening programs.

Cook, L. M., S. R. Kahn, et al. (2007). "Frequency of renal impairment, advanced age, obesity and cancer in venous thromboembolism patients in clinical practice." J Thromb Haemost **5**(5): 937-41.

BACKGROUND: Low-molecular-weight heparin (LMWH) dosed by weight is recommended as first-line therapy for the initial treatment of venous thromboembolism (VTE) and as monotherapy for long-term treatment of cancer-related VTE. In 'special populations' such as those with renal impairment or the elderly, weight-based dosing may be excessive, and capping the dose in obese patients may lead to inadequate dosing. OBJECTIVES: We determined the frequency of 'special population' characteristics (renal impairment, advanced age, obesity) and cancer among VTE patients in clinical practice, and assessed whether these characteristics appeared to influence the type and dose of anticoagulants prescribed. METHODS: During 2004-2005, among consecutive patients with VTE at two large Canadian hospitals, the proportions with the above characteristics were calculated and treatments prescribed were determined. RESULTS: Of 524 VTE patients, 31% were aged > 75 years. Moderate renal impairment [creatinine clearance (CrCl) 30-59 mL min(-1)] was present in 20% of patients, and severe renal impairment (CrCl < 30 mL min(-1)) in 5% of patients. LMWH was prescribed to 67% of patients with severe renal impairment and to 83% of patients with moderate renal impairment. Body weight was > 100 kg in 15% of patients. Underdosing of LMWH by > 10% was documented in 36% of such patients compared with 8% of patients < 100 kg (P < 0.001). Among 26% of patients with active cancer, only one-third were prescribed LMWH monotherapy. CONCLUSIONS: In clinical practice, renal impairment, advanced age, obesity and cancer are frequently present in patients with VTE. A considerable proportion of these patients may not receive the optimal type or dose of medication to treat VTE.

Courneya, K. S., P. T. Katzmarzyk, et al. (2008). "Physical activity and obesity in Canadian cancer survivors: population-based estimates from the 2005 Canadian Community Health Survey." Cancer **112**(11): 2475-82.

BACKGROUND: Physical inactivity and obesity are associated with poorer disease outcomes in several cancer survivor groups. Few studies, however, have provided population-based estimates of these risk factors in cancer survivors and compared them with individuals without a history of cancer. Here such estimates for the Canadian population are reported. METHODS: Data were obtained from the 2005 Canadian Community Health Survey consisting of computer-assisted interviews of 114,355 adults representing an estimated 23,285,548 Canadians. Participants self-reported their cancer history, height, and body weight to calculate body mass index and participation in various leisure-time activities. RESULTS: Fewer than 22% of Canadian cancer survivors were physically active and over 18% were obese. Few differences were observed between cancer survivors and those without a history of cancer except that: 1) prostate cancer survivors were more likely to be active (adjusted odds ratio [OR] = 1.27; 95% confidence interval [CI] = 1.01-1.59) and less likely to be obese (adjusted OR = 0.71; 95% CI = 0.56-0.90); 2) skin cancer survivors (nonmelanoma and melanoma) were more likely to be active (adjusted OR = 1.33; 95% CI = 1.12-1.59); and 3) obese breast cancer survivors were less likely to be active compared with obese women without a history of

cancer (adjusted OR = 0.51; 95% CI = 0.27-0.94). CONCLUSIONS: Canadian cancer survivors have low levels of physical activity and a high prevalence of obesity that, although comparable to the general population, may place them at higher risk for poorer disease outcomes. Population-based interventions to increase physical activity and promote a healthy body weight in Canadian cancer survivors are warranted.

Culp, S. and M. Porter (2009). "The effect of obesity and lower serum prostate-specific antigen levels on prostate-cancer screening results in American men." BJU Int **104**(10): 1457-61.

OBJECTIVE: To determine if lower serum total prostate specific antigen (PSA) levels in obese American men affect prostate-cancer screening results, as an increased body mass index (BMI) is inversely associated with PSA level, but the effect of this association on PSA screening results for prostate cancer is unknown. SUBJECTS AND METHODS: We analysed the most recent National Health and Nutrition Examination Surveys (NHANES 2001-2002, 2003-2004, and 2005-2006), a nationally representative cross-sectional sample of non-institutionalized adults aged > or =20 years. Logistic regression was used to estimate the odds of an 'abnormal' PSA level (4.0 or 2.5 ng/mL) based on BMI categories of normal (18.5-24.9 kg/m(2)), overweight (25-29.9) and obese (30-39.9) in men who were eligible for prostate-cancer screening with serum total PSA tests (age 40-75 years, BMI 18.5-39.9 kg/m(2), PSA <20 ng/mL). RESULTS: In all, 3152 participants with no known prostate cancer, representing 46 million American men, were eligible for prostate-cancer screening. After controlling for age and race, there was a statistically significant trend of a lower likelihood of having a serum total PSA level of > or =4.0 ng/mL with increased BMI. When men were stratified by race, this effect was apparent only in white non-Hispanic men, with obese men in this group having a 46% lower likelihood of having an 'abnormal' PSA level (odds ratio 0.54, 95% confidence interval 0.31-0.91; P = 0.024) than those with a normal BMI. There was no observable trend in either African-American or Hispanic men. In addition, there was no observable trend with a serum total PSA threshold of 2.5 ng/mL, regardless of race. CONCLUSIONS: Obese white non-Hispanic men are about half as likely as those with a normal BMI to have a PSA level of > or =4.0 ng/mL. These results might affect prostate-cancer screening with serum total PSA. Further studies are needed to better define the association of BMI and PSA in racial minority subgroups.

Dai, Q., Y. T. Gao, et al. (2009). "Oxidative stress, obesity, and breast cancer risk: results from the Shanghai Women's Health Study." J Clin Oncol **27**(15): 2482-8.

PURPOSE: Increased reactive oxygen species may exhaust the antioxidant capability of human defense systems, leading to oxidative stress and cancer development. Urinary F2-isoprostanes, secondary end products of lipid peroxidation, are more accurate markers of oxidative stress than other available biomarkers. No prospective study has investigated whether levels of 15-F(2t)-isoprostane (15-F(2t)-IsoP) and its metabolite 2,3-dinor-5,6-dihydro-15-F(2t)-IsoP (15-F(2t)-IsoPM) are related to breast cancer risk. PATIENTS AND METHODS: We conducted a nested case-control study within the Shanghai Women's Health Study, a population-based cohort study of 74,942 Chinese women between 40 and 70 years of age. Prediagnostic urinary 15-F(2t)-IsoP and 15-F(2t)-IsoPM were measured by gas chromatography mass spectrometry for 436 breast cancer cases and 852 individually matched controls. RESULTS: Urinary excretion of isoprostanes was not significantly different between cases and controls. However, among overweight women, levels of isoprostanes were positively associated with breast cancer risk, which became stronger with increasing body mass index (BMI). Among women with a BMI > or = 29, the odds ratio (OR) increased to 10.27 (95% CI, 2.41 to 43.80) for the highest compared with the lowest tertile of 15-F(2t)-IsoPM (P for trend = .003; P for interaction = .0004). In contrast, 15-F(2t)-IsoP and 15-F(2t)-IsoPM were inversely associated with breast cancer risk among nonoverweight women. Among women with a BMI < or = 23, breast cancer risk was reduced with increasing 15-F(2t)-IsoP levels in a dose-response manner (P for trend = .006), with an OR of 0.46 (95% CI, 0.26 to 0.80) for the highest tertile versus the lowest (P for interaction = .006). CONCLUSION: Our results suggest that the role of oxidative stress in breast cancer development may depend on adiposity.

Dai, Z., Y. C. Xu, et al. (2007). "Obesity and colorectal cancer risk: a meta-analysis of cohort studies." World J Gastroenterol **13**(31): 4199-206.

AIM: To evaluate the association between obesity and colorectal cancer risk. METHODS: We searched PubMed, EMBASE, and the Cochrane Library up to January 1, 2007. Cohort studies permitting the assessment of causal association between obesity and colorectal cancer, with clear definition of obesity and well-defined outcome of colorectal cancer were eligible. Study design, sample size at baseline, mean follow-up time, co-activators and study results were extracted. Pooled standardized

effect sizes were calculated. RESULTS: The pooled relative risk (RR) of colorectal cancer was 1.37 (95% CI: 1.21-1.56) for overweight and obese men, 1.07 (95% CI: 0.97-1.18) for women measured by body mass index (BMI). The pooled RR for the highest vs the lowest quantiles of BMI was 1.59 (95% CI: 1.35-1.86) for men and 1.22 (95% CI: 1.08-1.39) for women at risk of colon cancer, 1.16 (95% CI: 0.93-1.46) for men and 1.23 (95% CI: 0.98-1.54) for women at risk of rectal cancer. The pooled RR for the highest vs the lowest quantiles of waist circumference was 1.68 (95% CI: 1.36-2.08) for men and 1.48 (95% CI: 1.19-1.84) for women at risk of colon cancer, 1.26 (95% CI: 0.90-1.77) for men and 1.23 (95% CI: 0.81-1.86) for women at risk of rectal cancer. The pooled RR for the highest quantiles vs the lowest quantiles of waist-to-hip ratio was 1.91 (95% CI: 1.46-2.49) for men and 1.49 (95% CI 1.23-1.81) for women at risk of colon cancer, 1.93 (95% CI: 1.19-3.13) for men and 1.20 (95% CI: 0.81-1.78) for women at risk of rectal cancer. Compared with 'normal range', the pooled RR for proximal colon cancer was 1.14 (95% CI: 0.88-1.47) for the overweight and 1.41 (95% CI: 0.66-3.01) for the obese. The pooled RR for the highest quantiles vs the lowest quantiles was 2.05 (95% CI: 1.23-3.41) with waist circumference, 1.66 (95% CI: 0.69-3.99) with waist-to-hip ratio. Compared with 'normal range', the pooled RR for distal colon cancer was 1.38 (95% CI: 1.02-1.87) for the overweight and 1.23 (95% CI: 0.80-1.90) for the obese. The pooled RR for the highest quantiles vs the lowest quantiles was 1.86 (95% CI: 1.05-3.30) with waist circumference, and 1.79 (95% CI: 0.82-3.90) with waist-to-hip ratio. CONCLUSION: Obesity is a statistically significant risk factor for colorectal cancer and the relationship is more significant in men than in women among different cancer subsites. Indexes of abdominal obesity are more sensitive than those of overall obesity.

Dal Maso, L., A. Zucchetto, et al. (2008). "Effect of obesity and other lifestyle factors on mortality in women with breast cancer." Int J Cancer **123**(9): 2188-94.

A few lifestyle characteristics before cancer diagnosis have been suggested to modify the prognosis of breast cancer. Follow-up information from 1,453 women with incident invasive breast cancer, diagnosed between 1991 and 1994 and interviewed within the framework of an Italian multicenter case-control study, was used to assess the effect of obesity and of a large spectrum of other factors on breast cancer mortality. Five hundred and three deaths, including 398 breast cancer deaths, were identified. Hazard ratios (HR) for all-cause and breast cancer mortality and corresponding 95% confidence intervals (CI), were calculated using Cox proportional hazards models and adjusted for age and breast cancer characteristics (stage and receptor status). Increased risk of death for breast cancer emerged for body mass index (BMI) >/= 30 kg/m(2) (HR = 1.38; 95% CI: 1.02-1.86), compared to <25, or waist-to-hip ratio (WHR) >/= 0.85 (HR = 1.27; 95% CI: 0.98-1.64), compared to <0.80, and the strongest association was observed for women with BMI >/=30 and high WHR (>/=0.85), compared to women with BMI <25 and WHR < 0.85 (HR = 1.57, 95% CI: 1.08-2.27). The unfavorable effect of high BMI was similar in women <55 and >/=55 years of age, whereas it was stronger in women with I-II stage than III-IV stage breast cancer. Low vegetable and fruit consumption and current or past smoking were also associated to marginally worse breast cancer survival. No significant relationship with survival after breast cancer emerged for several other major lifestyle factors, including physical activity, alcohol drinking, exogenous hormones use and fat intake. High BMI was the lifestyle risk factor that most consistently modified breast cancer prognosis in our study.

Damadi, A. A., L. Julien, et al. (2008). "Does obesity influence lymph node harvest among patients undergoing colectomy for colon cancer?" Am Surg **74**(11): 1073-7.

Adequate lymph node harvest among patients undergoing colectomy for cancer is critical for staging and therapy. Obesity is prevalent in the American population. We investigated whether lymph node harvest was compromised in obese patients undergoing colectomy for cancer. Medical records of patients who had undergone colectomy for colon cancer were reviewed. We correlated the number of lymph nodes with body mass index (BMI) and compared the number of lymph nodes among patients with BMI less than 30 kg/m2 to those with BMI of 30 kg/m2 or greater ("obese"). Among all 191 patients, the correlation coefficient was 0.04 (P > 0.2). The mean number of nodes harvested from 122 nonobese patients was 12.4 +/- 6 and that for 69 obese patients 12.8 +/- 6 (P > 0.2). Among 130 patients undergoing right colectomy and 35 patients undergoing sigmoid colectomy, the correlation coefficients were 0.02 (P > 0.2) and 0.16 (P > 0.2), respectively. There was not a statistically significant difference in lymph node harvest between obese and nonobese patients (14.1 +/- 7 vs. 13.8 +/- 6, P > 0.2; and 11.8 +/- 6 vs. 8.6 +/- 5, P > 0.2), respectively. Obesity did not compromise the number of lymph nodes harvested from patients undergoing colectomy for colon cancer.

Dann, S. G., A. Selvaraj, et al. (2007). "mTOR Complex1-S6K1 signaling: at the crossroads of

obesity, diabetes and cancer." Trends Mol Med **13**(6): 252-9.

Recent studies demonstrate that the mammalian target of rapamycin (mTOR) and its effector, S6 kinase 1 (S6K1), lie at the crossroads of a nutrient-hormonal signaling network that is involved in specific pathological responses, including obesity, diabetes and cancer. mTOR exists in two complexes: mTOR Complex1, which is rapamycin-sensitive and phosphorylates S6K1 and initiation factor 4E binding proteins (4E-BPs), and mTOR Complex2, which is rapamycin-insensitive and phosphorylates protein kinase B (PKB, also known as Akt). Both mTOR complexes are stimulated by mitogens, but only mTOR Complex1 is under the control of nutrient and energy inputs. Thus, to orchestrate the control of homeostatic responses, mTOR Complex1 must integrate signals from distinct cues. Here, we review recent findings concerning the regulation and pathophysiology associated with mTOR Complex1 and S6K1.

Davies, B. J., M. C. Smaldone, et al. (2009). "The impact of obesity on overall and cancer specific survival in men with prostate cancer." J Urol **182**(1): 112-7; discussion 117.

PURPOSE: We examined the impact of obesity on disease specific and overall survival in patients with prostate cancer. MATERIALS AND METHODS: We identified 7,274 men from the Cancer of the Prostate Strategic Urological Research Endeavor database with clinically localized prostate cancer, known body mass index and clinicopathological disease characteristics. Patients were classified by body mass index as normal (less than 25 kg/m(2)), overweight (25 to 29.9 kg/m(2)), obese (30 to 34.9 kg/m(2)) and severely obese (35 kg/m(2) or greater). Associations between body mass index and need for secondary treatment, disease specific survival and overall survival were analyzed using univariate and multivariate models. RESULTS: Patients were classified by body mass index category as normal (28.8%), overweight (50%), obese (16.4%) and very obese (4.8%). Mean followup was 51.3 +/- 38.5 months. During followup there were 1,044 deaths with 220 (21.1%) from prostate cancer. Stratified by body mass index category the groups differed with regard to the need for secondary treatment ($p = 0.05$) and overall mortality ($p < 0.01$) but there were no significant differences with regard to disease specific survival ($p = 0.09$). On multivariate analysis age 65 to 74 years (HR 2.4, $p = 0.002$), age older than 75 years (HR 3.2, $p = 0.0001$), high risk disease (HR 1.6, $p < 0.0001$), conservative treatment (HR 1.2, $p < 0.0001$) and presence of diabetes (HR 1.6, $p < 0.0001$) were associated with decreased overall survival. Only conservative treatment (HR 1.4, $p < 0.0001$), high risk disease (HR 8.4, $p < 0.0001$) and intermediate risk disease (HR 2.5, $p = 0.004$) were associated with decreased disease specific survival. CONCLUSIONS: In a prospective, community based cohort we were unable to establish a relationship between body mass index and prostate cancer disease specific survival or overall survival.

DeRenne, C., J. K. Maeda, et al. (2008). "Afterschool physical activity program to reduce obesity-related cancer risk: a feasibility study." J Cancer Educ **23**(4): 230-4.

BACKGROUND: Cancer is linked to obesity, and Native Hawaiian childhood obesity rates are high. We examined the feasibility of incorporating a physical activity intervention into an afterschool program for elementary school children. METHODS: Anthropometric and fitness measures were taken at baseline and 12 weeks later for 68 students in 2 schools. In one, the supervisor delivered a model curriculum. In the other, a supervisor with physical education training created the curriculum. RESULTS: We found a significant decrease in skinfold thicknesses and increase in distance covered in the 3-minute walk-run test. CONCLUSIONS: Incorporating daily physical activity into afterschool programs is feasible and effective, but teacher interest is critical, and the nonmandatory nature of this venue may limit children's participation.

Dignam, J. J., K. Wieand, et al. (2006). "Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer." Breast Cancer Res Treat **97**(3): 245-54.

BACKGROUND: Several factors may contribute to poorer prognosis for obese breast cancer patients, including unfavorable disease features, the influence of fat on estrogen availability, co-morbidity, and socio-demographic factors. Both obesity and estrogen receptor negative (ER-) tumors are more prevalent in black women than in whites in North America. We evaluated obesity and race in relation to outcomes in women with ER-breast cancer. METHODS: Among 4,077 women from National Surgical Adjuvant Breast and Bowel Project clinical trials for node-negative, ER-breast cancer, we evaluated disease-free survival (DFS) and its constituents (tumor recurrence, contralateral breast cancer (CBC), second primary cancers, deaths prior to these events) and mortality in relation to body mass index (BMI) and race, using statistical modeling to account for other prognostic factors. RESULTS: Compared to those of normal weight (BMI< or =24.9), DFS hazard was greater for obese (BMI > or = 30) women [hazard ratio (HR)=1.16, 95% confidence

interval (CI)=1.01-1.33]. Obesity did not increase recurrence hazard, but did influence CBC (HR=2.08, 95% CI=1.22-3.55 in postmenopausal women) and second cancers (HR=1.49, 95% CI=1.06-2.10). Mortality increased with obesity; when partitioned by likely cause, those with BMI > or = 35.0 had greater risk of non-breast cancer mortality (HR=1.86, 95% CI=1.21-2.84). Relative to whites and adjusted for BMI, black women had greater hazard for DFS (HR=1.17, 95% CI=1.00-1.38), CBC (HR=1.37, 95% CI=0.94-1.99), and non-breast cancer deaths (HR=2.10, 95% CI=1.45-3.03); risk for deaths likely due to breast cancer was closer to that in whites (HR=1.18; 95% CI=0.93-1.50). CONCLUSIONS: For women with node-negative, ER-breast cancer from clinical trials, obesity did not increase recurrence risk, but was associated with greater risk for second cancers, CBC, and mortality, particularly non-breast cancer deaths. Less favorable prognosis for black women persists in clinical trials, and is in part attributable to non-breast cancer outcomes.

Dube, N. and M. L. Tremblay (2005). "Involvement of the small protein tyrosine phosphatases TC-PTP and PTP1B in signal transduction and diseases: from diabetes, obesity to cell cycle, and cancer." Biochim Biophys Acta **1754**(1-2): 108-17.

As in other fields of biomedical research, the use of gene-targeted mice by homologous recombination in embryonic stem cells has provided important findings on the function of several members of the protein tyrosine phosphatase (PTP) family. For instance, the phenotypic characterization of knockout mice has been critical in understanding the sites of action of the related PTPs protein tyrosine phosphatase 1B (PTP1B) and T-cell-PTP (TC-PTP). By their increased insulin sensitivity and insulin receptor hyperphosphorylation, PTP1B null mice demonstrated a clear function for this enzyme as a negative regulator of insulin signaling. As well, TC-PTP has also been recently involved in insulin signaling in vitro. Importantly, the high identity in their amino acid sequences suggests that they must be examined simultaneously as targets of drug development. Indeed, they possess different as well as overlapping substrates, which suggest complementary and overlapping roles of both TC-PTP and PTP1B. Here, we review the function of PTP1B and TC-PTP in diabetes, obesity, and processes related to cancer.

Efstathiou, J. A., K. Bae, et al. (2007). "Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31." Cancer **110**(12): 2691-9.

BACKGROUND: Greater body mass index (BMI) is associated with shorter time to prostate-specific antigen (PSA) failure following radical prostatectomy and radiation therapy (RT). Whether BMI is associated with prostate cancer-specific mortality (PCSM) was investigated in a large randomized trial of men treated with RT and androgen deprivation therapy (ADT) for locally advanced prostate cancer. METHODS: Between 1987 and 1992, 945 eligible men with locally advanced prostate cancer were enrolled in a phase 3 trial (RTOG 85-31) and randomized to RT and immediate goserelin or RT alone followed by goserelin at recurrence. Height and weight data were available at baseline for 788 (83%) subjects. Cox regression analyses were performed to evaluate the relations between BMI and all-cause mortality, PCSM, and nonprostate cancer mortality. Covariates included age, race, treatment arm, history of prostatectomy, nodal involvement, Gleason score, clinical stage, and BMI. RESULTS: The 5-year PCSM rate for men with BMI <25 kg/m(2) was 6.5%, compared with 13.1% and 12.2% in men with BMI > or =25 to <30 and BMI > or =30, respectively (Gray's P = .005). In multivariate analyses, greater BMI was significantly associated with higher PCSM (for BMI > or =25 to <30, hazard ratio [HR] 1.52, 95% confidence interval [CI], 1.02-2.27, P = .04; for BMI > or =30, HR 1.64, 95% CI, 1.01-2.66, P = .04). BMI was not associated with nonprostate cancer or all-cause mortality. CONCLUSIONS: Greater baseline BMI is independently associated with higher PCSM in men with locally advanced prostate cancer. Further studies are warranted to evaluate the mechanism(s) for increased cancer-specific mortality and to assess whether weight loss after prostate cancer diagnosis alters disease course.

Erkanli, S., F. Kayaselcuk, et al. (2006). "Impact of morbid obesity in surgical management of endometrial cancer: surgical morbidity, clinical and pathological aspects." Eur J Gynaecol Oncol **27**(4): 401-4.

OBJECTIVE: To evaluate the effect of body mass index (BMI) on clinical, surgical, pathologic features, and surgical morbidity in the management of patients with endometrial cancer. MATERIALS & METHODS: All endometrial cancer patients who were surgically treated in our institution between January 1, 2003 and January 1, 2006 were eligible for the study. Forty-two out of 60 patients were included in the analysis from our cancer database. The patients were divided into three groups: BMI < 30, BMI 30-40, BMI > 40. Statistical analysis was performed by SPSS for Windows (version 11; SPSS, Inc., Chicago, IL). RESULTS: Lymphadenectomy as part of surgical staging was performed in 90.5% of all patients. Although patients with a BMI > 40 were less likely to have positive lymph vascular space invasion (LVSI) (p = 0.042), chance of deep myometrial invasion and

positive lymph nodes (18%) were the same as for patients with a BMI < 30. Patients with a BMI > 40 had statistically longer operating times when compared to patients with a BMI < 40 (p = 0.039). Wound separation rate was statistically higher in the morbidly obese patients (p = 0.01). Average number of lymph nodes removed, hospital days, intraoperative and overall postoperative complication rates did not differ among the three groups (p > 0.05). CONCLUSIONS: This study confirms that comprehensive surgical staging can be performed adequately and safely in obese and morbidly obese endometrial cancer patients with no difference in length of hospital stay, intraoperative or postoperative complications. As a result adjuvant treatment of morbidly obese patients can be planned accordingly preventing under or over treatment.

Fader, A. N., L. N. Arriba, et al. (2009). "Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship." Gynecol Oncol **114**(1): 121-7.

Endometrial cancer is the most common gynecologic malignancy in the Western world and is strongly associated with obesity. Despite the fact that most cases are diagnosed in early, more favorable stages, endometrial cancer incidence and mortality rates are on the rise. Morbidly obese women with endometrial cancer are more likely to die of their co-morbidities and also of their cancers when compared to their leaner cohorts. Given the increasing rates of morbid obesity in the United States, it is essential to develop appropriate screening tools and guidelines to reduce cancer morbidity and death amongst this group. Through an analysis of the existing literature, we present a review of the epidemiologic trends in obesity and endometrial cancer, discuss the promising role of screening biomarker studies, review prevention efforts and modifiable risk factors, and ways in which health outcomes and quality of life for endometrial cancer survivors may be optimized.

Feigelson, H. S., L. R. Teras, et al. (2008). "Genetic variation in candidate obesity genes ADRB2, ADRB3, GHRL, HSD11B1, IRS1, IRS2, and SHC1 and risk for breast cancer in the Cancer Prevention Study II." Breast Cancer Res **10**(4): R57.

INTRODUCTION: Obesity has consistently been associated with postmenopausal breast cancer risk. Proteins that are secreted by adipose tissue or are involved in regulating body mass may play a role in breast tumor development. METHODS: We conducted a nested case-control study among postmenopausal women from the American Cancer Society Cancer Prevention Study II Nutrition Cohort to determine whether genes associated with obesity increase risk for breast cancer. Tagging single nucleotide polymorphisms (SNPs) were selected to capture common variation across seven candidate genes that encode adipose-related proteins: ADRB2, ADRB3, GHRL, HSD11B1, IRS1, IRS2, and SHC1. Thirty-nine SNPs were genotyped in 648 cases and 659 controls. Logistic regression models were used to examine the association between each tagging SNP and risk for breast cancer while adjusting for matching factors and potential confounders. We also examined whether these SNPs were associated with measures of adult adiposity. RESULTS: Two out of five tagging SNPs in HSD11B1 were associated with breast cancer (rs11807619, P = 0.006; rs932335, P = 0.0001). rs11807619 and rs932335 were highly correlated (r2 = 0.74) and, when modeled as a haplotype, only haplotypes containing the rs932335 C allele were associated with breast cancer. The rs932335 C allele was associated with a nearly twofold increased risk for breast cancer (odds ratio = 1.83, 95% confidence interval = 1.01-3.33 for C/C versus G/G). Three of the 11 SNPs for IRS2 were associated with breast cancer (rs4773082, P = 0.007; rs2289046, P = 0.016; rs754204, P = 0.03). When these three SNPs were examined as a haplotype, only the haplotype that included the G allele of rs2289046 was associated with breast cancer (odds ratio = 0.76, 95% confidence interval = 0.63-0.92 for TGC versus CAT). IRS2 rs2289046, rs754204, and rs12584136 were also associated with adult weight gain but only among cases. None of the other SNPs in any gene investigated were associated with breast cancer or adiposity. CONCLUSION: Our findings suggest that these tagging SNPs in HSD11B1 and IRS2 mark regions of the genome that may harbor risk alleles for breast cancer, and these associations are probably independent of adiposity.

Fleming, J. B., R. J. Gonzalez, et al. (2009). "Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma." Arch Surg **144**(3): 216-21.

OBJECTIVE: To examine the influence of obesity, as measured by body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), on clinicopathologic factors and survival after pancreatectomy to treat adenocarcinoma. DESIGN: Retrospective review and statistical analysis using prospectively collected data. SETTING: Referral center with a dedicated multidisciplinary pancreas cancer program. PATIENTS: Two hundred eighty-five consecutive patients with data available for BMI calculation who underwent potentially curative pancreas resection to treat adenocarcinoma from January 1, 1999, to October 31, 2006. MAIN OUTCOME MEASURE:

Influence of BMI and other known prognostic variables on the incidence of lymph node metastasis and disease-free and overall survival. RESULTS: We identified a subset of obese patients (BMI >35) who were at 12-fold risk of lymph node metastasis compared with nonobese patients (BMI < or =35). The estimated disease-free and overall survival rates were decreased in the obese patients, and the risk of cancer recurrence and death after pancreatectomy was nearly twice that in nonobese patients. CONCLUSIONS: Obese patients with a BMI of more than 35 are more likely to have node-positive pancreatic cancer and decreased survival after surgical resection. Data suggest that the negative influence of BMI of more than 35 on cancer-related end points is unrelated to the potential complexity of performing major oncologic surgery in obese patients.

Fontaine, K. R., M. Heo, et al. (2005). "Obesity and prostate cancer screening in the USA." Public Health **119**(8): 694-8.

OBJECTIVE: To estimate the association between body mass index (BMI: kg/m2) and prostate-specific antigen (PSA) cancer screening in a nationally representative sample of US men aged 50 years and older using data from the 2001 Behavioral Risk Factor Surveillance Survey. RESPONDENTS: Men aged 50 years or older classified by BMI as healthy weight range (18.5-24.9), overweight (25-29.9), obese class I (30-34.9), obese class II (35-39.9), and obese class III (> or =40). OUTCOME MEASURES: Interval since most recent screening for PSA. RESULTS: Adjusting for age, race, smoking, education, employment, income and health insurance status, we found that, compared with men in the healthy weight range, men in the overweight [odds ratio (OR)=1.13; 95% confidence interval (95% CI)=1.04-1.35], obese class I (OR=1.26; 95% CI=1.06-1.36) and obese class II (OR=1.14, 95% CI=1.02-1.26) categories were significantly more likely to have obtained a PSA test within the previous year. A similar pattern was observed when we examined other screening intervals (e.g. within past 2 years, within past 3 years, etc.). CONCLUSIONS: Among men aged 50 years and older, overweight and obesity is associated with obtaining a PSA test.

Fowke, J. H., S. S. Motley, et al. (2007). "Prostate volume modifies the association between obesity and prostate cancer or high-grade prostatic intraepithelial neoplasia." Cancer Causes Control **18**(4): 375-84.

The relationship between obesity and prostate cancer remains unclear. We investigated the effect of prostate volume on the obesity and prostate cancer association. With a multi-centered, rapid-recruitment protocol, weight and body size measurements were collected prior to diagnosis, and medical charts were reviewed for pathology results (n = 420 controls, 119 high-grade prostatic intraepithelial neoplasia (PIN) cases, and 286 cancer cases (41% Gleason > 6). In multivariable logistic regression models adjusting for age, PSA levels and history, DRE results, and number of cores at biopsy, the association between BMI and cancer was restricted to men with a smaller prostate volume (volume < 40 cm(3): OR(BMI > or = 30) = 2.17 (1.09, 4.32), p (trend) = 0.02; volume > or = 40 cm(3): OR(BMI > or = 30) = 0.77 (0.34, 1.77), p (trend) = 0.17; p (interaction) = 0.03). Similarly, the WHR and PIN association was significantly modified by prostate volume (volume < 40 cm(3): OR((WHR: Tertile 3 vs. T1)) = 3.76 (1.54, 9.21) (p (trend) < 0.01); volume > or = 40 m(3): OR((WHR: T3 vs. T1)) = 0.63 (0.32, 1.23) (p (trend) = 0.17); p (interaction) < 0.01). In conclusion, prostate volume acts as a modifier, and BMI and WHR are significantly associated with prostate cancer or PIN, respectively, in the absence of biopsy sampling error derived from obesity-related prostate enlargement.

Fowke, J. H., L. B. Signorello, et al. (2006). "Obesity and prostate cancer screening among African-American and Caucasian men." Prostate **66**(13): 1371-80.

BACKGROUND: Differential prostate-specific antigen (PSA) testing practices according to obesity-related comorbid conditions may contribute to inconsistent results in studies of obesity and prostate cancer. We investigated the relationship between obesity and PSA testing, and evaluated the role of prior diagnoses and disease screening on PSA testing patterns. METHODS: Men, 40 and 79 years old and without prior prostate cancer were recruited from 25 health centers in the Southern US (n = 11,558, 85% African-American). An extensive in-person interview measured medical and other characteristics of study participants, including PSA test histories, weight, height, demographics, and disease history. Odds ratios (OR) and (95% confidence intervals) from logistic regression summarized the body mass index (BMI) and PSA test association while adjusting for socio-economic status (SES). RESULTS: BMI between 25 and 40 was significantly associated with recent PSA testing (past 12 months) (OR(25.0-29.9) = 1.23 (1.09, 1.39); OR(30-34.9) = 1.36 (1.18, 1.57); OR(35.0-39.9) = 1.44 (1.18, 1.76); OR(> or =40) = 1.15 (0.87, 1.51)). Prior severe disease diagnoses, such as heart disease, did not influence the obesity and PSA test association. However, adjustment for prior high blood pressure or high cholesterol diagnoses reduced the BMI-PSA testing associations. Physician PSA test recommendations were not associated with BMI, and results did not appreciably vary by race.

CONCLUSIONS: Overweight and obese men were preferentially PSA tested within the past 12 months. BMI was not associated with physician screening recommendations. Data suggest that clinical diagnoses related to obesity increase clinical encounters that lead to preferential selection of obese men for prostate cancer diagnosis. This detection effect may bias epidemiologic investigations of obesity and prostate cancer incidence.

Freedland, S. J., E. Giovannucci, et al. (2006). "Are findings from studies of obesity and prostate cancer really in conflict?" Cancer Causes Control **17**(1): 5-9.

Recent studies on the association between obesity and prostate cancer appear to be in conflict. A recent prospective cohort study reported that the incidence of prostate cancer was lower among obese men under the age of 60 years and among those men with a family history of prostate cancer. Similarly, a case-control study found obesity was inversely associated with prostate cancer risk in men aged 40-64 years. However, several prospective cohort studies found that obese men are more likely to die from prostate cancer than non-obese men. Finally, two recent studies found that among men with prostate cancer, obese men were more likely to have a biochemical progression after surgery. We postulate that by closely examining the comparison groups used in these studies, these findings may, in fact, be in agreement. Specifically, this paradox within the literature may result from the possibility that obesity influences the development of aggressive (i.e., higher stage, higher grade, recurrence, death) and non-aggressive disease differently. We suggest that obesity may reduce the risk of non-aggressive disease but simultaneously increase the risk of aggressive disease. Finally, additional methodological issues are discussed that investigators need to be aware of to be able to draw inferences across studies of obesity and prostate cancer outcomes.

Freedland, S. J. and E. A. Platz (2007). "Obesity and prostate cancer: making sense out of apparently conflicting data." Epidemiol Rev **29**: 88-97.

Both obesity and prostate cancer are epidemic in Western society. Although initial epidemiologic data appeared conflicting, recent studies, especially large prospective studies published in the past 6-12 months, have clarified the association between obesity and prostate cancer. The aim of this paper is to review the epidemiologic data linking obesity and prostate cancer, with an emphasis on new data published since 2005. A PubMed search was done on the keywords, "prostate cancer" and "obesity." Relevant articles and their references were reviewed for data on the association between obesity and prostate cancer. Recent data suggest that obesity is associated with reduced risk of nonaggressive disease but increased risk of aggressive disease. This may in part be explained by an inherent bias in our ability to detect prostate cancer in obese men (lower prostate-specific antigen values and larger sized prostates making biopsy less accurate for finding an existing cancer). Ultimately, this leads to increased risk of cancer recurrence after primary therapy and increased risk of prostate cancer mortality. The biologic causes of these associations are likely multifactorial, although the lower testosterone levels among obese men appear to be one of the most promising explanations. The association between obesity and prostate cancer is complex. Emerging data suggest a differential effect of obesity by disease aggressiveness: obesity may reduce the risk of nonaggressive disease while it may promote aggressive disease.

Freedland, S. J., E. A. Platz, et al. (2006). "Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection." J Urol **175**(2): 500-4; discussion 504.

PURPOSE: Obesity has been associated with lower serum testosterone, theoretically resulting in decreased PSA production. Obesity has also been associated with prostatic enlargement, making the detection of existent cancer more difficult. Together these findings would result in an apparent protective effect of obesity on prostate cancer risk due to technical detection issues unrelated to cancer biology. We examined the association between BMI, and PSA and prostate weight in a cohort of men undergoing RP. MATERIALS AND METHODS: We evaluated the association of BMI with prostate weight and PSA using linear regression, adjusting for patient age at RP, year of RP, race, and pathological stage and grade in 1,414 men treated with RP between 1988 and 2004 at the 5 equal access medical centers that comprise the Shared Equal Access Regional Cancer Hospital Database. RESULTS: On multivariate analysis increasing BMI was associated with increasing prostate weight but only in men younger than 63 years and not in men 63 years or older (p-trend <0.001 and 0.44, respectively). In men younger than 63 years mean multivariate adjusted prostate weight +/- SE in those with a BMI of less than 25 vs 30 to 34.9 kg/m was 33.8 +/- 1.4 vs 41.4 +/- 1.6 gm. There was no significant association between BMI and preoperative PSA (p-trend = 0.70). CONCLUSIONS: In a cohort of men undergoing RP obesity was associated with larger prostate size but only in younger men. There was no association between BMI and PSA. Assuming equal PSA, the degree of prostatic enlargement observed in younger obese men in this study would be expected to

result in a modest decrease in the odds of detecting prostate cancer in a contemporary series of PSA screened men due to the decreased sensitivity of cancer detection related to larger prostate size. Obesity may appear protective for prostate cancer in younger men due to technical issues unrelated to cancer biology.

Freedland, S. J., L. Sun, et al. (2008). "Obesity and oncological outcome after radical prostatectomy: impact of prostate-specific antigen-based prostate cancer screening: results from the Shared Equal Access Regional Cancer Hospital and Duke Prostate Center databases." BJU Int **102**(8): 969-74.

OBJECTIVE: To indirectly test the hypothesis that prostate-specific antigen (PSA)-based screening is biased against obese men due to haemodilution of PSA, and thus results in delayed diagnosis and poorer outcome beyond the biological link between obesity and aggressive prostate cancer. PATIENTS AND METHODS: We sought to examine the association between body mass index (BMI) and the outcome of radical prostatectomy (RP) separately for men with PSA-detected cancers (cT1c) or with abnormal digital rectal examination (DRE) findings (cT2/T3), and stratified by year of treatment, using two large databases. We conducted a retrospective cohort study of 1375 and 2014 men treated by RP between 1988 and 2007 using the Shared Equal Access Regional Cancer Hospital (SEARCH) and Duke Prostate Center (DPC) databases. We evaluated the association between BMI and adverse pathological features and biochemical progression, using logistic regression and Cox proportional hazards models, adjusting for several clinical characteristics, respectively. Data were examined as a whole and as stratified by clinical stage (cT1c vs cT2/T3) and year of surgery (>or=2000 vs <2000). RESULTS: In both cohorts a higher BMI was associated with high-grade disease (P <or= 0.02) and positive surgical margins (P < 0.001) and these results did not vary by clinical stage. A higher BMI was significantly associated with biochemical progression (P <or= 0.03) in both cohorts. When stratified by clinical stage, obesity was significantly related to progression in both cohorts among men with T1c cancers (P <or= 0.004) but not in men with cT2/T3 cancers (P > 0.3). Among men with T1c disease, the association between BMI and biochemical progression was limited to men treated in 2000 or later (P <or= 0.002) and was not apparent in men treated before 2000 (P > 0.4). CONCLUSIONS: Obese men with PSA-detected cancers and treated with RP since 2000 were at significantly greater risk of biochemical progression, while obese men treated before 2000 or diagnosed with an abnormal DRE were not at significantly greater risk of progression. These findings support the hypothesis that current PSA-based screening is less effective at finding cancers in obese men, leading to more aggressive tumours at diagnosis. Lowering the PSA threshold for biopsy among obese men might help to improve outcomes among this high-risk group.

Freedland, S. J., J. Wen, et al. (2008). "Obesity is a significant risk factor for prostate cancer at the time of biopsy." Urology **72**(5): 1102-5.

OBJECTIVES: Studies suggest obesity is associated with decreased prostate cancer risk. We hypothesized obesity is biologically associated with increased risk, although this is obscured owing to hemodilution of prostate-specific antigen (PSA) and larger prostate size. METHODS: We retrospectively studied 441 consecutive men undergoing prostate biopsy between 1999 and 2003 at two equal access centers within the Veterans Affairs Greater Los Angeles Healthcare System. We estimated the association between obesity (body mass index >or= 30 kg/m(2)) and positive biopsy and Gleason >or=4+3 using logistic regression analysis adjusting for multiple clinical characteristics. RESULTS: A total of 123 men (28%) were obese and 149 men (34%) had cancer. Median PSA and age were 5.7 ng/mL and 63.9 years, respectively. Obese men had significantly lower PSA concentrations (P = .02) and larger prostate volumes (P = .04). Obesity was not significantly related to age (P = .19) or race (P = .37). On univariate analysis, obesity was not associated with prostate cancer risk (odds ratio [OR] 1.13, 95% confidence interval [CI] 0.73-1.75, P = .58). However, after adjusting for multiple clinical characteristics, obesity was associated with significantly increased prostate cancer risk (OR 1.98, 95% CI 1.17-3.32, P = .01). After multivariable adjustment, there was no significant association between obesity and high-grade disease (P = .18). CONCLUSIONS: Without adjustment for clinical characteristics, obesity was not significantly associated with prostate cancer risk in this equal-access, clinic-based population. However, after adjusting for the lower PSA levels and the larger prostate size, obesity was associated with a 98% increased prostate cancer risk. These findings support the fact that current prostate cancer screening practices may be biased against obese men.

Frezza, E. E., M. S. Wachtel, et al. (2006). "Influence of obesity on the risk of developing colon cancer." Gut **55**(2): 285-91.

Obesity is a risk factor for many diseases. Thirty per cent of Americans are viewed as super obese; therefore, we need to find a solution. We already know about the diseases associated with obesity such as high blood pressure, diabetes, sleep

apnoea, etc. Lately, there has been an increased interest in understanding if cancer is related to obesity. In this paper, we review the incidence of colon cancer and obesity. Insulin is the best established biochemical mediator between obesity and colon cancer. Hyperinsulinaemia, such as occurs in type II diabetes, is important in the pathogenesis of colon cancer. All adipose tissue is not equal. Visceral abdominal fat has been identified as the essential fat depot for pathogenetic theories that relate obesity and colon cancer. The genders differ as regards to how the relationship between obesity and colon cancer has been evaluated. Obesity imposes a greater risk of colon cancer for men of all ages and for premenopausal women than it does for postmenopausal women. Regular exercise reduces the risk of developing colon cancer and the risk of death from colon cancer should it develop. We believe that a combination of waist circumference (WC) and body mass index (BMI) measurements is recommended to assess the obesity related risk of developing colon cancer. Radiographic assessments of visceral abdominal fat may eventually prove to be the best means of assessing a patient's obesity related risk of developing colon cancer. Although WC is better established as a measure of obesity than BMI, the evidence for colon cancer risk is not secure on this point; combining BMI and WC measurements would appear, at present, to be the wisest approach for colon cancer risk assessment. Doctors who wish to decrease their patients' risk of dying of colon cancer should advise weight loss and exercise. Conversely, physicians and public health authorities should consider both exercise and obesity when designing colon cancer screening protocols. Morphometric cut offs should be adjusted, if possible, for age, sex, ethnicity, and height.

Frost, L., L. J. Hune, et al. (2005). "Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study." Am J Med **118**(5): 489-95.

PURPOSE: We examined the association between the body mass index analyzed as a continuous variable and by categorization according to World Health Organization criteria (normal weight, overweight and obesity) and the risk of a hospital (inpatient as well as outpatient) diagnosis of atrial fibrillation or flutter. METHODS: Population-based prospective cohort study conducted from December 1993 to December 2001 among 47589 participants (22482 men and 25107 women) without preexisting cardiovascular or endocrine disease and with a mean age at baseline of 56 years (range 50-64 years) in the Danish Diet, Cancer, and Health Study. Subjects were followed up in the Danish National Registry of Patients and in the Danish Civil Registration System. RESULTS: During follow-up (mean, 5.7 years) atrial fibrillation or flutter developed in 553 subjects (372 men and 181 women). The adjusted hazard ratio for atrial fibrillation or flutter per unit of increase in the body mass index was 1.08 (95% confidence interval [CI]: 1.05 to 1.11) in men and 1.06 (95% CI: 1.03 to 1.09) in women. When using normal weight as a reference, the adjusted hazard ratio for atrial fibrillation or flutter by overweight was 1.75 (95% CI: 1.35 to 2.27) in men and 1.39 (95% CI: 0.99 to 1.94) in women. The adjusted hazard ratio by obesity was 2.35 (95% CI: 1.70 to 3.25) in men and 1.99 (95% CI: 1.31 to 3.02) in women. CONCLUSION: Overweight and obesity are associated with an increased risk of a diagnosis of atrial fibrillation or flutter.

Gallicchio, L., M. A. McSorley, et al. (2007). "Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease." Cancer Detect Prev **31**(2): 95-101.

BACKGROUND: A cohort study was conducted among post-menopausal women to determine whether genetic polymorphisms in selected obesity-related genes (PPARG, LPL, LEPR, PON1, PON2, TNF-alpha) were associated with the progression of benign breast disease (BBD) to breast cancer and whether the selected polymorphisms modified the association between body mass and breast cancer among women with BBD. METHODS: Among participants in an ongoing cohort study, 994 Caucasian post-menopausal women had a breast biopsy for BBD. Of these women, 61 subsequently developed breast cancer. A short questionnaire was administered at baseline in 1989. Genotypes were determined using DNA extracted from blood collected in 1989. RESULTS: In this cohort, body mass index (BMI) was positively associated with the risk of developing breast cancer. In contrast, polymorphisms in PON1 (Gln192Arg) and LEPR (IVS2+6920) were associated with a decreased risk of developing invasive breast cancer. No statistically significant associations were observed for polymorphisms in PPARG, PON2, LPL, or TNF and breast cancer risk or for interactions between the polymorphisms and BMI and breast cancer risk. CONCLUSIONS: The findings suggest that specific polymorphisms in the PON1 and LEPR genes may play a role in progression of BBD to breast cancer among post-menopausal Caucasian women.

Gallina, A., P. I. Karakiewicz, et al. (2007). "Obesity does not predispose to more aggressive prostate cancer either at biopsy or radical prostatectomy in European men." Int J Cancer **121**(4): 791-5.

Many investigators suggested that obesity predisposes to adverse prostate cancer characteristics and outcomes. We tested the effect of obesity on the rate of aggressive prostate cancer at either prostate biopsy or radical prostatectomy (RP). Clinical and pathological data were available for 1,814 men. Univariable and multivariable logistic regression models addressed the rate of high grade prostate cancer (HGPCa) at either biopsy or final pathology. Clinical stage, prostate-specific antigen (PSA), percentage of free PSA and prostate volume were the base predictors. All models were fitted with and without body mass index (BMI), which quantified obesity. BMI and its reciprocal (InvBMI) were coded as cubic splines to allow nonlinear effects. Predictive accuracy (PA) was quantified with area under curve estimates, which were subjected to 200 bootstrap re-samples to reduce overfit bias. Gains in PA related to the inclusion of BMI were compared using the Mantel-Haenszel test. HGPCa at biopsy was detected in 562 (31%) and HGPCa at RP pathology was present in 931 (51.3%) men. In either univariable or multivariable models predicting HGPCa at biopsy, BMI or InvBMI failed to respectively reach statistical significance or add to multivariable PA (BMI gain = 0%, p = 1.0; InvBMI gain = -0.2%, p = 0.9). Conversely, in models predicting HGPCa at RP, BMI and InvBMI represented independent predictors but failed to increase PA (BMI gain = 0.7%, p = 0.6; InvBMI gain = 0.5, p = 0.7%). Obesity does not predispose to more aggressive prostate cancer at biopsy. Similarly, obesity does not change the ability to identify those who may harbor HGPCa at RP.

Garmey, E. G., Q. Liu, et al. (2008). "Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study." J Clin Oncol **26**(28): 4639-45.

PURPOSE: We examined the rate of increase in the body mass index (BMI; kg/m(2)) after final height attainment in survivors of acute lymphoblastic leukemia (ALL) and a noncancer comparison group. METHODS: Childhood Cancer Survivor Study (CCSS) is a retrospectively ascertained cohort study that prospectively tracks the health status of adults who were diagnosed with childhood cancer between 1970 and 1986 and a comparison group of siblings. Changes in BMI from baseline enrollment to time of completion of follow-up (mean interval, 7.8 years) were calculated for 1,451 ALL survivors (mean age, 32.3 years at follow-up) and 2,167 siblings of childhood cancer survivors (mean age, 35.9 years). RESULTS: The mean BMI of the CCSS sibling comparison group increased with age (women, 0.25 units/yr, 95% CI, 0.22 to 0.28 units; men, 0.23 units/yr, 95% CI, 0.20 to 0.25 units). Compared with CCSS siblings, ALL survivors who were treated with cranial radiation therapy (CRT) had a significantly greater increase in BMI (women, 0.41 units/yr, 95% CI, 0.37 to 0.45 units; men, 0.29 units/yr; 95% CI, 0.26 to 0.32 units). The rate of BMI increase was not significantly increased for ALL survivors who were treated with chemotherapy alone. Younger age at CRT exposure significantly modified risk. CONCLUSION: CRT used in the treatment of childhood ALL is associated with a greater rate of increasing BMI, particularly among women treated with CRT during the first decade of life. Health care professionals should be aware of this risk and interventions to reduce or manage weight gain are essential in this high-risk population.

Garofalo, C., M. Koda, et al. (2006). "Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli." Clin Cancer Res **12**(5): 1447-53.

PURPOSE: Recent in vitro studies suggested that the autocrine leptin loop might contribute to breast cancer development by enhancing cell growth and survival. To evaluate whether the leptin system could become a target in breast cancer therapy, we examined the expression of leptin and its receptor (ObR) in primary and metastatic breast cancer and noncancer mammary epithelium. We also studied whether the expression of leptin/ObR in breast cancer can be induced by obesity-related stimuli, such as elevated levels of insulin, insulin-like growth factor-I (IGF-I), estradiol, or hypoxic conditions. EXPERIMENTAL DESIGN: The expression of leptin and ObR was examined by immunohistochemistry in 148 primary breast cancers and 66 breast cancer metastases as well as in 90 benign mammary lesions. The effects of insulin, IGF-I, estradiol, and hypoxia on leptin and ObR mRNA expression were assessed by reverse transcription-PCR in MCF-7 and MDA-MB-231 breast cancer cell lines. RESULTS: Leptin and ObR were significantly overexpressed in primary and metastatic breast cancer relative to noncancer tissues. In primary tumors, leptin positively correlated with ObR, and both biomarkers were most abundant in G3 tumors. The expression of leptin mRNA was enhanced by insulin and hypoxia in MCF-7 and MDA-MB-231 cells, whereas IGF-I and estradiol stimulated leptin mRNA only in MCF-7 cells. ObR mRNA was induced by insulin, IGF-I, and estradiol in MCF-7 cells and by insulin and hypoxia in MDA-MB-231 cells. CONCLUSIONS: Leptin and ObR are overexpressed in breast cancer, possibly due to hypoxia and/or overexposure of cells to insulin, IGF-I, and/or estradiol.

Gong, Z., I. Agalliu, et al. (2007). "Obesity is associated with increased risks of prostate cancer metastasis and death after initial cancer diagnosis in middle-aged men." Cancer **109**(6): 1192-202.

BACKGROUND: Current research is inconclusive regarding the effect of obesity on outcomes after a prostate cancer diagnosis. The objective of this study was to examine associations between obesity and the risks of developing metastasis or prostate cancer-specific mortality in a population-based cohort of men with prostate cancer. METHODS: Seven hundred fifty-two middle-aged men with prostate cancer who were enrolled in a case-control study and remain under long-term follow-up for disease progression and mortality formed the study cohort. Body mass index (BMI) in the year before diagnosis was obtained at the time of initial interview. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of prostate cancer metastasis and mortality associated with obesity, controlling for age, race, smoking status, Gleason score, stage at diagnosis, diagnostic prostate-specific antigen level, and primary treatment. RESULTS: Obesity (BMI >or=30 kg/m(2)) was associated with a significant increase in prostate cancer mortality (HR, 2.64; 95% CI, 1.18-5.92). Among men who were diagnosed with local- or regional-stage disease, obesity also was associated with an increased risk of developing metastasis (HR, 3.61; 95% CI, 1.73-7.51). Associations generally were consistent across strata defined by Gleason score (2-6 or 7 [3 + 4] vs 7 [4 + 3] or 8-10), stage (local vs regional/distant for mortality), and primary treatment (androgen-deprivation therapy use: yes vs no). CONCLUSIONS: Obesity at the time of diagnosis was associated with increased risks of prostate cancer metastasis and death. The increased risk of prostate cancer death or metastasis associated with obesity largely was independent of key clinical prognostic factors at diagnosis.

Gong, Z., M. L. Neuhouser, et al. (2006). "Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial." Cancer Epidemiol Biomarkers Prev **15**(10): 1977-83.

Studies on the relationship between obesity and prostate cancer incidence are inconsistent. In part, this inconsistency may be due to a differential effect of obesity on low-grade and high-grade cancer or confounding of the association of obesity with prostate cancer risk by diabetes. We investigated the associations of obesity and diabetes with low-grade and high-grade prostate cancer risk. Data were from 10,258 participants (1,936 prostate cancers) in the Prostate Cancer Prevention Trial who all had cancer presence or absence determined by prostate biopsy. Multiple logistic regression was used to model the risk of total prostate cancer, and polytomous logistic regression was used to model the risk of low-grade and high-grade prostate cancer. Compared with men with body mass index < 25, obese men (body mass index > or =30) had an 18% [odds ratio (OR), 0.82; 95% confidence interval (95% CI), 0.69-0.98] decreased risk of low-grade prostate cancer (Gleason <7) and a 29% (OR, 1.29; 95% CI, 1.01-1.67) increased risk of high-grade prostate cancer (Gleason > or =7) or, alternatively, a 78% (OR, 1.78; 95% CI, 1.10-2.87) increased risk defining high-grade cancer as Gleason sum 8 to 10. Diabetes was associated with a 47% (OR, 0.53; 95% CI, 0.34-0.83) reduced risk of low-grade prostate cancer and a 28% (OR, 0.72; 95% CI, 0.55-0.94) reduced risk of high-grade prostate cancer. Associations of obesity or diabetes with cancer risk were not substantially changed by mutually statistical controlling for each other. Obesity increases the risk of high-grade but decreases the risk of low-grade prostate cancer, and this relationship is independent of the lower risk for prostate cancer among men with diabetes.

Goodwin, P. J., M. Ennis, et al. (2005). "Is leptin a mediator of adverse prognostic effects of obesity in breast cancer?" J Clin Oncol **23**(25): 6037-42.

PURPOSE: Leptin, an adipocyte-derived cytokine that is elevated in obesity, has been associated with carcinogenesis, tumor migration and invasion, enhancement of angiogenesis, and increased aromatase activity. It has been suggested that leptin may mediate adverse prognostic effects of obesity in breast cancer. PATIENTS AND METHODS: Four hundred seventy-one women with surgically resected T1-3, N0-1, M0 breast cancer were studied. Leptin was assayed in stored fasting blood specimens obtained before adjuvant therapy. Women were followed prospectively for distant disease-free survival (DDFS) and overall survival (OS). RESULTS: Patients ranged from 26 to 74 years of age, and staging was as follows: T1 = 262, T2 = 151, T3 = 23, TX = 35, N0 = 323, and N1 = 148. Estrogen receptor was positive in 286 patients, and progesterone receptor was positive in 259 patients. One hundred forty-five patients received adjuvant chemotherapy, 146 received adjuvant tamoxifen, 46 received both, and 134 received neither. Mean leptin was 15.2 +/- 10.1 ng/mL. Univariately, leptin was associated with OS (overall P = .049; P = .014 postmenopausal). Leptin was not associated with DDFS overall or in any menopausal subgroup (P > or = .19). In multivariate Cox modeling, leptin was not significantly associated with DDFS or OS (P = .11 and 0.075, respectively). Adjustment for insulin or body

mass index further reduced the association of leptin with outcome. CONCLUSION: Although leptin is strongly correlated with obesity and insulin, we could not show that it is independently associated with prognosis in early-stage breast cancer. Because we cannot rule out modest prognostic effects, we recommend additional research to explore this potential association, particularly in postmenopausal women.

Guallar-Castillon, P., F. Rodriguez-Artalejo, et al. (2007). "Intake of fried foods is associated with obesity in the cohort of Spanish adults from the European Prospective Investigation into Cancer and Nutrition." Am J Clin Nutr **86**(1): 198-205.

BACKGROUND: Consumption of fried food has been suggested to promote obesity, but this association has seldom been studied. OBJECTIVE: We aimed to assess the association of energy intake from fried food with general and central obesity in Spain, a Mediterranean country where frying with oil is a traditional cooking procedure. DESIGN: This was a cross-sectional study of 33 542 Spanish persons aged 29-69 y who were participating in the European Prospective Investigation into Cancer and Nutrition between 1992 and 1996. Dietary intake was assessed by a diet history questionnaire. Height, weight, and waist circumference were measured by trained interviewers. Analyses were performed with logistic regression and were adjusted for total energy intake and other confounders. RESULTS: The prevalence of general obesity [body mass index (in kg/m(2)) >or= 30] was 27.6% in men and 27.7% in women. Respective figures for central obesity (waist circumference >or= 102 cm in men and >or= 88 cm in women) were 34.5% and 42.6%. The average proportion of energy intake from fried food was 15.6% in men and 12.6% in women. The adjusted odds ratios for general obesity in the highest versus the lowest quintile of fried food intake were 1.26 (95% CI: 1.09, 1.45; P for trend < 0.001) in men and 1.25 (1.11, 1.41; P for trend < 0.001) in women. The corresponding values for central obesity were 1.17 (1.02, 1.34; P for trend < 0.003) in men and 1.27 (1.13, 1.42; P for trend < 0.001) in women. CONCLUSION: Fried food was positively associated with general and central obesity only among subjects in the highest quintile of energy intake from fried food.

Gumbs, A. A. (2008). "Obesity, pancreatitis, and pancreatic cancer." Obes Surg **18**(9): 1183-7.

The only universally accepted risk factors for the development of pancreatic cancer are a positive family history or a history of smoking. Although the contribution of pancreatitis to pancreatic carcinogenesis has been debated for decades in the epidemiology literature, the actual mechanism is still unclear. With the rising epidemic of obesity, scientists have begun to focus on the contribution of chronic inflammatory state of morbidly obese patients in an effort to better understand the contribution of inflammation to the comorbidities of obesity. Notably, population studies are beginning to show that one of the most serious potential comorbidities of obesity is an increased lifetime risk of developing cancer. In this article, the current literature that exists supporting this Chronic Inflammatory Hypothesis as it pertains to obesity and pancreatic carcinogenesis is reviewed. To date, studies have focused on interleukin-6, a cytokine known to play a role in obesity, chronic pancreatitis and pancreatic cancer. The anti-inflammatory adipocytokine, adiponectin, has also shown promise as a key player in this mechanism and has recently been found to be more specific than standard tumor markers in differentiating pancreatic cancer from chronic pancreatitis. If the pathogenesis of pancreatic cancer is related to hormone levels associated with obesity, such as adipocytokines, and cytokines associated with chronic inflammation, this could potentially lead to the development of new pancreatic cancer tumor markers and ultimately new therapies and methods of prevention.

Gunter, M. J. and M. F. Leitzmann (2006). "Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes." J Nutr Biochem **17**(3): 145-56.

There is increasing evidence that dysregulation of energy homeostasis is associated with colorectal carcinogenesis. Epidemiological data have consistently demonstrated a positive relation between increased body size and colorectal malignancy, whereas mechanistic studies have sought to uncover obesity-related carcinogenic pathways. The phenomenon of "insulin resistance" or the impaired ability to normalize plasma glucose levels has formed the core of these pathways, but other mechanisms have also been advanced. Obesity-induced insulin resistance leads to elevated levels of plasma insulin, glucose and fatty acids. Exposure of the colonocyte to heightened concentrations of insulin may induce a mitogenic effect within these cells, whereas exposure to glucose and fatty acids may induce metabolic perturbations, alterations in cell signaling pathways and oxidative stress. The importance of chronic inflammation in the pathogenesis of obesity has recently been highlighted and may represent an additional mechanism linking increased adiposity to colorectal carcinogenesis. This review provides an overview of the epidemiology of body size and colorectal neoplasia and outlines current knowledge of putative mechanisms advanced to explain this relation.

Family based studies have shown that the propensity to become obese is heritable, but this is only manifest in conditions of excess energy intake over expenditure. Inheritance of a genetic profile that predisposes to increased body size may also be predictive of colorectal cancer. Genomewide scans, linkage studies and candidate gene investigations have highlighted more than 400 chromosomal regions that may harbor variants that predispose to increased body size. The genetics underlying the pathogenesis of obesity are likely to be complex, but variants in a range of different genes have already been associated with increased body size and insulin resistance. These include genes encoding elements of insulin signaling, adipocyte metabolism and differentiation, and regulation of energy expenditure. A number of investigators have begun to study genetic variants within these pathways in relation to colorectal neoplasia, but at present data remain limited to a handful of studies. These pathways will be discussed with particular reference to genetic polymorphisms that have been associated with obesity and insulin resistance.

Ha, S. A., S. M. Shin, et al. (2009). "Dual action of apolipoprotein E-interacting HCCR-1 oncoprotein and its implication for breast cancer and obesity." J Cell Mol Med **13**(9B): 3868-75.

Obese women have an increased risk for post-menopausal breast cancer. The physiological mechanism by which obesity contributes to breast tumourigenesis is not understood. We previously showed that HCCR-1 oncogene contributes to breast tumourigenesis as a negative regulator of p53 and detection of HCCR-1 serological level was useful for the diagnosis of breast cancer(.) In this study, we found that the HCCR-1 level is elevated in breast cancer tissues and cell lines compared to normal breast tissues. We identified apolipoprotein E (ApoE) interacting with HCCR-1. Our data show that HCCR-1 inhibits anti-proliferative effect of ApoE, which was mediated by diminishing ApoE secretion of breast cancer cells. Finally, HCCR-1 induced the severe obesity in transgenic mice. Those obese mice showed severe hyperlipidaemia. In conclusion, our results suggest that HCCR-1 might play a role in the breast tumourigenesis while the overexpression of HCCR-1 induces the obesity probably by inhibiting the cholesterol-lowering effect of ApoE. Therefore, HCCR-1 seems to provide the molecular link between the obesity and the breast cancer risk.

Harvie, M. N., S. Bokhari, et al. (2007). "Adult weight gain and central obesity in women with and without a family history of breast cancer: a case control study." Fam Cancer **6**(3): 287-94.

Adult weight gain and central obesity can increase breast cancer risk. We determined the prevalence of adult weight gain and central obesity amongst women with a family history (FH) as compared to women with a population risk to determine whether adiposity could contribute to their increased risk. Adult weight gain, waist and waist:hip ratio (WHR) were determined amongst 475 women (aged 20-60 years) attending a regional FH breast cancer risk clinic, compared to 312 age matched women at population risk. Patterns of adult weight gain did not differ between women with and without a FH of breast cancer. The majority of weight gain occurred between the ages of 20 and 40 in both groups. Mean (sd) weight gain for women aged >40 years with a FH was 8.9 (10.3) kg compared to 9.1 (10.6) kg for controls ($p = 0.85$). Women with a FH had a significantly greater waist and WHR than controls. Mean (sd) waist was 83.7 (13) cm compared to 81.6 (11.3) cm for controls ($p < 0.01$). Mean (sd) WHR was 0.82 (0.1) compared to 0.80 (0.1) for controls ($p < 0.01$). FH of breast cancer was an independent predictor of having a WHR of >0.85; odds ratio (95% CI) = 1.42 (1.01-2.01) ($p = 0.044$). Significant weight gain between the ages of 20 and 40 and the prevalence of central obesity amongst FH women suggest the need for weight management within FH clinics.

Herman, D. R., P. A. Ganz, et al. (2005). "Obesity and cardiovascular risk factors in younger breast cancer survivors: The Cancer and Menopause Study (CAMS)." Breast Cancer Res Treat **93**(1): 13-23.

BACKGROUND: Breast cancer patients today can expect long-term survival; however, weight gain is a common problem after treatment and increases the risk for recurrence, cardiovascular disease and diabetes. The multi-ethnic cohort from the Cancer and Menopause Study, designed to examine the reproductive and late cardiovascular health effects of treatment in younger female breast cancer survivors (BCS), was used to describe the relationship of behavioral and treatment variables to body mass index (BMI), physical activity (PA), and cardiovascular risk factors. METHODS: Stage 0, I or II breast cancer survivors who were < or = 50 years at diagnosis and 2-10 years disease-free survivors (mean 5.9 +/- 2.3 years) were recruited from two tumor registries to complete a mail survey that included information on demographics, health-related quality of life, reproductive health, cancer treatment, PA, weight and height. A sub-sample completed an office visit where fasting blood lipids, blood pressure (BP), height and weight were measured. Linear regression analysis was used to model the following outcomes: BMI, PA, blood lipids and BP. RESULTS: Current BMI was

positively associated with higher BMI prior to diagnosis, unhappiness with body image and negatively associated with current total PA (model $p < 0.001$). More work, home and leisure PA were all positively associated with greater physical functioning and higher energy levels (all models, $p < 0.001$). Total and LDL cholesterol were positively associated with number of years since diagnosis and negatively associated with leisure PA (both models, $p < 0.001$), while systolic and diastolic BP were both positively associated with age, current use of BP medications and current BMI (models, $p < 0.001$). CONCLUSIONS: Obesity in these BCS is prevalent and associated with premorbid obesity and decreased current physical activity but not with adjuvant treatment. Given the negative health consequences of weight gain and obesity after breast cancer, continued study of the etiology of weight gain, and potential targets for weight gain prevention are required. Interventions that target PA may be important for weight maintenance in BCS.

Hjartaker, A., H. Langseth, et al. (2008). "Obesity and diabetes epidemics: cancer repercussions." Adv Exp Med Biol **630**: 72-93.

The prevalence of overweight (body mass index, BMI, between 25 and 30 kg/m2) and obesity (BMI of 30 kg/m2 or higher) is increasing rapidly worldwide, especially in developing countries and countries undergoing economic transition to a market economy. One consequence of obesity is an increased risk of developing type II diabetes. Overall, there is considerable evidence that overweight and obesity are associated with risk for some of the most common cancers. There is convincing evidence of a positive association between overweight/obesity and risk for adenocarcinoma of the oesophagus and the gastric cardia, colorectal cancer, postmenopausal breast cancer, endometrial cancer and kidney cancer (renal-cell). Premenopausal breast cancer seems to be inversely related to obesity. For all other cancer sites the evidence of an association between overweight/obesity and cancer is inadequate, although there are studies suggesting an increased risk of cancers of the liver, gallbladder, pancreas, thyroid gland and in lymphoid and haematopoietic tissue. Far less is known about the association between diabetes mellitus type I (also called insulin dependent diabetes mellitus or juvenile diabetes), type II diabetes (called non-insulin dependent diabetes mellitus or adult onset diabetes mellitus) and cancer risk. The most common type of diabetes mellitus, type II, seems to be associated with liver and pancreas cancer and probably with colorectal cancer. Some studies suggest an association with endometrial and postmenopausal breast cancer. Studies reporting on the association between type I diabetes mellitus, which is relatively rare in most populations and cancer risk are scanty, but suggest a possible association with endometrial cancer. Overweight and obesity, as well as type II diabetes mellitus are largely preventable through changes in lifestyle. The fundamental causes of the obesity epidemic-and consequently the diabetes type II epidemic-are societal, resulting from an environment that promotes sedentary lifestyles and over-consumption of energy. The health consequences and economic costs of the overweight, obesity and type II diabetes epidemics are enormous. Avoiding overweight and obesity, as well as preventing type II diabetes mellitus, is an important purpose to prevent cancer and other diseases. Prevention of obesity and type II diabetes should begin early in life and be based on the life-long health eating and physical activity patterns. Substantial public investments in preventing overweight, obesity and type II diabetes mellitus are both appropriate and necessary in order to have a major impact on their adverse health effects including cancer.

Hsing, A. W., L. C. Sakoda, et al. (2007). "Obesity, metabolic syndrome, and prostate cancer." Am J Clin Nutr **86**(3): s843-57.

Although obesity has been consistently linked to an increased risk of several malignancies, including cancers of the colon, gallbladder, kidney, and pancreas, its role in prostate cancer etiology remains elusive. Data on the association between obesity and prostate cancer incidence are inconsistent, and in some studies obesity is associated with an increase in risk of high-grade prostate cancer but with a decrease in risk of low-grade tumors. In contrast, obesity has been consistently associated with an increased risk of prostate cancer aggressiveness and mortality. The differential effects of obesity on subtypes of prostate cancer suggest etiologic heterogeneity in these tumors and complex interactions between androgen metabolism and several putative risk factors, including insulin resistance, diabetes, inflammation, and genetic susceptibility, on prostate cancer risk. Data on the role of abdominal obesity, insulin resistance, and metabolic syndrome in prostate cancer etiology are limited. Obesity has been shown to be associated with a state of low-grade chronic inflammation, and insulin resistance and the metabolic syndrome are associated with adverse metabolic profiles and with higher circulating concentrations of inflammation-related markers, including leptin, interleukin-6, and tumor necrosis factor-, many of which have been shown to enhance tumor growth. Thus, whether obesity and metabolic syndrome modulate the risk of prostate cancer through chronic inflammation needs to be investigated further.

Given that the prevalence of obesity and metabolic syndrome is increasing worldwide and that the world population is aging, the roles of obesity and metabolic syndrome in prostate carcinogenesis warrant further clarification.

Huang, X. F. and J. Z. Chen (2009). "Obesity, the PI3K/Akt signal pathway and colon cancer." Obes Rev **10**(6): 610-6.

Obesity is currently reaching epidemic levels worldwide and is a major predisposing factor for a variety of life-threatening diseases including diabetes, hypertension and cardiovascular diseases. Recently, it has also been suggested to be linked with cancer. Epidemiological studies have shown that obesity increases the risk of colon cancer by 1.5-2 fold with obesity-associated colon cancer accounting for 14-35% of total incidence. Several factors, altered in obesity, may be important in cancer development including increased levels of blood insulin, insulin-like growth factor I, leptin, TNF-alpha, IL-6 as well as decreased adiponectin. A unifying characteristic of all these factors is that they increase the activity of the PI3K/Akt signal pathway. The PI3K/Akt signal pathway in turn activates signals for cell survival, cell growth and cell cycle leading to carcinogenesis. Here we review the evidence that PI3K/Akt and its downstream targets are important in obesity-associated colon cancer and thus, that targeted inhibition of this pathway could be employed for the prevention of obesity-associated colon cancer and incorporated into the therapy regime for those with irremovable colon cancers.

Hursting, S. D., L. M. Lashinger, et al. (2008). "Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link." Best Pract Res Clin Endocrinol Metab **22**(4): 659-69.

The prevalence of obesity, an established epidemiologic risk factor for many cancers, has risen steadily for the past several decades in the US. The increasing rates of obesity among children are especially alarming and suggest continuing increases in the rates of obesity-related cancers for many years to come. Unfortunately, the mechanisms underlying the association between obesity and cancer are not well understood. In particular, the effects on the carcinogenesis process and mechanistic targets of interventions that modulate energy balance, such as reduced-calorie diets and physical activity, have not been well characterized. The purpose of this review is to provide a strong foundation for the translation of mechanism-based research in this area by describing key animal and human studies of energy balance modulations involving diet or physical activity and by focusing on the interrelated pathways affected by alterations in energy balance. Particular attention is placed on signaling through the insulin and insulin-like growth factor-1 receptors, including components of the Akt and mammalian target of rapamycin (mTOR) signaling pathways downstream of these growth factor receptors. These pathways have emerged as potential targets for disrupting the obesity-cancer link. The ultimate goal of this work is to provide the missing mechanistic information necessary to identify targets for the prevention and control of cancers related to or caused by excess body weight.

Hursting, S. D., N. P. Nunez, et al. (2007). "The obesity-cancer link: lessons learned from a fatless mouse." Cancer Res **67**(6): 2391-3.

Current dogma suggests that the positive correlation between obesity and cancer is driven by white adipose tissue that accompanies obesity, possibly through excess secretion of adipokines. Recent studies in fatless A-Zip/F1 mice, which have undetectable adipokine levels but display accelerated tumor formation, suggest that adipokines are not required for the enhanced tumor development. The A-Zip/F-1 mice are also diabetic and display elevated circulating levels of other factors frequently associated with obesity (insulin, insulin-like growth factor-1, and proinflammatory cytokines) and activation of several signaling pathways associated with carcinogenesis. In view of this information, the risk factors underlying the obesity-cancer link need to be revisited. We postulate that the pathways associated with insulin resistance and inflammation, rather than adipocyte-derived factors, may represent key prevention and therapeutic targets for disrupting the obesity-cancer link.

Ildaphonse, G., P. S. George, et al. (2009). "Obesity and kidney cancer risk in men: a meta-analysis (1992-2008)." Asian Pac J Cancer Prev **10**(2): 279-86.

We conducted a quantitative summary analysis to evaluate the recent evidence of kidney cancer risk according to body mass index (BMI) among men. The studies included in this quantitative review were all cohort and case-control studies, which provided information on kidney cancer risk associated with obesity/overweight, published between 1992 and 2008. The details of studies have been identified through searches on the MEDLINE database. We first estimated the risk associated with a unit increase in BMI (1 kg/m(2)) for individual studies using logit-linear model. After deriving the natural logarithm of the risk per unit of BMI for all studies, we calculated a pooled estimate and corresponding 95% confidence interval (CI) as a weighted average of the risk obtained in individual studies, by giving a weight

proportional to its precision. A total of 27 studies (13 cohort studies and 14 case-control studies) that provided kidney cancer risk according to BMI in men were included in the present analysis. The strength of association was almost similar in most of the cohort studies (relative risk (RR) ranged from 1.04-1.06 per unit increase in BMI) and in one study RR was 1.08. There was no heterogeneity across studies (p-value= 0.164). The pooled risk was 1.05 (95% CI= 1.04-1.06) per unit increase in BMI based on the cohort studies. The present analysis confirmed the evidence of kidney cancer risk with increased BMI in men and obesity may be responsible at least in part for the rising incidence rates.

Irigaray, P., J. A. Newby, et al. (2007). "Overweight/obesity and cancer genesis: more than a biological link." Biomed Pharmacother **61**(10): 665-78.

The classical view according to which overweight/obesity is related to cancer considers adipose tissue as an active and metabolic "organ", acting through endocrine, autocrine and paracrine processes. Consequently, it has been hypothesized, that genesis and progression of cancer may be caused by different biological factors acting through diverse mechanisms including changes in the synthesis and bioavailability of sex hormones, insulin resistance, release of growth factors and/or proinflammatory cytokines and abnormal energetic disposal and expenditure. We have shown that overweight/obesity can be experimentally induced by benzo[a]pyrene, a universal well characterized chemical pollutant and that overweight/obesity may in fact be caused by several types of chemical pollutants. In this paper we propose that in addition to the above hypothetical biological mechanisms, adipose tissue acts as a reservoir for lipophilic, liposoluble environmental carcinogens, so that chemical pollution may in fact generate both overweight/obesity and cancer. More precisely, we propose that many carcinogens, be they mutagens or promotors can be stored in the adipose tissue, be released at convenient dose in the blood circulation and therefore target peripheral tissues to induce carcinogenesis. Such carcinogens mainly include organochlorine pesticides and PCBs. Their association with an increased risk of cancer seems to be demonstrated for breast and prostate carcinoma, as well as for lymphoma, not only in obese patients, but also in normal weight or even leaner patients suggesting that the adipose tissue may act as a reservoir for environmental carcinogens in obese as well as in non-obese patients.

Irwin, M. L., A. McTiernan, et al. (2005). "Relationship of obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors." Cancer Epidemiol Biomarkers Prev **14**(12): 2881-8.

INTRODUCTION: Obese and physically inactive breast cancer patients may have poorer survival compared with lighter weight and more active women. Several obesity-related and physical activity-related hormones and peptides may explain this association, including insulin, leptin, insulin-like growth factor-I (IGF-I), and IGF-binding protein-3. Few studies have examined the associations between obesity, physical activity, and these hormones/peptides among breast cancer survivors. PURPOSE: To determine whether obesity and physical activity are associated with insulin, IGFs, and leptin levels in a population-based sample of 710 women diagnosed with in situ to stage IIIA breast cancer and enrolled in the Health, Eating, Activity, and Lifestyle Study. METHODS: We collected a blood sample and information on physical activity among women diagnosed 2 to 3 years earlier using an interview-administered questionnaire. Trained staff measured weight. C-peptide, leptin, and IGFs were assayed by RIA. Mean hormone levels within body mass index and physical activity categories were adjusted for confounders using analysis of covariance methods. RESULTS: We observed higher C-peptide (P for trend = 0.0001) and leptin (P for trend = 0.0001) levels and lower IGF-I levels (P for trend = 0.0001) with higher levels of body mass index. We observed lower C-peptide (P for trend = 0.001) and leptin (P for trend = 0.001) levels and higher IGF-I (P for trend = 0.0037) and IGF-binding protein-3 (P for trend = 0.055) levels with higher levels of physical activity. CONCLUSIONS: Increasing physical activity and decreasing body fat may be a reasonable intervention approach toward changing insulin and leptin, thereby potentially influencing breast cancer prognosis.

Jayachandran, J., W. J. Aronson, et al. (2008). "Obesity and positive surgical margins by anatomic location after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital database." BJU Int **102**(8): 964-8.

OBJECTIVES: To determine if there is predilection for any specific anatomical location of positive surgical margins (PSMs) after radical prostatectomy (RP) for prostate cancer in obese men, as previous studies found that obesity was associated with an increased risk of PSMs. PATIENTS AND METHODS: We analysed retrospectively 1434 men treated with RP between 1989 and 2007 within the Shared Equal Access Regional Cancer Hospital database. The association between increased body mass index (BMI) and overall and site-specific PSMs

was assessed using multivariate logistic regression. RESULTS: After adjusting for several preoperative clinical and pathological characteristics, a higher BMI was associated with an increased risk of PSMs both overall and at all specific anatomical locations (all P <or= 0.007). For mildly obese men, this risk was very similar across all anatomical sites (44-78% increased risk relative to men of normal weight). When BMI was coded as a continuous variable, the odds ratio for the risk of overall PSMs or at any specific locations was nearly identical at 1.05-1.06. Among men with a BMI of >or=35 kg/m2, there was more variation, with the highest excess risk of PSMs at the bladder neck and apex. CONCLUSIONS: Obesity was associated with an increased risk of overall PSMs and at all anatomical locations. Although the excess risk of PSMs was similar across all anatomical locations, there was a suggestion of a higher risk of apical margins among the most obese men, which if validated, further supports the importance of the apical dissection in all men and suggests added difficulty in obese patients.

Jayachandran, J., L. L. Banez, et al. (2009). "Obesity as a predictor of adverse outcome across black and white race: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database." Cancer **115**(22): 5263-71.

BACKGROUND: Across multiple studies, obesity has been associated with an increased risk of higher grade disease and prostate-specific antigen (PSA) recurrence after radical prostatectomy (RP). Whether these associations vary by race is unknown. In the current study, the authors examined the association between obesity and outcome after RP stratified by race. METHODS: A retrospective analysis was performed on 1415 men in the Shared Equal Access Regional Cancer Hospital (SEARCH) database who underwent RP between 1989 and 2008. The association between increased body mass index (BMI) and adverse pathology and biochemical recurrence was examined using multivariate logistic regression and Cox models, respectively. Data were examined stratified by race. RESULTS: After adjusting for preoperative clinical characteristics, higher BMI was associated with higher tumor grade (P = .008) and positive surgical margins (P < .001) in white men, and similar but statistically nonsignificant trends were observed in black men. No significant interaction was noted between race and BMI for associations with adverse pathology (P(interaction)> or =.12). After adjusting for preoperative clinical characteristics, higher BMI was associated with an increased risk of recurrence in both white men (P = .001) and black men (P = .03). After further adjusting for pathologic variables, higher BMI was associated with significantly increased risk of recurrence in white men (P = .002) and black men (P = .01). No significant interactions were observed between race and BMI for predicting biochemical progression adjusting either for preoperative factors (P(interaction) = .35) or for preoperative and pathologic features (P(interaction) = .47). CONCLUSIONS: Obesity was associated with a greater risk of recurrence among both black men and white men. Obesity did not appear to be more or less influential in 1 race than another but, rather, was identified as a risk factor for aggressive cancer regardless of race.

Jee, S. H., H. J. Kim, et al. (2005). "Obesity, insulin resistance and cancer risk." Yonsei Med J **46**(4): 449-55.

Obesity is a known cause of metabolic syndrome which includes Type II diabetes, hypertension, and dyslipidemia. It is well documented that insulin resistance contributes to the mortality and the incidence of metabolic syndromes including central obesity, dyslipidemia, hyperglycemia and hypertension. Both obesity and diabetes are emerging topics for researchers to consider as having a possible causal association with cancer since the two factors have been viewed as risk factors for cancer. The present paper introduced the hypothesis of a possible causal relationship between obesity, insulin resistance and cancer and reviews relevant existing studies in this area. More efforts and studies are needed to clarify the mechanisms and the common risk factors which might be incorporated into interventions to prevent cancer and cardiovascular diseases as top causes of death.

Jenkins, P., S. Elyan, et al. (2007). "Obesity is not associated with increased myelosuppression in patients receiving chemotherapy for breast cancer." Eur J Cancer **43**(3): 544-8.

Audits of adjuvant chemotherapy for breast cancer have revealed that obese patients receive a lower relative dose intensity (RDI). However, interpretation of these studies is complicated by the variable use of cytokine growth factors, empiric dose capping and first cycle dose reductions. We have analysed the impact of obesity on RDI in a cohort of 662 patients that is not confounded by these factors. Patients were classified as overweight or obese on the basis of a body mass index (BMI)>or=25 kg/m2. The mean RDI in patients with BMI>or=25 kg/m2 was actually significantly greater than in those with BMI<25 kg/m2 (p=0.03). Overweight patients were less likely to experience cycle delays due to prolonged myelosuppression (p<0.001), particularly towards the end of the treatment course. We conclude that drug doses need not be reduced on the basis of obesity.

Overall obese patients are in fact less likely to suffer haematological toxicity.

Johnson, I. T. and E. K. Lund (2007). "Review article: nutrition, obesity and colorectal cancer." Aliment Pharmacol Ther **26**(2): 161-81.

BACKGROUND: The age-adjusted incidence of colorectal cancer is higher in prosperous industrialized countries than elsewhere. Dietary factors may account for 75% of sporadic colorectal cancer in the west, but the mechanisms remain obscure. AIM: To review evidence for the effects of overweight and obesity, physical activity and specific dietary components on colorectal neoplasia. METHODS: English language papers cited on MEDLINE, obtained using search terms related to colorectal cancer, physical activity and body mass and specific food components were reviewed. RESULTS: There is evidence for adverse effects of overweight and obesity and protective effects of high physical activity against colon, but not for rectal cancer. These effects may reflect metabolic stress and chronic low-grade inflammation. There are also modest adverse effects of red and processed meat. There is evidence for protective effects of dietary fibre, but for fruits and vegetables the evidence remains weak and inconclusive. There is some evidence for protective effects of n-3 polyunsaturated fatty acids from fish, some micronutrients and possibly phytochemicals. The effects of many dietary constituents may depend upon genetic polymorphisms affecting a variety of genes. CONCLUSION: Further research should focus particularly on the effects of insulin-resistance, impaired glucose tolerance and chronic low-grade inflammation on the colonic mucosa.

Kane, C. J., W. W. Bassett, et al. (2005). "Obesity and prostate cancer clinical risk factors at presentation: data from CaPSURE." J Urol **173**(3): 732-6.

PURPOSE: We investigated the association of obesity with prostate cancer case demographics and clinical disease features at presentation. MATERIALS AND METHODS: Data were abstracted from CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor), a disease registry of 10,018 men with prostate cancer. A total of 2,952 men were included who were treated between 1989 and 2002, and had complete body mass index (BMI) information. BMI classes were defined as normal (less than 25 kg/m), overweight (25 to 29.9 kg/m), obese (30 to 34.9 kg/m) or very obese (35 kg/m or greater). Patients were categorized as having low, intermediate or high risk disease based on the D'Amico classification. Associations among BMI, risk and demographics were analyzed using univariate and multivariate models. RESULTS: Of the patients 29% had a normal BMI, 51% were overweight, 16% were obese and 5% were very obese. Patients who were overweight or obese were more likely to be young, have hypertension and diabetes, and have a lower education level. The overweight group had a lower serum prostate specific antigen ($p = 0.010$) and lower stage disease ($p = 0.030$) at diagnosis, but there was no association between Gleason score and obesity ($p = 0.57$). However, among men with a BMI of 25 kg/m or greater there was a positive correlation between increasing BMI and risk of being in a worse prognostic group at diagnosis ($p = 0.018$). CONCLUSIONS: Overweight and obese patients are more likely to be young at diagnosis and have multiple comorbidities. Men in the overweight and obese groups presented with lower risk prostate cancer at diagnosis. This may be due to earlier disease detection secondary to more frequent interaction with the medical community. Among overweight and obese patients increased obesity is associated with a slightly increased chance of having high risk prostate cancer at diagnosis.

Kaur, T. and Z. F. Zhang (2005). "Obesity, breast cancer and the role of adipocytokines." Asian Pac J Cancer Prev **6**(4): 547-52.

Obesity is a worldwide problem which impacts the risk and prognosis of some of the more common forms of cancer, including breast cancer in post-menopausal women. As the basis for understanding the potential mechanisms of obesity and cancer relationship has advanced, a number of new hypotheses have emerged. The adipocytokines are a complex group of biologically active polypeptides. Leptin is a growth hormone, secreted by adipose tissue, whose levels are normally elevated in obese individuals and may have a promoting effect on carcinogenesis and metastasis of breast cancer, possibly in an autocrine manner. Leptin interferes with the insulin signaling pathway and in type 2 diabetes plasma leptin levels are found to be correlated with the degree of insulin resistance, a relationship independent of body mass. This relationship might provide a mechanistic explanation for promotion potential.

Kerlikowske, K., R. Walker, et al. (2008). "Obesity, mammography use and accuracy, and advanced breast cancer risk." J Natl Cancer Inst **100**(23): 1724-33.

BACKGROUND: Being overweight or obese is associated with increased breast cancer risk and disease severity among postmenopausal women, but whether extent of mammography use and accuracy modify this association and further contribute to increases in disease severity at diagnosis among overweight and obese women is unclear. METHODS:

We prospectively collected data during 1996-2005 on 287,115 postmenopausal women not using hormone therapy (HT) who underwent 614,562 mammography examinations; 4,446 women were diagnosed with breast cancer within 12 months of a mammography examination. We calculated rates per 1,000 mammography examinations of large (>15 mm), advanced-stage (IIb, III, or IV), high-grade (3 or 4), estrogen receptor (ER)-positive and -negative, and screen-detected and non-screen-detected breast cancer across body mass index (BMI, kg/m(2)) groups defined as normal (18.5-24.9), overweight (25.0-29.9), obese class I (30.0-34.9), and obese class II/III (> or =35.0), adjusting for age, race/ethnicity, and mammography registry and use. All statistical tests were two-sided. RESULTS: Adjusted rates per 1000 mammography examinations of overall breast cancer increased across BMI groups (6.6 normal, 7.4 overweight, 7.9 obese I, 8.5 obese II/III; P(trend) < .001), as did rates of advanced disease, including large invasive (2.3 normal, 2.6 overweight, 2.9 obese I, 3.2 obese II/III; P(trend) < .001), advanced-stage (0.8 normal, 0.9 overweight, 1.3 obese I, 1.5 obese II/III; P(trend) < .001), and high nuclear grade (1.5 normal, 1.7 overweight, 1.7 obese I, 1.9 obese II/III; P(trend) = .10) tumors. Rates of ER-positive tumors increased across BMI groups (P(trend) < .001); rates of ER-negative tumors did not. Rates of screen-detected cancers were higher among overweight and obese women than normal and underweight women, but rates of non-screen-detected (false-negative) cancers were similar. Rates of advanced breast cancer increased across BMI groups regardless of extent of mammography use. CONCLUSIONS: Patterns of mammography use and mammography accuracy are not the primary reasons for higher rates of advanced breast cancer among overweight and obese postmenopausal women not using HT; thus, biologic differences in breast tumor development and/or progression may be important.

Kim, K. H., M. C. Kim, et al. (2006). "The impact of obesity on LADG for early gastric cancer." Gastric Cancer **9**(4): 303-7.

BACKGROUND: Laparoscopy-assisted distal gastrectomy (LADG) has become a viable alternative treatment for patients suffering with early gastric cancer. Surgeons have long thought that obesity might increase the rate of intraoperative or postoperative complications. We set out to clarify the effect that obesity has on performing LADG for the treatment of early gastric cancer. METHODS: We retrospectively reviewed 97 patients who had undergone LADG for early gastric cancer between May 1998 and March 2004. We measured the degree of obesity by using the body mass index (BMI; kg/m(2)), and we compared the surgical outcomes between the normal BMI group (BMI < 23 kg/m(2)) and the high BMI group (BMI > or = 23 kg/m(2)). We further subdivided the patients into four groups: normal BMI males and normal BMI females, and high BMI males and high BMI females, and we analyzed them in terms of operation times, numbers of retrieved lymph nodes, and rates of postoperative complications. RESULTS: There were no significant differences between the normal and high BMI groups in terms of the patients' characteristics, surgical outcomes, postoperative courses, postoperative complications, and operation times. There were no statistically significant differences in the number of retrieved lymph nodes or in the rate of postoperative complications among the four groups (P = 0.5030 and P = 0.3489, respectively). However, there was a statistically significant difference in operation times among the four groups (P = 0.004). Specifically, the males in the high BMI group required a longer operation time than did the females with a normal BMI (P = 0.006) and the females with a high BMI (P = 0.019). CONCLUSIONS: For LADG in patients with early gastric cancer, obesity may affect the operation time, and men with high BMI require a longer operation time than do women with normal or high BMI.

Koda, M., M. Sulkowska, et al. (2007). "Expression of the obesity hormone leptin and its receptor correlates with hypoxia-inducible factor-1 alpha in human colorectal cancer." Ann Oncol **18 Suppl 6**: vi116-9.

BACKGROUND: The obesity hormone, leptin, has been found to play a role in development and proliferation of normal and malignant tissues. Leptin activity is mediated through the leptin receptor (ObR) that is often expressed in different human cancer cells. Previously, we found that the expression of leptin and ObR can be stimulated by hypoxia-mimetic agents. The aim of this study was to analyze the abundance of and relationships among leptin, ObR and hypoxia-inducible factor-1alpha (HIF-1alpha, transcriptional regulator) in human colorectal cancer. MATERIALS AND METHODS: We investigated the expression of leptin, ObR and HIF-1alpha in colorectal cancer specimens from 135 patients who underwent curative resection. RESULTS: Immunoreactivity for leptin, ObR and HIF-1alpha protein was observed in 69 of 135 (51.1%), 129 of 135 (95.5%) and 88 of 135 (65.2%) of colorectal cancers, respectively. Statistically significant positive correlations were noted between leptin and HIF-1alpha (P = 0.005, r = 0.243), ObR and HIF-1alpha (P < 0.001, r = 0.325) as well as leptin and ObR (P < 0.001, r = 0.426) in the group of all patients as well as in various subgroups depending on clinicopathological

features. CONCLUSIONS: The results indicate that the leptin system is overexpressed in human colorectal cancer and this overexpression appears to be associated with the abundance of HIF-1alpha.

Koda, M., M. Sulkowska, et al. (2007). "Overexpression of the obesity hormone leptin in human colorectal cancer." J Clin Pathol **60**(8): 902-6.

BACKGROUND: Leptin is an adipocyte-derived neurohormone, high levels of which are found in obese individuals. Leptin controls energy expenditure, acting in the brain, and regulates different processes in peripheral organs. Recent studies have suggested that leptin may be involved in cancer development and progression. AIMS: To analyse leptin expression in human colorectal cancer as well as in colorectal mucosa and colorectal adenomas. METHODS: Leptin expression was assessed by immunohistochemistry in 166 colorectal cancers, 101 samples of colorectal mucosa and 41 adenomas. Leptin concentration in colorectal cancer was correlated with selected clinicopathological features. RESULTS: Immunoreactivity for leptin was observed in 51.2% (85/166) of primary colorectal cancers. In adenomas leptin expression was observed in 14.6% (6/41) of studied cases. In normal mucosa, leptin was present at low levels, except in tumour bordering areas where its concentration appeared to reflect levels in the adjacent cancer tissue. Leptin expression in colorectal cancer significantly correlated with tumour G2 grade ($p = 0.002$) as well as with histological type (adenocarcinoma) of tumours ($p = 0.044$). CONCLUSIONS: Results indicate that leptin is overexpressed in human colorectal cancer, which suggests that the hormone might contribute to colorectal cancer development and progression.

Kollarova, H., L. Machova, et al. (2008). "Is obesity a preventive factor for lung cancer?" Neoplasma **55**(1): 71-3.

Lung cancer is a disease with multifactorial etiology, smoking playing the most important role among its risk factors. Some studies, however, indicate an inverse association between increased body-mass index (BMI) and the risk of lung cancer. In this paper, the association between BMI and lung cancer risk is analysed in two independent studies. In the first study, 751 lung cancer patients were compared to 30 058 controls. In the second study, 91 lung cancer patients were matched to 91 healthy controls. An inversed association was found between increased BMI and lung cancer risk. The inverse association remained significant after adjustment for age, sex, and smoking.

Kristal, A. R., K. B. Arnold, et al. (2007). "Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial." J Urol **177**(4): 1395-400; quiz 1591.

PURPOSE: We examined risk factors for incident symptomatic benign prostate hyperplasia in 5,667 Prostate Cancer Prevention Trial placebo arm participants who were free of benign prostatic hyperplasia at baseline. MATERIALS AND METHODS: During 7 years benign prostatic hyperplasia symptoms were assessed annually using the International Prostate Symptom Score and benign prostatic hyperplasia treatment was assessed quarterly by structured interview. Total benign prostatic hyperplasia was defined as receipt of treatment or report of 2 International Prostate Symptom Score values greater than 14. Severe benign prostatic hyperplasia was defined as treatment or 2 International Prostate Symptom Score values of 20 or greater. Weight and body circumferences were measured by trained staff and demographic health related characteristics were collected by questionnaire. Cox proportional hazards models were used to calculate the covariate adjusted relative hazards of benign prostatic hyperplasia developing. RESULTS: The incidence of total benign prostatic hyperplasia was 34.4 per 1,000 person-years. The risk of total benign prostatic hyperplasia increased 4% ($p <0.001$) with each additional year of age. Risks for total benign prostatic hyperplasia were 41% higher for black ($p <0.03$) and Hispanic men ($p <0.06$) compared to white men, and for severe benign prostatic hyperplasia these increases were 68% ($p <0.01$) and 59% ($p <0.03$), respectively. Each 0.05 increase in waist-to-hip ratio (a measure of abdominal obesity) was associated with a 10% increased risk of total ($p <0.003$) and severe ($p <0.02$) benign prostatic hyperplasia. Neither smoking nor physical activity was associated with risk. CONCLUSIONS: Black race, Hispanic ethnicity and obesity, particularly abdominal obesity, are associated with increased benign prostatic hyperplasia risk. Weight loss may be helpful for the treatment or prevention of benign prostatic hyperplasia.

Kristal, A. R. and Z. Gong (2007). "Obesity and prostate cancer mortality." Future Oncol **3**(5): 557-67.

It has long been known that obesity modestly increases the risk of prostate cancer mortality. Only recently, however, have studies examined whether this association is due to an increased risk of aggressive disease and/or worse outcomes following initial diagnosis and treatment. This distinction is important, because if obesity increases the risk of metastasis and death following treatment, weight loss could be an effective adjunct treatment. We now have good

evidence that obesity increases the risk of aggressive prostate cancer, but reduces the risk of low-grade, nonaggressive cancer. In addition, several studies have found that obesity increases the risk of biochemical recurrence following prostatectomy; however, the few studies that have examined more definitive end points, metastases and death, have been less consistent. Furthermore, there are no studies that have examined whether weight loss after diagnosis favorably affects prostate cancer outcome. While accepting the current limitations in our knowledge base, it is our opinion that it is appropriate for physicians to counsel their patients to lose weight following prostate cancer diagnosis and motivate this change in behavior by emphasising the likely benefit of improving long-term outcome.

Kuhl, H. (2005). "Breast cancer risk in the WHI study: the problem of obesity." Maturitas **51**(1): 83-97.

In the climacteric, about 40% of the women have occult breast tumors the growth of which may be stimulated by hormones. Many genetic, reproductive and lifestyle factors may influence the incidence of breast cancer. Epidemiological data suggest that the increase in the relative risk (RR) of breast cancer induced by hormone replacement therapy (HRT) is comparable with that associated with early menarche, late menopause, late first birth, alcohol consumption, etc. One of the most important risk factors is obesity which exceeds the effect of HRT by far, and in overweight postmenopausal women the elevated risk of breast cancer is not further increased by HRT. As in the WHI study the majority of women was overweight or obese, this trial was unsuitable for the investigation of breast cancer risk. In the women treated with an estrogen/progestin combination, the RR of breast cancer rose only in those women who have been treated with hormones prior to the study, suggesting a selection bias. In the women not pretreated with hormones, it was not elevated. In the estrogen-only arm of the WHI study, there was no increase but a steady decrease in the RR of breast cancer during 6.8 years of estrogen therapy. This result was unexpected, as estrogens are known to facilitate the development and growth of breast tumors, and the effect is enhanced by the addition of progestins. Obese women are at high risk to develop a metabolic syndrome including insulin resistance and hyperinsulinemia. In postmenopausal women, elevated insulin levels are not only associated with an increased risk for cardiovascular disease, but also for breast cancer. This might explain the effects observed in both arms of the WHI study: HRT with relative low doses of estrogens may improve insulin resistance and, hence, reduce the elevated breast cancer risk in obese patients, whereas this beneficial estrogen effect may be antagonized by progestins. The principal options for the reduction of breast cancer risk in postmenopausal women are the prevention of overweight and obesity to avoid the development of hyperinsulinemia, the medical treatment of insulin resistance, the use of low doses of estrogens and the reduction of exposure to progestins. The latter might include long-cycles with the sequential use of appropriate progestins every 3 months for 14 days. There are large inter-individual variations in the proliferative response to estrogens of the endometrium. Control by vaginalsonography and progestin challenge tests may help to identify those women who may be candidates for low-dose estrogen-only therapy.

Kuper, M. A., I. Konigsrainer, et al. (2009). "Morbid obesity and subsequent pancreatic cancer: pylorus-preserving pancreatoduodenectomy after laparoscopic sleeve gastrectomy." Obes Surg **19**(3): 385-8.

Morbid obesity is a recognized risk factor for gastrointestinal cancer. Little is known about pancreatic cancer developing after gastric bypass surgery or about surgery for this type of tumor following bariatric surgery. This report describes a case of pancreatic head cancer identified 3 months after laparoscopic sleeve gastrectomy for morbid obesity. During routine follow-up, mild abdominal pain and elevated pancreatic enzymes prompted computed tomography, which revealed mild edematous pancreatitis. Hyperbilirubinemia developed, and magnetic resonance imaging showed a pancreatic head tumor. CA19-9 was elevated. After a pylorus-preserving pancreatic head resection, the postoperative course was uneventful. The patient received adjuvant chemotherapy. Unfortunately, at the time of writing (9 months postoperatively), a local recurrence and hepatic metastases were diagnosed. Patients treated with bariatric surgery who develop new symptoms or report constant mild symptoms should be evaluated using endoscopy and radiomorphological imaging. Interdisciplinary obesity treatment can then offer significant benefits for the patient, particularly in the case of pancreatic cancer, which is still difficult to diagnose. In addition, there is a need for epidemiological studies of patients who undergo bariatric surgery and subsequently develop cancer.

Kuriyama, S. (2006). "Impact of overweight and obesity on medical care costs, all-cause mortality, and the risk of cancer in Japan." J Epidemiol **16**(4): 139-44.

We conducted three prospective cohort studies that examined the association between body mass index (BMI) and health outcomes in Japan. Our studies found statistically significant relationships

between excess body weight and increased medical costs, all-cause mortality, and risk of cancer incidence. There was a U-shaped association between BMI and mean total costs. The estimated excess costs attributable to overweight and obesity was 3.2% of the total costs. This 3.2% is within the range reported in studies in Western countries (0.7%-6.8%). We observed statistically significant elevations in mortality risk in obese (BMI> or = 30.0 kg/m(2)) women and lean (BMI<18.5 kg/m(2)) men and women. Our prospective cohort study found statistically significant relationships between excess weight and increased risk in women of all cancers. The population attributable fraction (PAF) of all incident cancers in this population that were attributable to overweight and obesity were 4.5% in women, which were within the range reported from Western populations, from 3.2% for US women to 8.8% for Spanish women. Our data suggests that excess body weight is a problem not only in Western countries but also in Japan.

Kuriyama, S., Y. Tsubono, et al. (2005). "Obesity and risk of cancer in Japan." Int J Cancer **113**(1): 148-57.

We conducted a population-based prospective cohort study in Japan to examine the relationship between body mass index (BMI) and the risk of incidence of any cancer and of cancer at individual sites. Body mass index was calculated from self-administered body weight and height at baseline. Relative risks (RR) and 95% confidence intervals (CI) were calculated in multivariate proportional-hazards models. Among 27,539 persons (15,054 women and 12,485 men) aged 40 years or older who were free of cancer at enrollment in 1984, 1,672 (668 women and 1,004 men) developed cancer during 9 years of follow-up. In women, after adjustment for potential confounders, the RR of all cancers associated with different BMI, relative to a BMI of 18.5-24.9, were 1.04 (95% CI = 0.85-1.27) for BMI = 25.0-27.4, 1.29 (1.00-1.68) for BMI = 27.5-29.9 and 1.47 (1.06-2.05) for BMI >/=30.0 (p for trend = 0.007). Higher BMI was also significantly associated with higher risk of cancers of the colorectum, breast (postmenopausal), endometrium and gallbladder in women. In men, we observed significantly increased all-cancer risk among only never-smokers. Overweight and obesity could account for 4.5% (all subjects) or 6.2% (never-smokers) of the risk of any cancer in women and -0.2% (all subjects) or 3.7% (never-smokers) in men. The value for women was within the range among women reported from Western populations (3.2%-8.8%). Our data demonstrate that excess weight is a major cancer risk among Japanese women.

Kurzer, E., R. Leveillee, et al. (2006). "Obesity as a risk factor for complications during laparoscopic surgery for renal cancer: multivariate analysis." J Endourol **20**(10): 794-9.

BACKGROUND AND PURPOSE: A number of clinical variables are believed to be risk factors for complications of laparoscopic renal surgery. We reviewed our experience with laparoscopic surgery specifically for renal cancers to better clarify which clinical variables were significant risk factors. METHODS: Our laparoscopic experience with 210 cases of renal cancer from April 1999 through August 2004 was reviewed. Preoperative clinical characteristics were recorded. Complete information was available for 134 patients: 54 radical nephrectomies, 41 nephroureterectomies, 19 radiofrequency ablations, and 20 partial nephrectomies. Outcomes monitored included blood loss, length of hospital stay, conversion, blood transfusion, and intraoperative, minor postoperative, and major postoperative complications. Multivariate analysis was performed to determine whether any variable was a significant risk factor for adverse outcomes during or after laparoscopic surgery. RESULTS: The numbers of patients requiring operative conversion or blood transfusions were 6 (4.5%) and 20 (14.9%), respectively. Intraoperative, minor postoperative, and major postoperative complication occurred in 9 (6.7%), 22 (16.4%), and 11 (8.2%) patients, respectively. The year surgery was performed was inversely proportional to the incidence of minor postoperative complications, implying a protective association with the experience of the surgeon. On multivariate analysis, only body mass index (BMI) was found to be a significant risk factor for major postoperative complications with an odds ratio of 1.14 (P = 0.03). CONCLUSIONS: Laparoscopic surgery is safe, but with every unit increase in the BMI, the risk of a major complication increases by 14%.

Lagra, F., K. Karastergiou, et al. (2004). "Obesity and colorectal cancer." Tech Coloproctol **8 Suppl 1**: s161-3.

BACKGROUND: To correlate obesity and colorectal cancer for Greek living conditions. PATIENTS AND METHODS: We studied 97 patients, who over the last 5 years were diagnosed histopathologically with colorectal cancer. 75.3% of the patients were either overweight or centrally obese; secondly, 21.6% patients had diabetes, percentages higher than those in the population (statistically significant). Hyperinsulinaemia and resistance to insulin have been implicated in colorectal carcinogenesis. CONCLUSIONS: As our sample was small, no statistically significant evidence correlating

diet and/or physical activity to colorectal cancer has emerged.

Lamarre, N. S., M. R. Ruggieri, Sr., et al. (2007). "Effect of obese and lean Zucker rat sera on human and rat prostate cancer cells: implications in obesity-related prostate tumor biology." Urology **69**(1): 191-5.

OBJECTIVES: Several reports have demonstrated the effects of obesity on prostate cancer. Also several reports have linked expression of vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (FGF-2) to prostate cancer aggressiveness. The objective of this study was to determine whether a difference exists between lean and obese Zucker rat sera on proliferation prostate cancer cell lines, as well as to examine the differences in FGF-2 and VEGF concentrations. METHODS: Ten-week-old female obese and lean Zucker rat sera were subjected to charcoal stripping and tested for the proliferation of human LNCaP and rat AT3B-1 prostate cancer cells. An acetonitrile extract of the charcoal used to strip the sera was also tested for mitogenicity. VEGF and FGF-2 concentrations were determined by enzyme-linked immunosorbent assay. RESULTS: Both unstripped and charcoal-stripped obese rat sera had a greater mitogenic effect than did the lean sera on the LNCaP cell line. Charcoal stripping of both obese and lean sera reduced the mitogenic effect on the AT3B-1 cell line. The acetonitrile extract of the charcoal used to strip the sera was unable to recover this proliferative effect. The concentration of VEGF was greater in the obese serum than in the lean serum, and charcoal stripping reduced the concentrations of both FGF-2 and VEGF. CONCLUSIONS: The finding of greater VEGF in obese rat sera, as well as greater mitogenic responses on human prostate cancer cells in vitro, suggests this as one of the many possible mechanisms involved in obesity-related prostate cancer biology.

Lane, G. (2008). "Obesity and gynaecological cancer." Menopause Int **14**(1): 33-7.

Obesity is now considered to be a global epidemic. The problem of obesity has significant implications for the diagnosis and treatment of gynaecological cancer. The cancer most frequently associated with obesity is that of the endometrium. The risk of endometrial cancer is 2-3 times higher in overweight and obese women. Obesity also adversely affects survival in most studies. With regard to ovarian cancer the evidence is inconsistent. Obesity in young adulthood may be more important than that in later life. With regard to survival obesity has an adverse effect but not in early stage disease. Few data are available regarding cervical cancer and obesity. There is evidence that obesity is associated with adenocarcinoma rather than squamous carcinoma. Data on vulval cancer and obesity are scant.

Larsson, S. C., J. Permert, et al. (2005). "Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts." Br J Cancer **93**(11): 1310-5.

We examined the associations of body mass index (BMI), waist circumference, a history of diabetes, and cigarette smoking with risk of pancreatic cancer among 37,147 women and 45,906 men followed up during 560,666 person-years in the Swedish Mammography Cohort and the Cohort of Swedish Men; 136 incident cases of pancreatic cancer were diagnosed. The multivariate rate ratio (RR) of pancreatic cancer for obese women and men (BMI > or =30 kg/m(2)) was 1.81 (95% CI: 1.04-3.15) compared to those with a BMI of 20-25 kg/m(2). For a difference of 20 cm (about two standard deviations) in waist circumference, the multivariate RRs were 1.32 (95% CI: 0.73-2.37) among women and 1.74 (95% CI: 1.00-3.01) among men. Pancreatic cancer risk was associated with history of diabetes (multivariate RR: 1.88; 95% CI: 1.09-3.26) and cigarette smoking (multivariate RR for current compared with never smokers: 3.06; 95% CI: 1.99-4.72). Current smokers of > or =40 pack-years had a five-fold elevated risk compared with never smokers. Risk among past smokers approached the RR for never smokers within 5-10 years following smoking cessation. Findings from this prospective study support positive relationships of overall obesity, abdominal adiposity, diabetes and smoking with risk of pancreatic cancer.

Larsson, S. C., J. Rutegard, et al. (2006). "Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men." Eur J Cancer **42**(15): 2590-7.

We investigated the association between physical activity and colorectal cancer risk in a cohort of Swedish men. Information on physical activity was obtained at baseline in 1997 with a self-administered questionnaire from 45,906 men who were cancer-free at enrollment. During a mean follow-up of 7.1 years, 496 cases of colorectal cancer occurred. Leisure-time physical activity was inversely associated with colorectal cancer risk; the multivariate hazard ratio (HR) for 60 min or more per day of leisure-time physical activity compared with less than 10 min per day was 0.57 (95% CI 0.41-0.79; P for trend=0.001). Results were similar for colon (HR=0.56; 95% CI 0.37-0.83) and rectal cancer (HR=0.59; 95% CI 0.34-1.02). Home/housework activity was inversely associated with colon cancer risk (HR=0.68; 95% CI 0.48-0.96). No association was observed for

work/occupational activity. These results support a role of physical activity in reducing the risk of colon and rectal cancer.

Larsson, S. C. and A. Wolk (2007). "Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies." Am J Clin Nutr **86**(3): 556-65.

BACKGROUND: Whereas obesity has been associated with an increased risk of colon cancer in men, a weak or no association has been observed in women. Results for rectal cancer have also been inconsistent. OBJECTIVE: The objective was to perform a meta-analysis to summarize the available evidence from prospective studies on the associations of overall and abdominal obesity with the risk of colon and rectal cancer. DESIGN: We searched MEDLINE (1966-April 2007) and the references of the retrieved articles. Study-specific relative risks (RRs) were pooled by using a random-effects model. RESULTS: Thirty prospective studies were included in the meta-analysis of body mass index (BMI; in kg/m(2)). Overall, a 5-unit increase in BMI was related to an increased risk of colon cancer in both men (RR: 1.30; 95% CI: 1.25, 1.35) and women (RR: 1.12; 95% CI: 1.07, 1.18), but the association was stronger in men ($P < 0.001$). BMI was positively associated with rectal cancer in men (RR: 1.12; 95% CI: 1.09, 1.16) but not in women (RR: 1.03; 95% CI: 0.99, 1.08). The difference in RRs between cancer sites was statistically significant ($P < 0.001$ in men and $P = 0.04$ in women). Colon cancer risk increased with increasing waist circumference (per 10-cm increase) in both men (RR: 1.33; 95% CI: 1.19, 1.49) and women (RR: 1.16; 95% CI: 1.09, 1.23) and with increasing waist-hip ratio (per 0.1-unit increase) in both men (RR: 1.43; 95% CI: 1.19, 1.71) and women (RR: 1.20; 95% CI: 1.08, 1.33). CONCLUSIONS: The association between obesity and colon and rectal cancer risk varies by sex and cancer site.

Larsson, S. C. and A. Wolk (2007). "Obesity and the risk of gallbladder cancer: a meta-analysis." Br J Cancer **96**(9): 1457-61.

We performed a meta-analysis of studies of the association between excess body weight and risk of gallbladder cancer identified from MEDLINE and EMBASE databases from 1966 to February 2007 and the references of retrieved articles. A random-effects model was used to combine results from eight cohort studies and three case-control studies, with a total of 3288 cases. Compared with individuals of 'normal weight', the summary relative risk of gallbladder cancer for those who were overweight or obese was 1.15 (95% CI, 1.01-1.30) and 1.66 (95% CI, 1.47-1.88) respectively. The association with obesity was stronger for women (relative risk, 1.88; 95% CI, 1.66-2.13) than for men (relative risk, 1.35; 95% CI, 1.09-1.68). There was no statistically significant heterogeneity among the results of individual studies. This meta-analysis confirms the association between excess body weight and risk of gallbladder cancer.

Larsson, S. C. and A. Wolk (2007). "Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies." Br J Cancer **97**(7): 1005-8.

Cohort studies of excess body weight and risk of liver cancer were identified for a meta-analysis by searching MEDLINE and EMBASE databases from 1966 to June 2007 and the reference lists of retrieved articles. Results from individual studies were combined using a random-effects model. We identified 11 cohort studies, of which seven on overweight (with a total of 5037 cases) and 10 on obesity (with 6042 cases) were suitable for meta-analysis. Compared with persons of normal weight, the summary relative risks of liver cancer were 1.17 (95% confidence interval (CI): 1.02-1.34) for those who were overweight and 1.89 (95% CI: 1.51-2.36) for those who were obese. This meta-analysis finds that excess body weight is associated with an increased risk of liver cancer.

Lautenbach, A., A. Budde, et al. (2009). "Obesity and the associated mediators leptin, estrogen and IGF-I enhance the cell proliferation and early tumorigenesis of breast cancer cells." Nutr Cancer **61**(4): 484-91.

Breast cancer continues to be a major cause of cancer deaths in women. Estrogen, which is also produced by the adipose tissue, is held responsible for the elevated risk of breast cancer in obese women. However, the adipose tissue secrets hormones and adipokines such as leptin and IGF-I and these substances could also contribute to an increased breast cancer risk for obese women. In this study, the impact of obesity on cell proliferation was investigated. The carcinogen 7, 12, dimethylbenz[a]anthracene (DMBA) was administered to normal weight and diet-induced obese female Sprague-Dawley rats. Cell proliferation was evaluated by immunohistological staining of BrdU-incorporation. In the mammary glands and inguinal lymphatic nodes of the obese rats, cell proliferation was significantly increased, indicating a significant influence of obesity on breast cancer. Effects of leptin, estrogen, and IGF-I on the proliferation of MCF-7 cells in vitro were assessed using an MTT assay. Cell culture experiments demonstrated a mitogenic role of these three mediators on cell proliferation. Our data demonstrate a stimulative effect of substances produced by the adipose tissue on breast cancer. Body weight specific cell proliferation suggests that obesity-related

adipokines and mediators enhance cell proliferation and increase the risk for breast cancer.

Lee, S. A., K. M. Lee, et al. (2005). "Obesity and genetic polymorphism of ERCC2 and ERCC4 as modifiers of risk of breast cancer." Exp Mol Med **37**(2): 86-90.

To evaluate the relationship of genetic polymorphisms of ERCC2 and ERCC4 genes, both involved in nucleotide excision repair (NER), and the risk of breast cancer, a hospital-based case-control study was conducted in Korea. Histologically confirmed breast cancer cases (n = 574) and controls (n = 502) with no present or previous history of cancer were recruited from three teaching hospitals in Seoul during 1995-2001. Information on selected characteristics was collected by interviewed questionnaire. ERCC2 Asp(312)Asn (G>A) was genotyped by single-base extension assay and ERCC4 Ser(835)Ser (T>C) by dynamic allele-specific hybridization system. Although no significant association was observed between the genetic polymorphisms and the risk of breast cancer, women with both ERCC2 A allele- and ERCC4 C allele-containing genotypes showed a 2.6-fold risk (95% CI: 1.02-6.48) of breast cancer compared to women concurrently carrying the ERCC2 GG and ERCC4 TT genotypes. The breast cancer risk increased as the number of "at risk" genotypes increased with a borderline significance (P for trend = 0.07). Interactive effect was also observed between ERCC4 genotype and body mass idnex (BMI) for the breast cancer risk; the ERCC4 C allele containing genotypes posed a 1.7-fold (95% CI: 0.96-2.93) breast cancer risk in obese women (BMI>25 kg/m(2)) with a borderline significance. Our finding suggests that the combined effect of ERCC2 Asp(312)Asn and ERCC4 Ser(835)Ser genotypes might be associated with breast cancer risk in Korean women.

LeRoith, D., R. Novosyadlyy, et al. (2008). "Obesity and type 2 diabetes are associated with an increased risk of developing cancer and a worse prognosis; epidemiological and mechanistic evidence." Exp Clin Endocrinol Diabetes **116 Suppl 1**: S4-6.

Both obesity and Type 2 diabetes are independently associated with an increased risk of developing cancer and an increased mortality. The etiology is yet to be determined but insulin resistance and hyperinsulinemia maybe important factors. Hyperglycemia, hyperlipidemia and inflammatory cytokines in addition to the insulin-like growth factors are also possible factors involved in the process.

Li, A. J., R. G. Elmore, et al. (2007). "Hyperandrogenism, mediated by obesity and receptor polymorphisms, promotes aggressive epithelial ovarian cancer biology." Gynecol Oncol **107**(3): 420-3.

OBJECTIVE: Epidemiologic data suggest that aberrant androgen homeostasis may promote aggressive epithelial ovarian cancer biology. Hyperandrogenism results from both obesity and expression of polymorphic androgen receptor (AR) allelotypes harboring short cytosine-adenine-guanine (CAG) repeat sequences; both have been shown to independently correlate with poor overall survival in ovarian cancer. We have hypothesized that the combination of these factors further manifests an aggressive ovarian cancer phenotype. METHODS: Genotype analysis of the AR CAG polymorphism was performed on 81 patients with papillary serous epithelial ovarian cancer. Medical records were reviewed for body mass index (BMI), clinico-pathologic factors, and survival. Data were examined using the Fishers exact test, Kaplan-Meier survival, and Cox regression analyses. RESULTS: Overweight or obese women (BMI > or = 25) with a short AR allele (< or = 19 CAG repeats) demonstrated statistically shorter progression-free survival (9 months) when compared to underweight or ideal body weight women (BMI < 25) and a long AR allele (> 19 CAG repeats; 26 months, p=0.0002). Overweight/obese women with a short AR allele also demonstrated shorter overall survival (34 months) when compared to underweight/ideal body weight women with a long AR allele (59 months, p=0.036). On multivariate analyses, the combination of a short AR allele and BMI > 25 was an independent poor prognostic factor after controlling for age, stage, grade, optimal cytoreduction, and AR allele length and BMI independently (p=0.05). CONCLUSION: These data provide further evidence that suggest that hyperandrogenism promotes an aggressive epithelial ovarian cancer phenotype.

Lin, Y., S. Kikuchi, et al. (2007). "Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort." Int J Cancer **120**(12): 2665-71.

It is unclear whether body mass index (BMI) and physical activity are associated with the risk of pancreatic cancer in Asian populations. We examined these associations in the Japanese Collaborative Cohort Study for Evaluation of Cancer Risk. Our cohort study included 110,792 Japanese men and women at enrollment (1988-1990). Data on height, body weight (at baseline and at age 20 years) and physical activity were obtained from a questionnaire. Cox proportional hazards models were used to estimate the relative risks of pancreatic cancer mortality. We observed a total of 402 pancreatic cancer deaths during the follow-up period. Men with a

BMI of 30 or more at age 20 years had a 3.5-fold greater risk compared with men with a normal BMI. Women with a BMI of 27.5-29.9 at baseline had approximately 60% increased risk compared with women with a BMI of 20.0-22.4. In men, weight loss of 5 kg or more between 20 years of age and baseline age was associated with an increased risk of pancreatic cancer death. In contrast, women with weight loss of 5 kg or more over the same period had a decreased risk. Physical activity was not associated with pancreatic cancer risk in either men or women. Obesity in young adulthood may be associated with an increased risk of death from pancreatic cancer in Japanese men. The risk of pancreatic cancer in relation to BMI seems to differ according to sex and the period over which BMI was measured.

Litton, J. K., A. M. Gonzalez-Angulo, et al. (2008). "Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer." J Clin Oncol **26**(25): 4072-7.

PURPOSE: To understand the mechanism through which obesity in breast cancer patients is associated with poorer outcome, we evaluated body mass index (BMI) and response to neoadjuvant chemotherapy (NC) in women with operable breast cancer. PATIENTS AND METHODS: From May 1990 to July 2004, 1,169 patients were diagnosed with invasive breast cancer at M. D. Anderson Cancer Center and received NC before surgery. Patients were categorized as obese (BMI >or= 30 kg/m(2)), overweight (BMI of 25 to < 30 kg/m(2)), or normal/underweight (BMI < 25 kg/m(2)). Logistic regression was used to examine associations between BMI and pathologic complete response (pCR). Breast cancer-specific, progression-free, and overall survival times were examined using the Kaplan-Meier method and Cox proportional hazards regression analysis. All statistical tests were two-sided. RESULTS: Median age was 50 years; 30% of patients were obese, 32% were overweight, and 38% were normal or underweight. In multivariate analysis, there was no significant difference in pCR for obese compared with normal weight patients (odds ratio [OR] = 0.78; 95% CI, 0.49 to 1.26). Overweight and the combination of overweight and obese patients were significantly less likely to have a pCR (OR = 0.59; 95% CI, 0.37 to 0.95; and OR = 0.67; 95% CI, 0.45 to 0.99, respectively). Obese patients were more likely to have hormone-negative tumors (P < .01), stage III tumors (P < .01), and worse overall survival (P = .006) at a median follow-up time of 4.1 years. CONCLUSION: Higher BMI was associated with worse pCR to NC. In addition, its association with worse overall survival suggests that greater attention should be focused on this risk factor to optimize the care of breast cancer patients.

Loi, S., R. L. Milne, et al. (2005). "Obesity and outcomes in premenopausal and postmenopausal breast cancer." Cancer Epidemiol Biomarkers Prev **14**(7): 1686-91.

PURPOSE: Obesity is associated with adverse outcomes in postmenopausal women with breast cancer. In premenopausal women, the association is less clear. METHODS: A population-based sample of 1,360 Australian women with breast cancer before the age of 60 years, 47% diagnosed before age 40, and 74% premenopausal, was studied prospectively for a median of 5 years (range, 0.2-10.8 years). Obesity was defined as a body mass index of > or =30 kg/m2. The hazard ratio (HR) for adverse clinical outcome associated with obesity was estimated using Cox proportional hazard survival models. RESULTS: Obesity increased with age (P < 0.001) and was associated with increased breast cancer recurrence (P = 0.02) and death (P = 0.06), larger tumors (P = 0.002), and more involved axillary nodes (P = 0.003) but not with hormone receptor status (P > or = 0.6) or with first cycle adjuvant chemotherapy dose reductions (P = 0.1). Adjusting for number of axillary nodes, age at diagnosis, tumor size, grade, and hormone receptor status, obese women of all ages were more likely than nonobese women to have disease recurrence [HR, 1.57; 95% confidence interval (95% CI), 1.11-2.22; P = 0.02] and to die from any cause during follow-up (HR, 1.56; 95% CI, 1.01-2.40; P = 0.05). In premenopausal women, the adjusted HRs were 1.50 (95% CI, 1.00-2.26; P = 0.06) and 1.71 (95% CI, 1.05-2.77; P = 0.04), respectively. CONCLUSIONS: Obesity is independently associated with poorer outcomes in premenopausal women, as it is in postmenopausal women, and this is not entirely explained by differences in tumor size or nodal status. Given the high and increasing prevalence of obesity in western countries, more research on improving the treatment of obese breast cancer patients is warranted.

Lorincz, A. M. and S. Sukumar (2006). "Molecular links between obesity and breast cancer." Endocr Relat Cancer **13**(2): 279-92.

Breast cancer continues to be a major health problem for women in the USA and worldwide. There is a need to identify and take steps to alter modifiable breast cancer risks. Conditions of obesity and overweight are risk factors that have reached epidemic proportions. This article reviews the evidence in the literature that test mechanism-based hypotheses which attempt to provide a molecular basis for a causal link between obesity and breast cancer risk, particularly the effects of metabolic syndrome and insulin

resistance, peripheral estrogen aromatization in adipose tissue, and direct effect of adipokines. Future areas for study and implications for therapy are discussed.

Luo, J., K. L. Margolis, et al. (2008). "Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States)." Br J Cancer **99**(3): 527-31.

A total of 138,503 women in the Women's Health Initiative in the United States were followed (for an average of 7.7 years) through 12 September 2005 to examine obesity, especially central obesity in relation to pancreatic cancer (n=251). Women in the highest quintile of waist-to-hip ratio had 70% (95% confidence interval 10-160%) excess risk of pancreatic cancer compared with women in the lowest quintile.

Lynch, L., D. O'Shea, et al. (2009). "Invariant NKT cells and CD1d(+) cells amass in human omentum and are depleted in patients with cancer and obesity." Eur J Immunol **39**(7): 1893-901.

Invariant NKT (iNKT) cells recognize lipid antigens presented by CD1d and respond rapidly by killing tumor cells and release cytokines that activate and regulate adaptive immune responses. They are essential for tumor rejection in various mouse models, but clinical trials in humans involving iNKT cells have been less successful, partly due to their rarity in humans compared with mice. Here we describe an accumulation of functional iNKT cells in human omentum, a migratory organ with healing properties. Analysis of 39 omental samples revealed that T cells are the predominant lymphoid cell type and of these, 10% expressed the invariant Valpha24Jalpha18 TCR chain, found on iNKT cells, higher than in any other human organ tested to date. About 15% of omental hematopoietic cells expressed CD1d, compared with 1% in blood ($p<0.001$). Enriched omental iNKT cells killed CD1d(+) targets and released IFN-gamma and IL-4 upon activation. Omental iNKT-cell frequencies were lower in patients with severe obesity ($p=0.005$), and with colorectal carcinoma ($p=0.004$) compared with lean healthy subjects. These data suggest a novel role for the omentum in immune regulation and tumor immunity and identify it as a potential source of iNKT cells for therapeutic use.

Machova, L., L. Cizek, et al. (2007). "Association between obesity and cancer incidence in the population of the District Sumperk, Czech Republic." Onkologie **30**(11): 538-42.

BACKGROUND: Excess body weight was shown to be associated with risk of several types of cancer. In the Czech Republic, malignant tumors are the second leading cause of death. The aim of this study was to assess the association between the most frequent types of cancer and obesity. METHODS: A case-control study was accomplished, using data from the National Cancer Registry and from a preventive oncologic checkup database. Cases were defined as persons from the studied population who developed skin, breast, colorectal, prostate, lung, cervical, endometrial, kidney, ovarian, urinary bladder, stomach, pancreatic, or gallbladder cancers from 1987 to 2002. Controls were cancer-free men and women from the population. Among the cancer patients and healthy controls, proportions of obese, overweight, and nonobese individuals were compared, and odds ratios (OR) were computed. RESULTS: After adjustment for confounders, obese men had a significantly increased risk of colorectal cancer (OR: 2.07, 95% CI: 1.56-2.76) and kidney cancer (OR: 1.92, 95% CI: 1.14-3.24). Obese women were at higher risk of endometrial cancer (OR: 3.25, 95% CI: 1.65-6.37). An inverse association was observed between obesity and lung cancer (in men: OR: 0.49, 95% CI: 0.37-0.66; in women: OR: 0.41, 95% CI: 0.21-0.80). CONCLUSION: Obesity is associated with several frequent types of tumors and represents an important preventable cause of cancer in the population of the District Sumperk, Czech Republic.

Maehle, B. O., S. Tretli, et al. (2004). "The associations of obesity, lymph node status and prognosis in breast cancer patients: dependence on estrogen and progesterone receptor status." Apmis **112**(6): 349-57.

Breast cancer patients who are obese have a higher risk of lymph node metastases and a poorer prognosis than those who are slim. It has been claimed that estrogens derived from fat are important for these associations. If estrogens are important, these relationships must be stronger in the hormone receptor-positive than in the hormone receptor-negative groups. Body mass index (BMI) was used as a measure of obesity. The second, third, and fourth quintiles of BMI were treated as one group and termed 'medium'. Patients in the fifth quintile were termed 'obese' and those in the first quintile 'slim'. The number of women with unilateral disease treated with modified radical mastectomy and included in the study was 1211. Of all patients included, obese patients had a 1.53 higher risk of lymph node metastases compared to slim patients ($p=0.02$). In the PgR-negative group, obesity gave a 3.08 times higher risk of lymph node metastases ($p=0.03$). The risk of dying of breast cancer tended to be higher in obese than in slim patients when all patients in the study were compared (relative risk=1.38, $p=0.06$). BMI did not show a statistically significant relationship with

prognosis if only hormone receptor status was considered. However, if lymph node status and hormone receptor status were taken together, the association was strong and reversed in the lymph node-positive group with ER-negative tumours. The adjusted relative risk was 0.33, showing that slim patients had a 3.03 (1.0/0.33) times higher risk of dying of breast cancer compared to obese patients (p=0.002). These results indicate that non-hormonal mechanisms could be important.

Majed, B., T. Moreau, et al. (2009). "Overweight, obesity and breast cancer prognosis: optimal body size indicator cut-points." Breast Cancer Res Treat **115**(1): 193-203.

BACKGROUND: Evidence from the data provided in numerous published articles indicates that obesity and overweight can have a negative prognosis role in breast cancer. However, different Body Size Indicators (BSI) and cut-points have been employed and may partly explain discrepancies between the findings of various studies. MATERIAL AND METHODS: 14,709 women were recruited, treated and followed for a first unilateral breast cancer. After randomly splitting the patients' data into two groups, a maximum statistical outcome approach was used to select optimal BSI cut-points from a "training sample", when prognosis events were investigated. External validation was then carried out using a "validation sample", and agreement between the selected optimal BSI cut-points was assessed. Body Mass Index (BMI), weight (W), Ideal Weight Ratio (IWR) and Body Surface Area (BSA) were used, and were assessed at the time of diagnosis. RESULTS: The selected optimal BSI cut-points were reliable when overall survival, metastasis recurrence and disease free interval events were investigated. The chosen BMI cut-point values matched the overweight cut-point value given by the World Health Organization. Agreement between defined binary BSI was acceptable; however, it varied from "fair" to "very good". Analysis of second primary cancer occurrence and contralateral recurrence events was not conclusive. When local and node recurrence events were taken into account, the results were inconsistent and were linked to an unconfirmed relationship between stoutness and these prognosis events. CONCLUSIONS: Efficient, optimal BSI cut-points indicate a poorer prognosis, illustrated by a shortened overall survival and an increase of metastasis recurrences, from a BMI value of 25 kg/m(2), a W value of 60 kg, an IWR value of 20% and a BSA value of 1.7 m(2). Further BSI cut-point investigations are needed, taking into account contralateral recurrence and second primary cancer events.

Majed, B., T. Moreau, et al. (2008). "Is obesity an independent prognosis factor in woman breast cancer?" Breast Cancer Res Treat **111**(2): 329-42.

BACKGROUND: Breast cancer and obesity represent important public health issues in most western countries. A number of studies found a negative prognosis effect of obesity or excess of weight in woman breast cancer. However, to date, this issue remains controversial. The objectives of this study were to confirm the prognosis role of obesity on a large cohort of patients and to investigate a potential independent effect. MATERIALS AND METHODS: We constituted a cohort of 14,709 patients who were recruited and treated at the Curie Institute (Paris) from 1981 to 1999. These patients were followed prospectively for a first unilateral invasive breast cancer without distant metastasis. Obesity was defined by a Body Mass Index (BMI) above 30 kg/m(2) according to the World Health Organization recommendations. RESULTS: Obese patients (8%) presented more extended tumors at diagnosis time suggesting a delayed breast cancer diagnosis. However, obesity appeared as a negative prognosis factor for several events in respectively univariate and multivariate survival analysis: metastasis recurrence (HR = 1.32[1.19-1.48]; HR = 1.12[1.00-1.26]), disease free interval (1.20[1.08-1.32]; 1.10[0.99-1.22]), overall survival (1.43[1.28-1.60]; 1.12[0.99-1.25]) and second primary cancer outcome (1.57[1.19-2.07]; 1.43[1.09-1.89]). Even if obese patients presented more advanced tumors at diagnosis time, multivariate analysis showed that there was a relevant independent effect. Other BMI codings, distinguishing overweight patients or using BMI as a continuous variable, showed a consistent correlation between BMI's value and prognosis effect. Interaction analysis revealed a more important obesity effect in the presence of tumor estrogen receptors and among limited extent tumors. CONCLUSIONS: This survey confirms the prognosis role of obesity on one of the largest cohort by investigating several prognosis events. While independent obesity effect linked to hormonal disorders appeared consistent as obesity's mechanism, we stress that obesity prognosis effect was also related to breast cancer presentation at diagnosis time.

Major, L. H. (2009). "Break it to me harshly: the effects of intersecting news frames in lung cancer and obesity coverage." J Health Commun **14**(2): 174-88.

By examining the publicly identified top two health problems in the United States, this research, using an experimental design, investigates whether different news frame combinations intensify or diminish framing effects. In this study, the cognitive dimension and affective dimension of framing defined

as thematic/episodic and gain/loss, respectively, are manipulated to determine if changing the way newspaper stories report obesity and lung cancer will alter the readers' attribution of societal and individual responsibility. This study revealed a significant interaction between thematic framing and loss framing on societal attribution of responsibility for the health issues-lung cancer and obesity.

Makino, H., C. Kunisaki, et al. (2008). "Effect of obesity on intraoperative bleeding volume in open gastrectomy with D2 lymph-node dissection for gastric cancer." Patient Saf Surg **2**: 7.

BACKGROUND: To investigate the effect of obesity on open gastrectomy with D2 lymph-node dissection. METHODS: Between January 2005 and March 2007, 100 patients with preoperatively diagnosed gastric cancer who underwent open gastrectomy with D2 lymph-node dissection were enrolled in this study. Of these, 61 patients underwent open distal gastrectomy (ODG) and 39 patients underwent open total gastrectomy (OTG). Patients were classified as having a high body-mass index (BMI; >/= 25.0 kg/m2; n = 21) or a normal BMI (<25.0 kg/m2; n = 79). The visceral fat area (VFA) and subcutaneous fat area (SFA) were assessed as identifiers of obesity using FatScan software. Patients were classified as having a high VFA (>/= 100 cm2; n = 34) or a normal VFA (<100 cm2; n = 66). The relationship between obesity and short-term patient outcomes after open gastrectomy was evaluated. Patients were classified as having high intraoperative blood loss (IBL; >/= 300 ml; n = 42) or low IBL (<300 ml; n = 58). Univariate and multivariate analyses were used to identify predictive factors for high IBL. RESULTS: Significantly increased IBL was seen in the following: patients with high BMI versus normal BMI; patients with gastric cancer in the upper third of the stomach versus gastric cancer in the middle or lower third of the stomach; patients who underwent OTG versus ODG; patients who underwent splenectomy versus no splenectomy; and patients with high VFA versus low VFA. BMI and VFA were significantly greater in the high IBL group than in the low IBL group. There was no significant difference in morbidity between the high IBL group and the low IBL group. Multivariate analysis revealed that patient age, OTG and high BMI or high VFA independently predicted high IBL. CONCLUSION: It is necessary to perform operative manipulations with particular care in patients with high BMI or high VFA in order to reduce the IBL during D2 gastrectomy.

Marshall, S. (2006). "Role of insulin, adipocyte hormones, and nutrient-sensing pathways in regulating fuel metabolism and energy homeostasis: a nutritional perspective of diabetes, obesity, and cancer." Sci STKE **2006**(346): re7.

Traditionally, nutrients such as glucose and amino acids have been viewed as substrates for the generation of high-energy molecules and as precursors for the biosynthesis of macromolecules. However, it is now apparent that nutrients also function as signaling molecules in functionally diverse signal transduction pathways. Glucose and amino acids trigger signaling cascades that regulate various aspects of fuel and energy metabolism and control the growth, proliferation, and survival of cells. Here, we provide a functional and regulatory overview of three well-established nutrient signaling pathways-the hexosamine signaling pathway, the mTOR (mammalian target of rapamycin) signaling pathway, and the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. Nutrient signaling pathways are interconnected, coupled to insulin signaling, and linked to the release of metabolic hormones from adipose tissue. Thus, nutrient signaling pathways do not function in isolation. Rather, they appear to serve as components of a larger "metabolic regulatory network" that controls fuel and energy metabolism (at the cell, tissue, and whole-body levels) and links nutrient availability with cell growth and proliferation. Understanding the diverse roles of nutrients and delineating nutrient signaling pathways should facilitate drug discovery research and the search for novel therapeutic compounds to prevent and treat various human diseases such as diabetes, obesity, and cancer.

Maruthur, N. M., S. D. Bolen, et al. (2009). "The association of obesity and cervical cancer screening: a systematic review and meta-analysis." Obesity (Silver Spring) **17**(2): 375-81.

Obese women are at an increased risk of death from cervical cancer, but the explanation for this is unknown. Through our systematic review, we sought to determine whether obesity is associated with cervical cancer screening and whether this association differs by race. We identified original articles evaluating the relationship between body weight and Papanicolaou (Pap) testing in the United States through electronic (PubMed, CINAHL, and the Cochrane Library) and manual searching. We excluded studies in special populations or those not written in English. Two reviewers sequentially extracted study data and independently extracted quality using standardized forms. A total of 4,132 citations yielded 11 relevant studies. Ten studies suggested an inverse association between obesity and cervical cancer screening. Compared to women with a normal BMI, the combined odds ratios (95% CI) for Pap testing were 0.91 (0.80-1.03), 0.81 (0.70-0.93),

0.75 (0.64-0.88), and 0.62 (0.55-0.69) for the overweight and class I, class II, and class III obesity categories, respectively. Three out of four studies that presented the results by race found this held true for white women, but no study found this for black women. In conclusion, obese women are less likely to report being screened for cervical cancer than their lean counterparts, and this does not hold true for black women. Less screening may partly explain the higher cervical cancer mortality seen in obese white women.

Masaki, T. and H. Yoshimatsu (2008). "Obesity, adipocytokines and cancer." Transl Oncogenomics **3**: 45-52.

A great amount of literature has demonstrated a connection between obesity, visceral fat and the metabolic disorders such as hyperglycemia, hypertension, and hyperlipidemia. Lately, there has been an increased interest in understanding if cancer is related to obesity and visceral fat accumulation. The prevalence of both obesity and cancer are increasing and there has been keen interest in the relationship between visceral adiposity and the biology of cancers. White adipose tissue (WAT) provides a limitless capacity for triglyceride storage vital for survival. The concurrent rise in insulin, glucose, and lipids during meals stimulates triglyceride formation and storage in WAT. WAT is also recognized as an endocrine organ that secretes multiple cytokines such as leptin and adiponectin. In addition, leptin and adiponectin have been adipocytokines that attracted attention for cancer research. Thus, in this review, we will describe recent progress made in obesity, visceral adiposity, leptin and adiponectin in the involvement of various cancers.

Mathew, A., P. S. George, et al. (2009). "Obesity and kidney cancer risk in women: a meta-analysis (1992-2008)." Asian Pac J Cancer Prev **10**(3): 471-8.

We conducted a quantitative summary analysis to assess whether obesity carries higher relative risk in women than men. The studies included in this quantitative review were all cohort and case-control studies, which provided information on kidney cancer risk associated with obesity/overweight, published between 1992 and 2008. The details of studies have been identified through searches on the MEDLINE database. We first estimated the risk associated with a unit increase in BMI (1 kg/m(2)) for individual studies using logit-linear model. After deriving the natural logarithm of the risk per unit of BMI for all studies, we calculated a pooled estimate and corresponding 95% confidence interval (CI) as a weighted average of the risk values obtained in individual studies, by giving a weight proportional to its precision. A total of 28 studies (15 cohort studies and 13 case-control studies) provided kidney cancer risk according to BMI in women. The relative risks (RR), which showed statistical significance, ranged from 1.04 to 1.12 per unit increase in BMI in various cohort studies. The pooled risk was 1.06 (95% CI=1.05-1.07) per unit increase in BMI based on cohort studies. Among all the studies, which reported association in both men and women, the pooled risk was slightly higher in women. In conclusion, the present analysis reported slightly a higher kidney cancer risk due to obesity in women than men. Increasing prevalence of obesity with higher proportion among women may be responsible for the rising incidence rates in women.

Matthews, K. S., J. M. Straughn, Jr., et al. (2009). "The effect of obesity on survival in patients with ovarian cancer." Gynecol Oncol **112**(2): 389-93.

OBJECTIVE: Data has suggested obesity as an independent prognostic factor for lower survival in patients with epithelial ovarian cancer (EOC). We sought to determine if obesity portends a disadvantage to surgical outcomes at the time of initial surgery affecting survival. METHODS: A retrospective chart review of patients diagnosed with EOC was performed. All patients underwent primary cytoreductive surgery followed by taxane/platinum-based chemotherapy. Patient demographics, surgicopathologic and survival data were evaluated. Patients were compared based on body mass index (BMI) (<30 vs. > or =30) and BMI strata (underweight, normal weight, overweight, obese and morbidly obese). Survival analyses were performed with the Kaplan Meier method and compared using the log rank test, chi(2) test, and Fischer's exact test. RESULTS: 304 patients were identified. 71 patients (23%) were obese (BMI>30). The groups were similar in regard to stage, grade, histology, and chemotherapy administered. In regard to surgical outcomes, no difference was seen in estimated blood loss (EBL), operating room (OR) time, or operative complications excluding wound complications. Optimal debulking rates were similar in obese and non-obese patients (52% vs. 51% respectively, p=0.88). There was no statistical difference in progression free survival (17 vs. 11 months) or overall survival (48 vs. 40 months) between the two groups or across BMI strata. CONCLUSION: Although obesity has been reported as an independent prognostic factor for survival, this data demonstrates that survival rates are similar between obese and non-obese patients when optimal debulking statuses are the same. Therefore, maximal effort should be directed towards optimal debulking obese patients with EOC.

McKean-Cowdin, R., X. Li, et al. (2007). "The ADRB3 Trp64Arg variant and obesity in African-

American breast cancer cases." Int J Obes (Lond) **31**(7): 1110-8.

OBJECTIVE: To determine if a missense change at codon 64 of ADRB3 (Trp64Arg), a candidate obesity gene, is associated with obesity and levels of subcutaneous or visceral fat in African-American breast cancer cases. Several observational studies have found that women, who are overweight or obese at the time of diagnosis, as well as those who gain weight after diagnosis, are at greater risk for breast cancer recurrence and death than non-overweight women. DESIGN: Prospective cohort of breast cancer cases. SUBJECTS: 219 African-American breast cancer patients participating in the Los Angeles component of the Health, Eating, Activity and Lifestyle Study. MEASURES: ADRB3 Trp64Arg genotype, measures of weight including body mass index (BMI), weight gain (weight 5 years before diagnosis compared with weight at 30 months after diagnosis), obesity (BMI> or =30 kg/m(2)), waist/hip circumference and visceral or subcutaneous fat were determined by magnetic resonance imaging. RESULTS: African-American women who were homozygous for the ADRB3 wild-type allele had significantly higher mean visceral fat levels than women who carried the variant (P=0.04), and were significantly more likely to be obese (odd ratios (OR)=2.1, 95% confidence interval (CI)=1.1-4.2). The association with obesity was most pronounced among women who were premenopausal (OR=4.8, 95% CI=1.3-18), who received chemotherapy for their breast cancer (OR=6.1, 95% CI=1.8-20), or who were not physically active (OR=3.9, 95% CI=1.5-9.7). CONCLUSION: The wild-type allele of the ADRB3 missense change was associated with measures of obesity in our sample of African-American women. The association was modified by menopausal status, history of chemotherapy and modest levels of physical activity. These results will need to be confirmed in an independent sample.

McTiernan, A. (2005). "Obesity and cancer: the risks, science, and potential management strategies." Oncology (Williston Park) **19**(7): 871-81; discussion 881-2, 885-6.

Overweight and obesity increase the risk of developing several cancers. Once cancer develops, individuals may be at increased risk of recurrence and poorer survival if they are overweight or obese. A statistically significant association between overweight or obesity and breast cancer recurrence or survival has been observed in the majority of population-based case series; however, adiposity has been shown to have less of an effect on prognosis in the clinical trial setting. Weight gain after breast cancer diagnosis may also be associated with decreased prognosis. New evidence suggests that overweight/obesity vs normal weight may increase the risk of poor prognosis among resected colon cancer patients and the risk of chemical recurrence inprostate cancer patients. Furthermore, obese cancer patients are at increased risk for developing problems following surgery, including wound complication, lymphedema, second cancers, and the chronic diseases affecting obese individuals without cancer such as cardiovascular disease and diabetes. Mechanisms proposed to explain the association between obesity and reduced prognosis include adipose tissue-induced increased concentrations of estrogens and testosterone, insulin, bioavailable insulin-like growth factors, leptin, and cytokines. Additional proposed mechanisms include reduced immune functioning, chemotherapy dosing, and differences in diet and physical activity in obese and nonobese patients. There have been no randomized clinical trials testing the effect of weight loss on recurrence or survival in overweight or obese cancer patients, however. In the absence of clinical trial data, normal weight, overweight, and obese patients should be advised to avoid weight gain through the cancer treatment process. In addition, weight loss is probably safe, and perhaps helpful, for overweight and obese cancer survivors who are otherwise healthy.

Meenakshisundaram, R. and C. Gragnoli (2009). "CDK4 IVS4-nt40 AA genotype and obesity-associated tumors/cancer in Italians - a case-control study." J Exp Clin Cancer Res **28**: 42.

BACKGROUND: Cell cycle checkpoint regulation is crucial for prevention of tumor in mammalian cells. Cyclin-dependant kinase 4 (CDK4) is important in cell cycle regulation, as it controls the G1-S phase of the cell cycle. CDK4 has potential mitogenic properties through phosphorylation of target proteins. We aimed at identifying a role of CDK4 IVS4-nt40 G-->A gene variant in benign and/or malignant tumors and in obesity-associated benign and/or malignant tumors in an Italian adult subject dataset. METHODS: We recruited 263 unrelated Italian subjects: 106 subjects had at least one benign tumor and 46 subjects had at least one malignant tumor, while 116 subjects had at least two tumors and/or cancers. We collected BMI data for 90% of them: 186 subjects had a BMI>or=30 Kg/m2 and 52 subjects had a BMI >or= 30 Kg/m2. We performed statistical power calculations in our datasets. DNA samples were directly sequenced with specific primers for the CDK4 IVS4-nt40 G-->A variant. Genotype association tests with disease were performed. RESULTS: In our study, no significant association of the CDK4 IVS4-nt40 AA genotype with cancer and/or tumors/cancer are/is detected.

However, the CDK4 IVS4-nt40 AA genotype is significantly associated with cancer and tumors/cancer in obese patients. CONCLUSION: This finding is interesting since obesity is a risk factor for tumors and cancer. This study should prompt further work aiming at establishing the role of CDK4 in contributing to tumor/cancer genetic risk predisposition, as well as its role as a potentially effective therapeutic target gene for obesity-associated tumor/cancer management.

Menendez, J. A., L. Vellon, et al. (2005). "Antitumoral actions of the anti-obesity drug orlistat (XenicalTM) in breast cancer cells: blockade of cell cycle progression, promotion of apoptotic cell death and PEA3-mediated transcriptional repression of Her2/neu (erbB-2) oncogene." Ann Oncol **16**(8): 1253-67.

BACKGROUND: Orlistat (Xenicaltrade mark), a US Food and Drug Administration (FDA)-approved drug for bodyweight loss, has recently been demonstrated to exhibit antitumor properties towards prostate cancer cells by virtue of its ability to block the lipogenic activity of fatty acid synthase (FAS). FAS (oncogenic antigen-519) is up-regulated in about 50% of breast cancers, is an indicator of poor prognosis, and has recently been functionally associated with the Her2/neu (erbB-2) oncogene. MATERIALS AND METHODS: We assessed the antitumoral effects of orlistat against the human breast cancer cell line SK-Br3, an in vitro paradigm of FAS and Her2/neu overexpression in breast cancer. RESULTS: Cell cycle analyses revealed that micromolar concentrations of orlistat induced, in a time- and dose-dependent manner, significant changes in the distribution of cell populations including a complete loss of G2-M phase, S-phase accumulation and a concomitant increase in the emerging sub-G1 (apoptotic) cells. Poly (ADP-ribose) polymerase (PARP) cleavage, an early event required for cells committed to apoptosis, was more predominant in orlistat-treated G1 phase cells. When we characterized signaling molecules participating in the cellular events following orlistat-induced inhibition of FAS activity and preceded inhibition of breast cancer cell proliferation, a dramatic down-regulation of Her2/neu-coded p185(Her2/neu) oncoprotein was found in orlistat-treated SK-Br3 cells (>90% reduction). Interestingly, a significant accumulation of the DNA-binding protein PEA3, a member of the Ets transcription factor family that specifically targets a PEA3-binding motif present on the Her2/neu gene promoter and down-regulates its activity, was observed in orlistat-treated SK-Br3 cells. When a Luciferase reporter gene driven by the Her2/neu promoter was transiently transfected in SK-Br3 cells, orlistat exposure was found to dramatically repress the promoter activity of Her2/neu gene, whereas a Her2/neu promoter bearing a mutated binding DNA sequence was not subject to negative regulation by orlistat, thus demonstrating that the intact PEA3 binding site on the Her2/neu promoter is required for the orlistat-induced transcriptional repression of Her2/neu overexpression. RNA interference (RNAi)-mediated silencing of FAS gene expression similarly repressed Her2/neu gene expression in a PEA3-dependent manner, thus ruling out a role for non-FAS orlistat-mediated effects. When the combination of orlistat and the anti-Her2/neu antibody trastuzumab (Herceptintrade mark) in either concurrent (orlistat + trastuzumab) or sequential (orlistat --> trastuzumab; trastuzumab --> orlistat) schedules was tested for synergism, addition or antagonism using the combination index (CI) method of Chou-Talalay, co-exposure of orlistat and trastuzumab demonstrated strong synergistic effects (CI10-90 = 0.110-0.847), whereas sequential exposure to orlistat followed by trastuzumab (CI10-90 = 0.380-1.210) and trastuzumab followed by orlistat (CI10-90 = 0.605-1.278) mainly showed additive or antagonistic interactions. Indeed, orlistat-induced FAS inhibition synergistically promoted apoptotic cell death when concurrently combined with trastuzumab as determined by an ELISA for histone-associated DNA fragments. Importantly, the degree of FAS expression in a panel of human breast cancer cell lines was predictive of sensitivity to orlistat-induced anti-proliferative effects as determined by a MTT-based characterization of metabolically viable breast cancer cells. Moreover, hypersensitivity to orlistat-induced cytotoxicity was observed in MCF-7 breast cancer cells engineered to overexpress Her2/neu (MCF-7/Her2-18 cells), which exhibit a significant up-regulation of FAS expression and activity. CONCLUSIONS: These findings reveal that the development of more potent and/or bioavailable orlistat's variants targeting the lipogenic activity of FAS may open a novel therapeutic avenue for treating Her2/neu-overexpressing breast carcinomas.

Mistry, T., J. E. Digby, et al. (2007). "Obesity and prostate cancer: a role for adipokines." Eur Urol **52**(1): 46-53.

OBJECTIVES: Many studies have investigated the association between obesity and prostate cancer risk but have yielded inconsistent results. Recent evidence suggests a particular role for obesity in prostate cancer progression. Many studies have investigated the roles of adipose tissue-derived factors (adipokines) as putative molecular mediators between obesity and prostate cancer. This review provides an overview of current evidence that supports such a role for adipokines. METHODS: A

comprehensive literature review was carried out using PubMed to search for articles relating to prostate cancer and the following adipokines: leptin, interleukin 6, vascular endothelial growth factor (VEGF), and adiponectin. RESULTS: Prostate cancer cells are exposed to adipokines either via the circulation or through locally produced adipokines following invasion of the retropubic fat pad. Circulating levels of most adipokines are positively correlated with obesity; adiponectin is inversely correlated with obesity. High circulating levels of leptin, interleukin 6, and VEGF are associated with increased prostate cancer risk and increased aggressiveness. Adiponectin levels are lower in patients with prostate cancer and are inversely associated with grade of disease. Adipokines exert a variety of biologic effects on prostate cancer cells, modulating cellular differentiation, apoptosis, proliferation, and angiogenesis. CONCLUSIONS: Evidence suggests a role for obesity and adipokines in promoting the progression of established prostate cancer. Adipokines may contribute to the molecular basis for the association between obesity and prostate cancer, but the complex pathophysiology of both these disease states requires further studies.

Modugno, F., K. E. Kip, et al. (2006). "Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer." Int J Cancer **118**(5): 1292-301.

Hormone therapy (HT) and body mass index (BMI) have been associated with postmenopausal breast cancer. Because estrogen metabolism may affect breast cancer risk and can be altered by weight and HT, it might play a role in the HT-BMI-breast cancer associations. We undertook a nested case-control study within the Observational Study of the Women's Health Initiative. Baseline levels of 2- and 16alpha-hydroxy estrone (2-OHE1 and 16alpha-OHE1) were measured in 200 women who developed breast cancer during follow-up and 200 healthy controls matched to cases by ethnicity, enrollment date, clinic site, type of HT and years since menopause. Wilcoxon nonparametric tests were used to compare estrogen metabolite levels between cases and controls. Conditional logistic regression was used to assess the relationship between BMI, estrogen metabolites and breast cancer risk. 16alpha-OHE1 levels were modestly but significantly higher in HT users among cases (median 356 pg/ml vs. 315 pg/ml) and controls (354 pg/ml vs. 298 pg/ml). 2-OHE1 levels were substantially and significantly higher in HT users among cases (369 pg/ml vs. 125 pg/ml) and controls (347 pg/ml vs. 134 pg/ml). For non-HT users only, greater BMI and higher 16alpha-OHE1 levels were individually and jointly associated with increased breast cancer risk (OR for women with high BMI and high 16alpha-OHE1 compared to those with low BMI and low 16alpha-OHE1 = 3.51, 95% CI = 1.34-9.16). No associations between BMI, estrogen metabolism and breast cancer risk were found for HT users. Estrogen metabolism differs according to both BMI and HT use, potentially explaining the interaction between BMI and HT in relation to breast cancer risk.

Moghaddam, A. A., M. Woodward, et al. (2007). "Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events." Cancer Epidemiol Biomarkers Prev **16**(12): 2533-47.

BACKGROUND: Colorectal cancer is the second most common cause of death and illness in developed countries. Previous reviews have suggested that obesity may be associated with 30% to 60% greater risk of colorectal cancer, but little consideration was given to the possible effect of publication bias on the reported association. METHODS: Relevant studies were identified through EMBASE and MEDLINE. Studies were included if they had published quantitative estimates of the association between general obesity [defined here as body mass index (BMI) > or = 30 kg/m(2)] and central obesity (measured using waist circumference) and colorectal cancer. Random-effects meta-analyses were done, involving 70,000 cases of incident colorectal cancer from 31 studies, of which 23 were cohort studies and 8 were case-control studies. RESULTS: After pooling and correcting for publication bias, the estimated relative risk of colorectal cancer was 1.19 [95% confidence interval (95% CI), 1.11-1.29], comparing obese (BMI > or = 30 kg/m(2)) with normal weight (BMI <25 kg/m(2)) people; and 1.45 (95% CI, 1.31-1.61), comparing those with the highest, to the lowest, level of central obesity. After correcting for publication bias, the risk of colorectal cancer was 1.41 (95% CI, 1.30-1.54) in men compared with 1.08 (95% CI, 0.98-1.18) for women (P(heterogeneity) <0.001). There was evidence of a dose-response relationship between BMI and colorectal cancer: for a 2 kg/m(2) increase in BMI, the risk of colorectal cancer increased by 7% (4-10%). For a 2-cm increase in waist circumference, the risk increased by 4% (2-5%). CONCLUSIONS: Obesity has a direct and independent relationship with colorectal cancer, although the strength of the association with general obesity is smaller than previously reported.

Moon, H. G., Y. T. Ju, et al. (2008). "Visceral obesity may affect oncologic outcome in patients with colorectal cancer." Ann Surg Oncol **15**(7): 1918-22.

PURPOSE: Obesity is closely related to the development of colorectal cancer as well as other metabolic complications. We investigated the prognostic significance of visceral obesity and body mass index (BMI) in 161 resectable colorectal cancer patients. METHODS: Ratios of visceral fat area (VFA) to subcutaneous fat area (SFA) were measured from the digital images of patients' computed tomography taken before the surgery, and patients were divided into those with high and those with low VFA/SFA ratio according to the degree of proportional visceral adiposity, and into an overweight and a normal-weight group according to their preoperative BMI. RESULTS: The overweight group showed a borderline decrease in cumulative disease-free survival compared to the normal-weight group (P = 0.064). Patients with high VFA/SFA ratio (more than 50 percentiles) had significantly lower cumulative disease-free survival rate compared to patients with low VFA/SFA ratio (P = 0.008). BMI and visceral adiposity showed no influence on overall survival of patients. CONCLUSION: Increased visceral adiposity was a significant predictor of disease-free survival in patients with resectable colorectal cancer. The prognostic significance of visceral adiposity should further be determined in a larger set of patients.

Morley, B., M. Wakefield, et al. (2009). "Impact of a mass media campaign linking abdominal obesity and cancer: a natural exposure evaluation." Health Educ Res **24**(6): 1069-79.

A mass media campaign aired in the Australian state of Victoria aimed to increase awareness and encourage identification of the abdominal circumference for men and women that placed them at increased risk of cancer. The evaluation assessed the extent to which ad exposure was associated with improvement in awareness, intentions and behaviours with respect to weight and cancer. Respondents were overweight or obese adults aged 30-69 years and exposure to the advertisement occurred via commercial television programmes in a natural setting. Questionnaire assessment occurred before, immediately after and 2 weeks following exposure to the advertising, and a comparison group who did not recall the ad completed the same interviews. For the main analyses, the exposure group was those who recalled the advertisement at post-exposure and follow-up (n = 101). Those who did not recall it at either stage comprised the unexposed group (n = 81). The campaign achieved its primary objective of increased awareness of the link between obesity and cancer and the specific waist sizes indicative of risk, as well as increased behavioural intentions with respect to weight and cancer. However, it did not have an effect on self-awareness of weight status, perceived personal risk of cancer or weight loss behaviour.

Morton, L. M., S. S. Wang, et al. (2006). "DRD2 genetic variation in relation to smoking and obesity in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial." Pharmacogenet Genomics **16**(12): 901-10.

OBJECTIVES: Cigarette smoking is the leading cause of morbidity and mortality worldwide. We investigated the association between smoking behavior and genetic variations in the D2 dopamine receptor (DRD2), which mediates nicotine dependence. To assess the specificity of genetic effects, we also investigated other reward-motivated characteristics (obesity, alcohol consumption). METHODS: Four single nucleotide polymorphisms in DRD2 were genotyped in 2374 participants selected randomly from the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial after stratifying by sex, age, and smoking status. Smoking, obesity, and alcohol consumption were assessed by questionnaire. Single nucleotide polymorphism and haplotype associations were estimated using odds ratios (ORs) and 95% confidence intervals derived from conditional logistic regression models, adjusted for race/ethnicity. RESULTS: DRD2 polymorphisms were associated with the risk of remaining a current smoker and obesity. Current smokers were more likely than former smokers to possess the variant TaqIA allele (rsmusical sharp1800497) in a dose-dependent model (ORCT=1.2, ORTT=1.5, P for linear trend=0.007). The DRD2 haplotype T-C-T-A [TaqIA(C/T)-957(T/C)-IVS6-83(G/T)- -50977(A/G)] was more common among current than former smokers (OR=1.3, P=0.006), particularly among heavy smokers (21+ cigarettes per day; OR=1.6, P=0.006), and was more common among obese than normal weight individuals (OR=1.4, P=0.02). CONCLUSIONS: Genetic variation in DRD2 is a modifier of the reward-motivated characteristics, smoking and obesity. As fewer than 15% of smokers who attempt to quit are able to maintain abstinence for greater than 3 months, our results support that DRD2 is an appropriate molecular target for smoking cessation treatments. Our results further support evaluation of DRD2 antagonists for obesity therapies.

Murray, L. and Y. Romero (2009). "Role of obesity in Barrett's esophagus and cancer." Surg Oncol Clin N Am **18**(3): 439-52.

The incidence of esophageal adenocarcinoma (EAC) has increased dramatically in the western world, and there also appears to have been an increase in the incidence of Barrett's esophagus and

gastroesophageal reflux disease in recent years. The contemporaneous increase in obesity has focused interest on whether obesity is a risk factor for EAC and its precursors. This article reviews current evidence for the role that overweight/obesity and body fat distribution have in development of the esophagitis metaplasia-dysplasia-adenocarcinoma sequence. Particular attention is paid to the stage at which adiposity may act to influence the risk of EAC, because this determines the importance of weight control and weight loss at each stage in the disease spectrum for the prevention of EAC.

Murthy, N. S., S. Mukherjee, et al. (2009). "Dietary factors and cancer chemoprevention: an overview of obesity-related malignancies." J Postgrad Med **55**(1): 45-54.

Obesity is a growing health problem in developed nations and in countries that are in the process of westernization like India. Obesity is linked with several health disorders such as hypertension and cardiovascular diseases, Type 2 diabetes, dyslipidemia and certain cancers. Currently, obesity-related malignancies, e.g., cancers of the breast, prostate and colon are the leading cancers in the industrialized societies. An increased amount of fat or adipose tissue in an overweight or obese person probably influences the development of cancer by releasing several hormone-like factors or adipokines. The majority of adipokines are pro-inflammatory, which promote pathological conditions like insulin resistance and cancer. On the other hand, many recent studies have shown that adiponectin, an anti-inflammatory adipokine, has anti-cancer and insulin-sensitizing effects. Adiponectin exerts its physiological functions chiefly by activation of AMP kinase via adiponectin receptors. Interestingly, several fruits and vegetables may contain adiponectin-like molecules or may increase the biosynthesis of adiponectin in our body. Studies on adiponectin analogues or adiponectin receptor agonists are a promising area of cancer chemoprevention research. In general, fruits and vegetables contain various dietary substances such as vitamins, minerals (like calcium and selenium), fiber and phytochemicals or phenolic compounds (like flavonoids and vanilloids), which may act as anti-cancer agents. Similarly, several dietary constituents including phytochemicals may have anti-obesity effects. Consumption of such dietary compounds along with caloric restriction and physical activity may be helpful in preventing obesity-related cancers. For this review article, we searched PubMed primarily to get the relevant literature.

Muto, Y., S. Sato, et al. (2006). "Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis." Hepatol Res **35**(3): 204-14.

We conducted a multicenter, randomized, controlled trial to investigate the effect of long-term oral supplementation with branched-chain amino acids (BCAA) on the event-free survival in 622 patients with decompensated cirrhosis. In the present study, the development of liver cancer was analyzed as an endpoint in particular. Subjects received either treatment with BCAA at 12g/day or dietary therapy containing the matched daily energy and protein intake. A Cox regression analysis was carried out to estimate the hazard ratios for different background factors stratified by treatment group. Liver cancer was noted in 89 patients. The risk for liver cancer was significantly higher for males, patients with concurrent diabetes mellitus, patients with an alpha-fetoprotein (AFP) level of 20ng/mL or higher, patients with higher body mass index (BMI), and patients with lower serum albumin levels. When the BCAA group and the diet group were compared for factors that interacted with the treatment arms, the risk for liver cancer was significantly reduced in the BCAA group with a BMI of 25 or higher and with an AFP level of 20ng/mL or higher. Oral supplemental treatment with BCAA may reduce the risk of liver cancer in cirrhotic patients with these specific factors.

Nathan, P. C., V. Jovcevska, et al. (2006). "The prevalence of overweight and obesity in pediatric survivors of cancer." J Pediatr **149**(4): 518-25.

OBJECTIVE: To compare the prevalence of overweight in a cohort of pediatric survivors of cancer with that in the general population. STUDY DESIGN: We reviewed the charts of 441 cancer survivors followed at a Canadian tertiary care pediatric hospital and calculated their most recent body mass index. We compared this cohort with population data generated from the Canadian Community Health Survey. RESULTS: At a median age of 14.7 years (range, 3.4 to 19.5 years) and a median time from diagnosis of 9.7 years (range, 3.4 to 19.2 years), 140 of 441 patients (31.7%) were overweight or obese. Only 12 of the 441 patients (2.7%) were underweight. Males age 6 to 11 years (odds ratio [OR] = 2.29; 95% confidence interval [CI] = 1.36 to 3.86; P < .001) and male survivors of acute lymphoblastic leukemia (OR = 1.55; 95% CI = 1.03 to 2.52; P = .04) were more likely to be overweight than the general population. No other age or diagnostic group had an increased risk of overweight. CONCLUSIONS: The prevalence of overweight was not increased in this cohort compared with the general population. However, almost 1/3 of

these patients are overweight, necessitating a clinical and research focus on preventing and combating overweight in childhood cancer survivors.

Nitori, N., H. Hasegawa, et al. (2009). "Impact of visceral obesity on short-term outcome after laparoscopic surgery for colorectal cancer: a single Japanese center study." Surg Laparosc Endosc Percutan Tech **19**(4): 324-7.

PURPOSE: This prospective study was conducted to clarify the association between the short-term outcome of laparoscopic colorectal surgery and visceral obesity (VO) based on waist circumference (WC). METHODS: WC and body mass index (BMI) were preoperatively measured in 98 consecutive patients with colorectal cancer undergoing laparoscopic surgery between June 2004 and February 2006. VO was defined as both BMI >or=25 kg/m2 and WC >or=85 cm in male patients, or WC >or=90 cm in female patients. RESULTS: The patients were divided into VO (n=21) and non-VO (n=77). Systemic complications were significantly more frequent in VO than in non-VO (19.0% vs. 3.9%, P=0.036), and VO was the only significant independent risk factor (odds ratio 8.1, P=0.018). BMI itself had no impact on outcome. CONCLUSIONS: WC is a potentially useful index for the assessment of surgical risk in laparoscopic colorectal surgery.

Nock, N. L., C. L. Thompson, et al. (2008). "Associations between obesity and changes in adult BMI over time and colon cancer risk." Obesity (Silver Spring) **16**(5): 1099-104.

Obesity has been associated with increased colon cancer risk in epidemiological studies; however, the specific time periods during which obesity may be most relevant as well as how changes in adult body size over time affect colon cancer risk have not been well explored. We evaluated potential associations between BMI in each age decade(20s, 30s, 40s, 50s, and 2 years before study recruitment ("recruitment period")) and in BMI changes over timeand colon cancer risk in a population-based case-control study comprising 438 cases and 491 controls. We found that obese (BMI>or=30.0 kg/m2) compared to normal (BMI>or=18.5 to <25.0 kg/m2) body size at the recruitment period was associated with increased colon cancer risk (odds ratio (OR)=1.54; 95% confidence interval (CI)=1.03-2.31; P=0.03). No associations were observed for obese body size in the other age decades. An increased risk was found for changes in BMI between the 30s decade and the recruitment period of 5-10 kg/m2 (OR=1.54; 95%CI=1.02-2.34; P=0.04) and >10 kg/m2 (OR=2.40; 95% CI=1.23-4.66; P=0.01) (P trend=0.01). Stratification by gender revealed that BMI changes>10 kg/m2 increased risk in women but not men. Similar results were found for BMI changes between the 20s decade and the recruitment period but effect sizes were smaller. Our results provide additional support to obesity's role in colon cancer and suggest large body size increases exceeding 10 kg/m2 may potentially be more important after age 30, particularly among women; however, prospective studies with sex hormone, growth factor, and pro-inflammatory biomarkers are needed to provide insights to the underlying biological mechanism(s).

Olsen, C. M., A. C. Green, et al. (2007). "Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis." Eur J Cancer **43**(4): 690-709.

Obesity is a risk factor for several hormone-related cancers but evidence for an effect on risk of epithelial ovarian cancer remains inconclusive. Many studies evaluating this association have had insufficient statistical power to detect modest effects, particularly for histological subtypes of ovarian cancer. We have therefore assembled the published evidence on obesity and ovarian cancer in a systematic literature review and meta-analysis. We identified eligible studies using Medline and manual review of retrieved references, and included all population-based studies that assessed the association between overweight, body mass index (BMI25-29.9) and obesity (BMI30) and histologically confirmed ovarian cancer. Meta-analysis was restricted to those studies that expressed effect as an odds ratio (OR), risk ratio, or standardised incidence ratio and 95% confidence interval (CI). We identified 28 eligible studies, of which 16 on adult obesity and 9 on obesity in early adulthood were suitable for meta-analysis. Overall, 24 of 28 studies reported a positive association between obesity and ovarian cancer, and in 10 this reached statistical significance. The pooled effect estimate for adult obesity was 1.3 (95%CI1.1-1.5) with a smaller increased risk for overweight (OR1.2;95%CI1.0-1.3). The pooled OR was stronger among case-control studies (OR=1.5) than cohort studies (OR=1.1). Overweight/obesity in early adulthood was also associated with an increased risk of ovarian cancer. There was no evidence that the association varied for the different histological subtypes of ovarian cancer. Ovarian cancer should be added to the list of cancers likely to be related to obesity.

O'Malley, R. L. and S. S. Taneja (2006). "Obesity and prostate cancer." Can J Urol **13 Suppl 2**: 11-7.

The relationship between obesity and prostate cancer is currently a hotly debated topic, but despite the number of publications devoted to the topic, the actual nature of the relationship remains uncertain.

Obesity has been shown to have a direct relationship with the incidence of prostate cancer in a number of studies but an equal number of studies have shown no association. The relationship is further obscured with recent findings that obesity in younger obese men may actually be protective against prostate cancer. Confounding factors include the lack of correlation of body mass index (BMI) as a measure of central obesity and the lack of consistency in timing of BMI measurements, i.e. before or after diagnosis and in young or advanced adulthood. Evidence for increased BMI as a risk factor for prostate cancer is unclear, but less ambiguous is the mounting substantiation that obesity is associated with prognostically worse disease, poorer post-surgical outcomes and increased prostate cancer mortality, irregardless of margin status. From a biologic perspective, one can put forth a number of potential mechanisms by which obesity might promote prostate cancer and/or prostate cancer progression including; low levels of testosterone, increased levels of estrogen, co-existing diabetes or metabolic syndrome, increased circulating insulin-growth factor-one (IGF-1), increased levels of leptin, decreased levels of adiponectin and increased dietary saturated fats. Evidence for the association of these factors with prostate cancer are examined herein. The timing of serum measurements is crucial in elucidating whether these factors have causative influence on prostate cancer or rather are produced by the prostate cancer cells and are better understood as markers of disease. The interaction between obesity and prostate cancer is important to clarify because it will have impact on the prevention, prognostication and treatment of prostate cancer. Future study with careful attention to avoid the methodological pitfalls of the past need be accomplished to bear out the nature of the interaction of obesity and prostate cancer.

Osorio-Costa, F., G. Z. Rocha, et al. (2009). "Epidemiological and molecular mechanisms aspects linking obesity and cancer." Arq Bras Endocrinol Metabol **53**(2): 213-26.

About 25% of cancer cases globally are due to excess weight and a sedentary lifestyle. These results are alarming, as the world knows a pandemic of obesity and, in consequence, insulin resistance. Obesity may increase risk for various cancers by several mechanisms, including increasing sex and metabolic hormones, and inflammation. Here, we present a review of epidemiological and molecular evidences linking obesity and cancer--particularly colorectal, post-menopausal breast, endometrial, pancreatic, high grade prostate, hepatocellular, gallbladder, kidney and esophageal adenocarcinoma. The expected striking increase in the incidence of cancer in the near future related to obesity turns the knowledge of this field of great impact as it is needed to the development of strategies to prevent and treat this disease.

Palma, D., T. Pickles, et al. (2007). "Obesity as a predictor of biochemical recurrence and survival after radiation therapy for prostate cancer." BJU Int **100**(2): 315-9.

OBJECTIVE: Obesity has been demonstrated to predict biochemical progression in men undergoing radical prostatectomy for prostate adenocarcinoma, and is associated with a higher risk of biochemical and clinical relapse after radiation therapy (RT). We evaluated if obesity, determined by body mass index (BMI), is associated with adverse disease characteristics, pre-treatment serum testosterone, biochemical disease free survival (bDFS), disease-specific survival (DSS), or overall survival (OS) in patients undergoing radical external beam radiation therapy for prostate cancer. PATIENTS AND METHODS: A cohort of 706 patients with localized prostate adenocarcinoma treated with RT between 1993 and 2001 were categorized as obese (BMI > or = 30 kg/m(2)), overweight (BMI 25-29.9 kg/m(2)) or normal (BMI < 25 kg/m(2)). The association between BMI, disease characteristics, and progression were evaluated by Chi-square and ANOVA tests, Kaplan-Meier survival analysis, and Cox regression analysis. RESULTS: 195 patients (27.6%) were normal weight, 358 (50.7%) were overweight and 153 (21.7%) were obese. Obese men had lower serum testosterone levels than overweight and normal-weight men (means 12.8, 14.1, and 15.7 nmol/L, respectively; $p < 0.001$). The BMI groups did not differ in Gleason score, pretreatment PSA, or stage. On multivariate analysis, BMI group was predictive of reduced bDFS ($p = 0.02$) and DSS ($p = 0.008$), with a trend toward reduced OS ($p = 0.062$). CONCLUSION: Obesity was associated with lower serum testosterone levels but not with adverse pretreatment pathological features. Obese men have a higher risk of biochemical recurrence and prostate-cancer specific death after RT.

Pan, S. Y., M. DesMeules, et al. (2006). "Obesity, high energy intake, lack of physical activity, and the risk of kidney cancer." Cancer Epidemiol Biomarkers Prev **15**(12): 2453-60.

The authors conducted a population-based case-control study of 810 cases with histologically confirmed incident kidney cancer and 3,106 controls to assess the effect of obesity, energy intake, and recreational physical activity on renal cell and non-renal cell cancer risk in Canada from 1994 to 1997. Compared with normal body mass index (BMI; 18.5 to <25.0 kg/m2), obesity (BMI, >or=30.0 kg/m2) was

associated with multivariable-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of 2.57 (2.02-3.28) for renal cell cancer and 2.79 (1.70-4.60) for non-renal cell cancer. The OR (95% CI) associated with the highest quartiles of calorie intake was 1.30 (1.02-1.66) for renal cell cancer and 1.53 (0.92-2.53) for non-renal cell cancer. Compared with the lowest quartile of total recreational physical activity, the highest quartile of total activity was associated with an OR (95% CI) of 1.00 (0.78-1.28) and 0.79 (0.46-1.36) for the two subtypes. There were no apparent differences between men and women about these associations. The influence of obesity and physical activity on the risk of renal cell and non-renal cell cancer did not change by age, whereas the effect of excess energy intake was stronger among older people. No significant effect modifications of physical activity on BMI among both genders and of energy intake on BMI among men were observed, with a synergic effect of obesity and high energy intake on renal cell cancer risk found among women. This study suggests that obesity and excess energy intake are important etiologic risk factors for renal cell and non-renal cell cancer. The role of physical activity needs further investigation.

Pan, S. Y., K. C. Johnson, et al. (2004). "Association of obesity and cancer risk in Canada." Am J Epidemiol **159**(3): 259-68.

The authors conducted a population-based, case-control study of 21,022 incident cases of 19 types of cancer and 5,039 controls aged 20-76 years during 1994-1997 to examine the association between obesity and the risks of various cancers. Compared with people with a body mass index of less than 25 kg/m(2), obese (body mass index of > or = 30 kg/m(2)) men and women had an increased risk of overall cancer (multivariable adjusted odds ratio = 1.34, 95% confidence interval (CI): 1.22, 1.48), non-Hodgkin's lymphoma (odds ratio = 1.46, 95% CI: 1.24, 1.72), leukemia (odds ratio = 1.61, 95% CI: 1.32, 1.96), multiple myeloma (odds ratio = 2.06, 95% CI: 1.46, 2.89), and cancers of the kidney (odds ratio = 2.74, 95% CI: 2.30, 3.25), colon (odds ratio = 1.93, 95% CI: 1.61, 2.31), rectum (odds ratio = 1.65, 95% CI: 1.36, 2.00), pancreas (odds ratio = 1.51, 95% CI: 1.19, 1.92), breast (in postmenopausal women) (odds ratio = 1.66, 95% CI: 1.33, 2.06), ovary (odds ratio = 1.95, 95% CI: 1.44, 2.64), and prostate (odds ratio = 1.27, 95% CI: 1.09, 1.47). Overall, excess body mass accounted for 7.7% of all cancers in Canada-9.7% in men and 5.9% in women. This study provides further evidence that obesity increases the risk of overall cancer, non-Hodgkin's lymphoma, leukemia, multiple myeloma, and cancers of the kidney, colon, rectum, breast (in postmenopausal women), pancreas, ovary, and prostate.

Pandeya, N., G. M. Williams, et al. (2009). "Do low control response rates always affect the findings? Assessments of smoking and obesity in two Australian case-control studies of cancer." Aust N Z J Public Health **33**(4): 312-9.

OBJECTIVE: Participation rates have been declining in case-control studies, particularly among controls, raising concerns about possible bias. Formal assessments of the effect of low participation on odds ratios (OR) are seldom presented however. We sought to quantify possible bias using multiple imputation techniques. METHODS: Using data from two Australian case-control studies, we estimated the relative risks of oesophageal squamous cell carcinoma (OSCC) and adenocarcinoma (OAC), and serous ovarian cancer (SOC) associated with smoking and body mass index (BMI). We compared ORs observed using self-reported data from participating controls with ORs derived using imputed exposures for non-participating controls. RESULTS: Participating controls were less likely than non-participants to smoke currently. Smoking remained significantly associated with oesophageal cancer even under the most extreme assumption of smoking prevalence among non-participants (OSCC: observed OR 6.54, 4.62-9.28, imputed OR 3.94, 2.83-5.49; OAC: observed OR 2.69, 1.87-3.85 imputed OR 1.58, 1.13-2.22). For SOC however, risks associated with smoking were attenuated to null under plausible smoking assumptions among non-participants. BMI distributions were similar among participating and non-participating controls, and risk estimates were essentially unchanged. CONCLUSION AND IMPLICATIONS: Bias is not an inevitable consequence of low control participation and depends on the association examined. Sensitivity analyses can assist in interpretation of results.

Park, S. M., M. K. Lim, et al. (2007). "Prediagnosis smoking, obesity, insulin resistance, and second primary cancer risk in male cancer survivors: National Health Insurance Corporation Study." J Clin Oncol **25**(30): 4835-43.

PURPOSE: Smoking, obesity, and insulin resistance are well-known risk factors for cancer, yet few epidemiology studies evaluate their role as risk factors for a second primary cancer (SPC). PATIENTS AND METHODS: We identified 14,181 men with a first cancer from the National Health Insurance Corporation Study cohort. We obtained data on fasting glucose level, body mass index (BMI), and smoking history from an enrollment interview (1996). We obtained SPC incidence data for 1996 through

2002 from the Korean Central Cancer Registry. We used the standard Poisson regression model to estimate the age- and multivariate-adjusted relative risk (RR) for SPCs in relation to smoking history, BMI, and insulin resistance before diagnosis. RESULTS: We observed 204 patients with SPC. The overall age-standardized incidence rate of SPC was 603.2 occurrences per 100,000 person-years, which was about 2.3 times higher than that of first cancer in the general male population. Multivariate regression revealed that lung (RR, 3.69; 95% CI, 1.35 to 10.09) and smoking-related (RR, 2.02; 95% CI, 1.02 to 4.03) SPCs were significantly associated with smoking. Obese patients (BMI > or = 25 kg/m2) had significantly elevated RRs for colorectal (RR, 3.45; 95% CI, 1.50 to 7.93) and genitourinary (RR, 3.61; 95% CI, 1.36 to 9.54) SPCs. Patients with a fasting serum glucose concentration > or = 126 mg/dL had a higher RR for hepatopancreatobiliary (RR, 3.33; 95% CI, 1.33 to 8.37) and smoking-related (1.93; 95% CI, 1.01 to 3.68) SPCs. CONCLUSION: Prediagnosis smoking history, obesity, and insulin resistance were risk factors for several SPCs. These findings suggest that more thorough surveillance and screening for SPCs is needed for the cancer survivors with these risk factors.

Park, S. M., M. K. Lim, et al. (2006). "Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study." J Clin Oncol **24**(31): 5017-24.

PURPOSE: Although many studies have demonstrated that smoking, alcohol, obesity, and insulin resistance are risk factors for cancer, the role of those factors on cancer survival has been less studied. PATIENTS AND METHODS: The study participants were 14,578 men with a first cancer derived from a cohort of 901,979 male government employees and teachers who participated in a national health examination program in 1996. We obtained mortality data for those years from the Korean Statistical Office. We used a standard Poisson regression model to estimate the hazard ratio (HR) for survival in relation to smoking, alcohol, obesity, and insulin resistance before diagnosis. RESULTS: Poor survival of all cancer combined (HR, 1.24; 95% CI, 1.16 to 1.33), cancer of the lung (HR, 1.45; 95% CI, 1.15 to 1.82), and cancer of the liver (HR, 1.36; 95% CI, 1.21 to 1.53) were significantly associated with smoking. Compared with the nondrinker, heavy drinkers had worse outcomes for head and neck (HR, 1.85; 95% CI, 1.23 to 2.79) and liver (HR, 1.25; 95% CI, 1.11 to 1.41) cancer, with dose-dependent relationships. Patients with a fasting serum glucose level above 126 mg/dL had a higher mortality rate for stomach (HR, 1.52; 95% CI, 1.25 to 1.84) and lung (HR, 1.48; 95% CI, 1.18 to 1.87) cancer. Higher body mass index was significantly associated with longer survival in head and neck (HR, 0.54; 95% CI, 0.39 to 0.74) and esophagus (HR, 0.44; 95% CI, 0.28 to 0.68) cancer. CONCLUSION: Prediagnosis risk factors for cancer development (smoking, alcohol consumption, obesity, and insulin resistance) had a statistically significant effect on survival among male cancer patients.

Patel, A. V., C. Rodriguez, et al. (2005). "Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort." Cancer Epidemiol Biomarkers Prev **14**(2): 459-66.

BACKGROUND: Obesity and physical activity, in part through their effects on insulin sensitivity, may be modifiable risk factors for pancreatic cancer. METHODS: The authors analyzed data from the American Cancer Society Cancer Prevention Study II Nutrition Cohort to examine the association between measures of adiposity, recreational physical activity, and pancreatic cancer risk. Information on current weight and weight at age 18, location of weight gain, and recreational physical activity were obtained at baseline in 1992 via a self-administered questionnaire for 145,627 men and women who were cancer-free at enrollment. During the 7 years of follow-up, 242 incident pancreatic cancer cases were identified among these participants. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) and to adjust for potential confounding factors including personal history of diabetes and smoking. RESULTS: We observed an increased risk of pancreatic cancer among obese [body mass index (BMI) >/= 30] men and women compared with men and women of normal BMI [<25; RR, 2.08; 95% confidence interval (95% CI), 1.48-2.93, P(trend) = 0.0001]. After adjustment for between BMI, risk of pancreatic cancer was independently increased among men and women who reported a tendency for central weight gain compared with men and women reporting a tendency for peripheral weight gain (RR, 1.45; 95% CI, 1.02-2.07). We observed no difference in pancreatic cancer incidence rates between men and women who were most active (>31.5 metabolic equivalent hours per week) at baseline compared with men and women who reported no recreational physical activity (RR, 1.20; 95% CI, 0.63-2.27). CONCLUSION: This study, along with several recent studies, supports the hypothesis that obesity and central adiposity are associated with pancreatic cancer risk.

Pavelka, J. C., I. Ben-Shachar, et al. (2004). "Morbid obesity and endometrial cancer: surgical, clinical, and

pathologic outcomes in surgically managed patients." Gynecol Oncol **95**(3): 588-92.

OBJECTIVE: To evaluate surgical, clinical, and pathologic outcomes of patients with endometrial cancer managed with primary surgery when stratified by body mass index (BMI). METHODS: A review of 356 consecutive patients undergoing primary surgical management of endometrial carcinoma by a single gynecologic oncology service from 1997 to 2003 was undertaken. Patients were divided into three groups based on preoperative BMI. Data regarding surgical and pathologic outcomes were compared. RESULTS: Twenty-two percent of patients had a BMI >40, 38% were 30-40, and 40% were <30. Overall, 90% underwent some surgical staging, including 93%, 92%, and 81% of those with a BMI <30, 30-40, and >40, respectively. In fully staged patients, a median 23 lymph nodes were removed in all groups, without a significant difference in the number of aortic nodes recovered between the heaviest and lightest groups. Aortic lymphadenectomy was performed in 48% patients with BMI >40 compared with 74% of patients with BMI <30. Intraoperative and postoperative complications were rare and similar between groups. Patients with BMI >40 were more commonly diagnosed with grade 1 tumor than patients with BMI <30. Rates of nodal metastasis were similar between groups and occurred in 11% of patients overall. In those with a BMI >40, extrauterine disease was encountered in 12% of patients. CONCLUSIONS: While surgical staging of morbidly obese patients is difficult, adequate lymphadenectomy can be performed safely; although aortic nodes are less commonly resected in this population. Staging remains important in obese women, as the risk of extrauterine disease, including lymph node metastasis, is similar to that in women with ideal body weight.

Pavelka, J. C., R. S. Brown, et al. (2006). "Effect of obesity on survival in epithelial ovarian cancer." Cancer **107**(7): 1520-4.

BACKGROUND: Epidemiologic studies suggest that obese women are more likely to die of ovarian cancer than those of ideal body weight, but it is not known whether increased incidence, comorbidities common to obese women, or altered tumor biology is responsible for this difference. The current study attempted to determine the influence of excess body weight on ovarian cancer survival, disease progression, and clinicopathologic factors. METHODS: The records of patients undergoing surgery for epithelial ovarian cancer at Cedars Sinai Medical Center between January 1, 1996 and June 30, 2003 were reviewed for height, weight, age, comorbidities, and treatment-specific details. Statistical analyses included the Fisher exact test, Kaplan-Meier survival, and Cox regression analyses. RESULTS: In all, 216 patients were identified. Eight percent were underweight (body mass index [BMI] < 18.5), 50% were ideal body weight (18.5 </= BMI < 25), 25% were overweight (25 </= BMI < 30), and 16% were obese (BMI >/= 30). Age, comorbidities including coronary artery disease and venous thromboembolism, and rates of optimal surgical cytoreduction were similar among BMI strata. Diabetes and hypertension were more common in obese women. Ten (29%) of the obese patients had International Federation of Gynecology and Obstetrics (FIGO) Stage I disease, compared with 19 (10%) of the patients with BMI < 30 (P = .01). In a subcohort of 149 patients with Stage III or IV disease, a significant trend was identified favoring increased BMI as an independent negative factor for disease-free (P = .02) and overall (P = .02) survival. CONCLUSIONS: Obese patients were more likely to have disease limited to the ovaries. For patients with advanced stage disease, obesity was independently associated with both shorter time to recurrence and shorter overall survival. These findings suggest an effect of excess body weight on tumor biology, and studies are under way to elucidate the molecular and hormonal mechanisms underlying these clinical observations.

Pendas, A. M., A. R. Folgueras, et al. (2004). "Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice." Mol Cell Biol **24**(12): 5304-13.

Matrix metalloproteinase 19 (MMP-19) is a member of the MMP family of endopeptidases that, in contrast to most MMPs, is widely expressed in human tissues under normal quiescent conditions. MMP-19 has been found to be associated with ovulation and angiogenic processes and is deregulated in diverse pathological conditions such as rheumatoid arthritis and cancer. To gain further insights into the in vivo functions of this protease, we have generated mutant mice deficient in Mmp19. These mice are viable and fertile and do not display any obvious abnormalities. However, Mmp19-null mice develop a diet-induced obesity due to adipocyte hypertrophy and exhibit decreased susceptibility to skin tumors induced by chemical carcinogens. Based on these results, we suggest that this enzyme plays an in vivo role in some of the tissue remodeling events associated with adipogenesis, as well as in pathological processes such as tumor progression.

Percik, R. and M. Stumvoll (2009). "Obesity and cancer." Exp Clin Endocrinol Diabetes **117**(10): 563-6.

Epidemiological studies have suggested that obesity is associated with increased risk of several

cancer types including colon, esophagus, breast (in postmenopausal women), endometrium, kidney, liver, gallbladder and pancreas. Suggested mechanisms include increased intake of potentially carcinogenic food ingredients along with excessive amount of calories, loss of cancer protective effects due to reduced physical activity, carcinogenic factors released from increased adipose tissue mass and "secondary" associations via "precursor" condition such as gallstones. The increased cancer risk in patients with obesity is a neglected topic which deserves more scientific attention. Because of its extreme chronicity and co-association with numerous other conditions true causality and underlying mechanisms are difficult to study. Nevertheless, a large body of literature is already available which provides concepts for future research.

Pezzilli, R., A. M. Morselli-Labate, et al. (2005). "Obesity and the risk of pancreatic cancer: an italian multicenter study." Pancreas **31**(3): 221-4.

OBJECTIVE: The purpose of this work was to determine whether obesity is a risk factor for pancreatic cancer. METHODS: We studied 400 patients with this tumor and 400 controls matched for sex and age from various Italian cities. We used a standardized questionnaire that was compiled at personal interview, with particular attention to body weight at the time of the interview, and for those with the tumor, their weight before onset of the disease. Body mass index (BMI) was calculated as the patient's weight in kilograms divided by their height in meters squared. RESULTS: The risk of pancreatic cancer adjusted for smoking was 5-fold higher ($P < 0.001$) in patients with a BMI less than 23 kg/m2 after diagnosis compared with patients with a BMI ranging from 23 to 29.9 kg/m2, whereas the risk in patients with BMI of at least 30 kg/m2 was not significant ($P = 0.689$). Taking into account BMI before diagnosis, smoking was confirmed as a significant risk factor (odds ratio = 1.68; $P = 0.001$) for pancreatic cancer, whereas no significant relationship was found between BMI classes and the risk of pancreatic cancer ($P = 0.984$). CONCLUSIONS: These findings indicate that obesity is not a risk factor for pancreatic cancer.

Pichard, C., G. Plu-Bureau, et al. (2008). "Insulin resistance, obesity and breast cancer risk." Maturitas **60**(1): 19-30.

Breast cancer (BC) is one of the most important problems of public health. Among the avoidable risk factors during a woman's life, overweight and obesity are very important ones. Furthermore they are increasing worldwide. The risk of breast cancer is traditionally linked to obesity in postmenopausal women; conversely, it is neutral or even protective in premenopausal women. Since the initiator and promoter factors for BC act over a long time, it seems unlikely that the menopausal transition may have too big an impact on the role of obesity in the magnitude of the risk. We reviewed the literature in an attempt to understand this paradox, with particular attention to the body fat distribution and its impact on insulin resistance. The association of insulin resistance and obesity with BC risk are biologically plausible and consistent. Estradiol (E2) and IGFs act as mitogens in breast cancer cells. They act together and reciprocally. However the clinical and biological methods to assess the impact of insulin resistance are not always accurate. Furthermore insulin resistance is far from being a constant feature in obesity, particularly in premenopausal women; this complicates the analysis and explains the discrepancies in large prospective trials. The most consistent clinical feature to assess risk across epidemiological studies seems to be weight gain during lifetime. Loss of weight is associated with a lower risk for postmenopausal BC compared with weight maintenance. This observation should be an encouragement for women since loss of weight may be an effective strategy for breast cancer risk reduction.

Pierce, J. P., M. L. Stefanick, et al. (2007). "Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity." J Clin Oncol **25**(17): 2345-51.

PURPOSE: Single-variable analyses have associated physical activity, diet, and obesity with survival after breast cancer. This report investigates interactions among these variables. PATIENTS AND METHODS: A prospective study was performed of 1,490 women diagnosed and treated for early-stage breast cancer between 1991 and 2000. Enrollment was an average of 2 years postdiagnosis. Only seven women were lost to follow-up through December 2005. RESULTS: In univariate analysis, reduced mortality was weakly associated with higher vegetable-fruit consumption, increased physical activity, and a body mass index that was neither low weight nor obese. In a multivariate Cox model, only the combination of consuming five or more daily servings of vegetables-fruits, and accumulating 540+ metabolic equivalent tasks-min/wk (equivalent to walking 30 minutes 6 d/wk), was associated with a significant survival advantage (hazard ratio, 0.56; 95% CI, 0.31 to 0.98). The approximate 50% reduction in risk associated with these healthy lifestyle behaviors was observed in both obese and nonobese women, although fewer obese women were physically active with a healthy dietary pattern (16% v 30%). Among those who adhered to this healthy lifestyle, there was

no apparent effect of obesity on survival. The effect was stronger in women who had hormone receptor-positive cancers. CONCLUSION: A minority of breast cancer survivors follow a healthy lifestyle that includes both recommended intakes of vegetables-fruits and moderate levels of physical activity. The strong protective effect observed suggests a need for additional investigation of the effect of the combined influence of diet and physical activity on breast cancer survival.

Polesel, J., D. Serraino, et al. (2009). "Cigarette smoking and endometrial cancer risk: the modifying effect of obesity." Eur J Cancer Prev **18**(6): 476-81.

The objective of this study was to evaluate the association between cigarette smoking and endometrial cancer risk by investigating potential modifying effects of menopausal status, obesity, and exogenous hormones. We pooled data from three case-control studies with the same study design conducted in Italy and Switzerland between 1982 and 2006. Overall, 1446 incident endometrial cancers and 4076 hospital controls were enrolled. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models, conditioned on study and centre, and adjusted for age, period of interview, age at menarche, parity, and body mass index. In comparison with never smokers, current smokers showed reduced endometrial cancer risk (OR: 0.80; 95% CI: 0.66-0.96), with a 28% decrease in risk for smoking >/= 20 cigarettes/day. The association did not vary according to menopausal status, oral contraceptive use, or hormone replacement therapy. However, heterogeneity emerged according to body mass index among postmenopausal women, with obese women showing the greatest risk reduction for current smoking (OR: 0.47; 95% CI: 0.27-0.81). In postmenopausal women, obesity turned out to be an important modifier of the association between cigarette smoking and the risk of endometrial cancer. This finding calls for caution in interpreting the favorable effects of cigarette smoking, considering the toxic and carcinogenic effects of tobacco.

Porter, G. A., K. M. Inglis, et al. (2006). "Effect of obesity on presentation of breast cancer." Ann Surg Oncol **13**(3): 327-32.

BACKGROUND: Obesity has been shown to be associated with reduced survival in patients with invasive breast cancer (IBC), although the mechanisms for this finding are unclear. The objective of this study was to examine the effect of obesity on the presentation and pathologic staging of IBC. METHODS: From February 15, 2002, to February 15, 2004, all patients undergoing surgery for primary IBC at two institutions were enrolled in a prospective cohort study. National Institutes of Health criteria were used to categorize patients: normal or underweight (NW; body mass index <25 kg/m(2)), overweight (OW; body mass index 25-29.9 kg/m(2)), and obese or severely obese (OB; body mass index > or =30 kg/m(2)). Presentation and pathologic factors were then compared among groups. RESULTS: The study cohort consisted of 519 patients; 166 (32%) were NW, 177 (34%) were OW, and 176 (34%) were OB. OW (46%) and OB (39%) patients were more likely to be diagnosed with IBC via screening mammography compared with NW (31%) patients (P = .01), although no differences were found between groups with respect to previous use of screening mammography. Aggressive pathologic features, including lymph node metastases, advanced tumor-node-metastasis stage, and grade were found more commonly among OB patients. CONCLUSIONS: OW and OB patients were more likely to receive a diagnosis via screening mammography, thus suggesting that mammography may play a more important role in OW and OB patients. Despite this, OB patients presented with larger, more advanced tumors; this may help to explain obesity-associated survival differences in IBC patients. This is important information given the prevalence of obesity in North America.

Porter, M. P. and J. L. Stanford (2005). "Obesity and the risk of prostate cancer." Prostate **62**(4): 316-21.

BACKGROUND: Prostate cancer and obesity are common diseases among men in the United States. A link between obesity and prostate cancer risk has potential implications in understanding prostate cancer genesis and screening strategies. METHODS: We conducted a population-based case-control study examining the relationship between body mass index (BMI) and prostate cancer risk. Incident cases of prostate cancer were identified in King County, Washington, using the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Interviews were completed with 753 men ages 40-64 that were diagnosed with prostate cancer between 1993 and 1996. Interviews were also completed with 703 age-matched controls identified from the same population through random digit dialing. Logistic regression was performed to generate odds ratios and 95% confidence intervals while controlling for age, race, education, smoking, family history, prostate cancer screening, dietary fat, and caloric intake. RESULTS: BMI was inversely related to prostate cancer risk (P for trend=0.04). Men with a BMI > 29 kg/m2 had the lowest risk of prostate cancer (odds ratio=0.77; 95% confidence interval=0.56, 1.06). Weight was also inversely associated with prostate cancer risk (P for trend=0.03), however,

height was not. CONCLUSIONS: The results of this study support the hypothesis that obesity is inversely associated with prostate cancer risk in middle-aged men.

Portugal, R. D. (2005). "Obesity and dose individualization in cancer chemotherapy: the role of body surface area and body mass index." Med Hypotheses **65**(4): 748-51.

It is generally accepted that anti-neoplastic chemotherapy dose should be calculated according to body surface area (BSA). This approach does not account for the presence of obesity. Hence, patients with the same BSA will receive the same chemotherapy dose, regardless the presence of obesity. Since this may cause of toxicity in some obese patients, practice of limit BSA is usual. Currently, the body mass index (BMI) is largely used as a marker of obesity and both BSA and BMI include only height (h) and weight(w) in their formula. We put forward the hypothesis that the BMI should also be taken in account for calculation of chemotherapy dose for obese patients (BMI > 30 kg/m2). In this article, we present a correction to BSA (CBSA) based on the BMI to be tested in obese patients. Our main result is given by the equationCBSA=K(alpha1h(alpha2+2kappa)w(alpha3-kappa)),whereand kappa, alpha1, alpha2, alpha3 are constants. We show examples of how to calculate the CBSA. This simple strategy may limit drug exposition and maintain greater efficacy than a fixed limitation of BSA.

Prasad, N. K., M. Tandon, et al. (2008). "High expression of obesity-linked phosphatase SHIP2 in invasive breast cancer correlates with reduced disease-free survival." Tumour Biol **29**(5): 330-41.

SH2-containing 5'-inositol phosphatase (SHIP2) is a known regulator of insulin function. Genetic knockout of SHIP2 in mice causes mild insulin hypersensitivity and prevents high-fat-diet-induced obesity. SHIP2 also regulates actin remodeling and epidermal growth factor receptor (EGFR) turnover and supports breast cancer; and metastatic growth. To determine the clinical significance of SHIP2 expression in breast cancer and its relationship to relevant oncogenic molecules, SHIP2 expression was determined immunohistochemically in 285 primary breast cancers; 140 ductal carcinomas in situ (DCIS) and 145 invasive carcinomas. Forty-five percent of the specimens showed high SHIP2 levels in cancer cells while only 15% of adjacent normal cells expressed high SHIP2 levels ($p < 0.0001$). In cancer cells, the risk of SHIP2 overexpression is elevated (a) in women aged < or =50 years (relative risk, RR = 4.13; 95% confidence interval, CI, 2.5-6.9) compared to women aged >50 years (RR = 2.37; 95% CI 1.6-3.5; $p = 0.0003$), and (b) in invasive carcinomas (RR = 3.52; 95% CI 2.3-5.5) compared with DCIS (RR = 2.22; 95% CI 1.5-3.5; $p = 0.0009$). Patients with higher SHIP2 levels in invasive carcinomas had significantly reduced disease-free ($p = 0.0025$) and overall survival periods ($p = 0.0228$). In invasive carcinomas, SHIP2 correlated with estrogen receptor absence ($p = 0.003$) and EGFR presence ($p = 0.0147$). In conclusion, SHIP2 is an important biomarker for breast cancer.

Presti, J. C., Jr. (2005). "Obesity and prostate cancer." Curr Opin Urol **15**(1): 13-6.

PURPOSE OF REVIEW: This review provides an update on research into the association between obesity and prostate cancer. RECENT FINDINGS: The US Health Professional Study reported an inverse relationship between risk for prostate cancer and obesity in men under the age of 60 or in those with a positive family history for prostate cancer. Others found no association between obesity and risk for the disease. Regarding detection, obesity does not impact upon measurement of prostate specific antigen as a method of detecting prostate cancer; however, in a referral population there was an inverse association between detection rate and obesity. In three radical prostatectomy series, obesity was associated with worse pathological features and higher biochemical relapse rates. Possible mechanisms for the association between obesity and prostate cancer include the impact on serum testosterone, leptin, insulin-like growth factor I, and interleukin-6 levels. SUMMARY: A growing body of evidence suggests that obesity may impact upon risk, detection and outcome with regard to prostate cancer.

Pruthi, R. S., K. Swords, et al. (2009). "The impact of obesity on the diagnosis of prostate cancer using a modern extended biopsy scheme." J Urol **181**(2): 574-7; discussion 578.

PURPOSE: The effect of obesity on prostate cancer detection and behavior remains uncertain. We evaluated the impact of obesity, as measured by body mass index, in a case series of 500 consecutive men who underwent a modern 10 to 12 core biopsy approach. MATERIALS AND METHODS: We retrospectively reviewed the records of a consecutive series of 500 men who underwent transrectal ultrasound guided prostate biopsy using a 10 to 12 core biopsy scheme. Variables, including patient age, prostate specific antigen, prostate specific antigen density, digital rectal examination findings, transrectal ultrasound prostate volume and biopsy outcome, including grade, were compared to anthropometric measures, including body mass index. RESULTS: Of

the men 26% were obese according to body mass index (greater than 30 kg/m(2)). A total of 223 men (45%) had a positive biopsy. Obese men were younger (62.0 vs 63.8 years), had a larger prostate (57.7 vs 47.8 cc) and were less likely to have any abnormality on digital rectal examination (19.6% vs 30.8%). Obese men were also less likely to have a positive biopsy based on chi-square analysis (38.8% vs 46.2%). On statistical modeling for the OR in nonobese vs obese men there was a trend toward lower detection based on crude and age adjusted ORs but not on multivariate OR controlling for age, prostate specific antigen and prostate volume. In addition, when examining for high grade disease (Gleason 4 + 3 or greater), no differences were observed on OR modeling. In men with negative biopsies those who were obese vs nonobese had a larger prostate volume and trended toward a higher median prostate specific antigen and age. These differences and trends were not observed in obese men with positive biopsies. CONCLUSIONS: Of men undergoing prostate biopsy using a modern extended biopsy scheme obese men were younger, had a larger prostate and were less likely to have abnormal digital rectal examinations. Although some trends toward a lower detection rate in obese men were observed, such differences were not observed on multivariate analysis, nor were any differences observed in the incidence of higher grade tumors, thus questioning the effect of obesity on prostate cancer detection and behavior in our cases series.

Qian, Y. and J. G. Fan (2005). "Obesity, fatty liver and liver cancer." Hepatobiliary Pancreat Dis Int **4**(2): 173-7.

BACKGROUND: It has been suggested that obesity and fatty liver may be associated with the morbidity and mortality of liver cancer, and the early diagnosis and effective treatment of fatty liver coupled with liver cancer are supposed to improve the prognosis of obese patients. This review was attempted to understand the relationship between obesity, fatty liver and liver cancer. DATA RESOURCES: An English-language literature search using PUBMED (1990-2004) on obesity, fatty liver and liver cancer and other related articles in Chinese. RESULTS: Obesity is associated with the risk of death from all cancers and from cancers at individual sites including liver cancer, and it is an independent risk factor for hepatocellular carcinoma (HCC) in patients with alcoholic cirrhosis and cryptogenic cirrhosis. Because nonalcoholic steatohepatitis has been implicated as a major cause of cryptogenic cirrhosis, the development of HCC may be part of progressive nature of this condition. CONCLUSIONS: Obesity is associated with the incidence and mortality of HCC. More frequent surveillance for HCC may be warranted in obese patients with fatty liver and attempts should be made to interrupt the progression from simple hepatic steatosis to steatohepatitis, cirrhosis and ultimately HCC.

Rapp, K., J. Schroeder, et al. (2005). "Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria." Br J Cancer **93**(9): 1062-7.

We investigated the relation of overweight and obesity with cancer in a population-based cohort of more than 145 000 Austrian adults over an average of 9.9 years. Incident cancers (n=6241) were identified through the state cancer registry. Using Cox proportional-hazards models adjusted for smoking and occupation, increases in relative body weight in men were associated with colon cancer (hazard rate (HR) ratio 2.48; 95% confidence interval (CI): 1.15, 5.39 for body mass index (BMI) > or =35 kg m(-2)) and pancreatic cancer (HR 2.34, 95% CI: 1.17, 4.66 for BMI>30 kg m(-2)) compared to participants with normal weight (BMI 18.5-24.9 kg m(-2)). In women, there was a weak positive association between increasing BMI and all cancers combined, and strong associations with non-Hodgkin's lymphomas (HR 2.86, 95% CI: 1.49, 5.49 for BMI> or =30 kg m(-2)) and cancers of the uterine corpus (HR 3.93, 95% CI: 2.35, 6.56 for BMI> or =35 kg m(-2)). Incidence of breast cancer was positively associated with high BMI only after age 65 years. These findings provide further evidence that overweight is associated with the incidence of several types of cancer.

Reilly, J. J. (2009). "Obesity during and after Treatment for Childhood Cancer." Endocr Dev **15**: 40-58.

Obesity is a common complication of treatment for some childhood cancers, particularly acute lymphoblastic leukaemia (ALL) and craniopharyngioma. Evidence-based guidance is available for the general paediatric population on the diagnosis, aetiology, consequences, prevention and treatment of obesity, and this should be considered as the starting point for considering such issues in patients with malignancy. In ALL, a high proportion of patients show rapid and excessive weight gain soon after diagnosis which originates partly in lifestyle, in particular via markedly reduced levels of physical activity. Good evidence on risk factors for obesity in ALL is available, and the natural history and aetiology of obesity in ALL are now fairly well understood, while for craniopharyngioma the natural history is reasonably well understood. Understanding the natural history and aetiology of obesity should facilitate preventive interventions in the future. Evidence on preventive interventions is required urgently, and it

should focus on promotion of a reduction in sedentary behaviour and increases in physical activity. Such interventions should be helpful in obesity prevention, but could also have a wide range of additional benefits in the prevention or amelioration of other late effects of treatment.

Renehan, A. G., J. Frystyk, et al. (2006). "Obesity and cancer risk: the role of the insulin-IGF axis." Trends Endocrinol Metab **17**(8): 328-36.

Accumulating epidemiological evidence shows that being either overweight or obese, in other words having excess body weight (EBW), is associated with an increased risk of several, common, adult cancers. The molecular mechanisms that underlie these associations are not understood fully, but insulin resistance is likely to be important. The insulin-cancer hypothesis postulates that chronic hyperinsulinemia is associated with decreased concentrations of insulin-like growth factor binding protein1 (IGFBP-1) and IGFBP-2, leading to increased availability of IGF-I and concomitant changes in the cellular environment that favor tumor formation. However, the situation is likely to be more complex because hyperinsulinemia is also associated with alterations in related molecular systems (e.g. sex steroids and adipocytokines). As the prevalence of EBW increases to epidemic proportions, untangling the links between EBW and the insulin-IGF axis and its wider molecular interactions will become increasingly important in the development of preventive strategies.

Renehan, A. G., D. L. Roberts, et al. (2008). "Obesity and cancer: pathophysiological and biological mechanisms." Arch Physiol Biochem **114**(1): 71-83.

Excess body weight (overweight and obesity) is characterized by chronic hyperinsulinaemia and insulin resistance, and is implicated both in cancer risk and cancer mortality. The list of cancers at increased risk of development in an "obesogenic" environment include common adult cancers such as endometrium, post-menopausal breast, colon and kidney, but also less common malignancies such as leukaemia, multiple myeloma, and non-Hodgkin's lymphoma. The pathophysiological and biological mechanisms underpinning these associations are only starting to be understood. Insulin resistance is at the heart of many, but there are several other candidate systems including insulin-like growth factors, sex steroids, adipokines, obesity-related inflammatory markers, the nuclear factor kappa beta (NF-kappa B) system and oxidative stresses. With such as diversity of obesity-related cancers, it is unlikely that there is a "one system fits all" mechanism. While public health strategies to curb the spread of the obesity epidemic appear ineffective, there is a need to better understand the processes linking obesity and cancer as a pre-requisite to the development of new approaches to the prevention and treatment of obesity-related cancers.

Ribeiro, R., C. Lopes, et al. (2006). "The link between obesity and prostate cancer: the leptin pathway and therapeutic perspectives." Prostate Cancer Prostatic Dis **9**(1): 19-24.

Obesity-associated prostate cancer (PCa) remains controversial, although most studies rely on body mass index evaluation, which is an indirect measure of fatness. Studies using body fat measurement and disease stratification according to PCa stage found stronger associations between obesity and PCa. Leptin is a pleiotrophic hormone mainly synthesized by adipocytes that acts in peripheral organs such as the prostate. This article reviews obesity-associated leptin's pathophysiological role in PCa progression. PCa development results from some known risk factors. Currently, there is enough evidence suggesting that leptin is an additional factor involved in advanced PCa occurrence, and obesity association with high-grade disease. Life-long exposure to genetic and/or environmental susceptibility factors that predispose to obesity and higher leptin levels may increase the risk for advanced PCa.

Robinson, W. R., J. Stevens, et al. (2005). "Obesity before age 30 years and risk of advanced prostate cancer." Am J Epidemiol **161**(12): 1107-14.

Adult obesity has shown little association with prostate cancer risk, but obesity at younger ages may be associated with reduced risk. In 1997-2000, the relation between obesity before age 30 years and incident advanced prostate cancer was investigated in a population-based case-control study of African-American and White men (568 cases, 544 controls) in California. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusted for age, race, family history of prostate cancer, and saturated fat intake. Measures of obesity for age 10 years tended to be inversely associated with prostate cancer (odds ratio (OR) = 0.79, 95% confidence interval (CI): 0.46, 1.38 for selecting the "obese" pictogram and OR = 0.76, 95% CI: 0.52, 1.11 for reporting being heavier than peers). The decreased risk was more pronounced at ages 20-29 years (OR = 0.53, 95% CI: 0.28, 1.00 for the "obese" drawing, OR = 0.59, 95% CI: 0.40, 0.88 for being heavier than peers, and OR = 0.40, 95% CI: 0.20, 0.81 for body mass index > or =30 kg/m(2)). In addition, both "obese" and small waist size at ages 20-29 years showed inverse trends. This research implicating early-life body size in prostate cancer development

helps to elucidate causal mechanisms, such as altered sex hormone profiles during critical developmental periods, potentially involved in development of the disease.

Rogers, L. Q., K. S. Courneya, et al. (2008). "Lifestyle behaviors, obesity, and perceived health among men with and without a diagnosis of prostate cancer: a population-based, cross-sectional study." BMC Public Health **8**: 23.

BACKGROUND: A better understanding of how prostate cancer survivors differ from men without prostate cancer and whether these potential differences vary across demographic subgroups will help to focus and prioritize future public health interventions for improving the health and well-being of prostate cancer survivors. Therefore, our study aims were to compare lifestyle behaviors, body mass index (BMI), and perceived health in men with and without a diagnosis of prostate cancer in a national, population-based sample and to explore whether these comparisons differ for demographic subgroups. METHODS: In a cross-sectional study, men aged > or = 40 were identified from the Behavioral Risk Factor Surveillance System (BRFSS) 2002 data (n = 63,662). Respondents reporting history of prostate cancer (n = 2,524) were compared with non prostate cancer controls (n = 61,138) with regard to daily fruit and vegetable servings (FVPD), smoking, alcohol, sedentary behavior, BMI, and perceived health. Multivariable logistic regression calculated adjusted odds ratios (OR) and 95% confidence intervals (CI) for the entire sample and for age, race, education, and urbanicity subgroups. RESULTS: Men with prostate cancer did not differ from men without prostate cancer with regard to smoking, alcohol, sedentary behavior, and obesity but were more likely to consume >/= 5 FVPD (OR, 95% CI: 1.30, 1.09-1.56) and report poor or fair health (OR, 95% CI: 1.62, 1.33-1.97). Subgroup analyses demonstrated attenuation of the higher likelihood of > or = 5 FVPD among prostate cancer survivors in rural respondents (OR, 95% CI: 0.98, 0.72-1.33). Poorer perceived health was greatest if < or = 65 years of age (OR, 95% CI: 2.54, 1.79-3.60) and nonsignificant if black (OR, 95% CI: 1.41, 0.70-2.82). Smoking and alcohol which were not significant for the sample as a whole, demonstrated significant associations in certain subgroups. CONCLUSION: Although efforts to enhance perceived health and healthy lifestyle behaviors among prostate cancer survivors are warranted, demographic subgroups such as prostate cancer survivors < or = 65 and rural populations may require more aggressive interventions.

Romieu, I. and M. Lajous (2009). "The role of obesity, physical activity and dietary factors on the risk for breast cancer: Mexican experience." Salud Publica Mex **51 Suppl 2**: s172-80.

We provide an overview of the role of adiposity, physical activity and diet in the risk for breast cancer in Mexican women. Lack of physical activity, diets high in carbohydrates and in glycemic load and low intake of folate and vitamin B12 have been shown to increase the risk of breast cancer in Mexican women, in particular postmenopausal breast cancer. Other dietary factors that may begin to play a more relevant role in breast cancer incidence in Mexico are alcohol intake and vitamin D status. Recommendations to maintain a healthy weight, practice moderate physical activity, decrease intake of rapidly absorbed carbohydrates and increase consumption of fruits and vegetables could have an important impact on the epidemic of breast cancer in Mexico.

Rose, D. P., D. Komninou, et al. (2004). "Obesity, adipocytokines, and insulin resistance in breast cancer." Obes Rev **5**(3): 153-65.

The adipocytokines are biologically active polypeptides that are produced either exclusively or substantially by the adipocytes, and act by endocrine, paracrine, and autocrine mechanisms. Most have been associated with obesity, hyperinsulinaemia, type 2 diabetes, and chronic vascular disease; in addition, six adipocytokines--vascular endothelial growth factor, hepatocyte growth factor, leptin, tumour necrosis factor-alpha, heparin-binding epidermal growth factor-like growth factor, and interleukin-6--promote angiogenesis while one, adiponectin, is inhibitory. Obesity and insulin resistance have both been identified as risk factors for breast cancer and are associated with late-stage disease and poor prognosis. Angiogenesis is essential for breast cancer development and progression, and so it is plausible that obesity-related increases in adipocytokine production and a reduction in adiponectin may adversely affect breast cancer outcome by their angiogenesis-related activities. There is also experimental evidence that some adipocytokines can act directly on breast cancer cells to stimulate their proliferation and invasive capacity. Thus, adipocytokines may provide a biological mechanism by which obesity and insulin resistance are causally associated with breast cancer risk and poor prognosis. Both experimental and clinical studies are needed to develop this concept, and particularly in oestrogen-independent breast cancers where preventive and therapeutic options are limited.

Rose, D. P. and L. Vona-Davis (2009). "Influence of obesity on breast cancer receptor status and prognosis." Expert Rev Anticancer Ther **9**(8): 1091-101.

Pre-existing obesity and postoperative weight gain are related to a poor prognosis in breast cancer regardless of menopausal status. Delayed diagnosis may be one cause, but of more biological significance, especially in younger women, is the association of adiposity with estrogen receptor-negative tumors with a propensity for distant metastasis. After the menopause, the major mechanism for the relationship is the elevated estrogen synthesis by adipose tissue; these hormone-dependent tumors are estrogen receptor-positive. Insulin and some adipokines also stimulate breast cancer growth and metastasis, both directly and most probably by enhanced angiogenesis. Weight control is important, not only to target breast cancer progression, but also to reduce the risk of nonbreast cancer mortality risk associated with excess adiposity.

Rosen, A. B. and E. C. Schneider (2004). "Colorectal cancer screening disparities related to obesity and gender." J Gen Intern Med **19**(4): 332-8.

BACKGROUND: Obesity is associated with a higher incidence of colorectal cancer and increased colorectal cancer mortality. Obese women are less likely to undergo breast and cervical cancer screening than nonobese women. It is not known whether obesity is associated with a lower likelihood of colorectal cancer screening. OBJECTIVE: To evaluate whether there is an association between body mass index (BMI) and rates of colorectal cancer screening. To examine whether BMI-related disparities in colorectal cancer screening differ between men and women. DESIGN AND SETTING: The Behavioral Risk Factor Surveillance System, a cross-sectional random-digit telephone survey of noninstitutionalized adults conducted by the Centers for Disease Control and Prevention and state health departments in the 50 states and Washington, DC in 1999. PATIENTS: Survey respondents (N= 52886) between 51 and 80 years of age representing 64563332 U.S. adults eligible for colorectal cancer screening. INTERVENTIONS AND MEASUREMENTS: Adjusted rates of self-reported colorectal cancer screening with fecal occult blood testing within the past year or endoscopic screening (sigmoidoscopy or colonoscopy) within the past 5 years. RESULTS: The colorectal cancer screening rate was 43.8% overall. The rate of screening by FOBT within the last year or endoscopic screening within the past 5 years was 39.5% for the morbidly obese group, 45.0% for the obese group, 44.3% for the overweight group, and 43.5% for the normal weight group. The difference in screening rates was entirely attributable to differences in BMI among women. After statistical adjustment for potential confounders, morbidly obese women were less likely than normal weight women to be screened (adjusted rate difference, -5.6%; 95% confidence interval, -8.5 to -2.6). Screening rates among normal weight, overweight, and obese women, and among men in different weight groups did not differ significantly. CONCLUSIONS: Colorectal cancer screening rates among age-eligible persons in the U.S. are disturbingly low. Morbidly obese women, who are at higher risk than others to develop and to die from colorectal cancer, are less likely to be screened. Efforts to increase colorectal cancer screening are needed for all age-eligible groups, but should also include targeted screening of morbidly obese women since they could reap substantial clinical benefits from screening.

Rosenberg, L., K. Czene, et al. (2009). "Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy?" Br J Cancer **100**(9): 1486-91.

High body mass index (BMI) and use of hormone replacement therapy (HRT) increase the risk of postmenopausal breast cancer. It has been shown that BMI modifies the effect of HRT, as its influence is most pronounced in lean women. We investigated the influence of BMI and HRT on prognosis in 2640 postmenopausal women diagnosed with breast cancer in Sweden in 1993-1995, taking into account HRT and mammography before diagnosis. Logistic and Cox regression were used. In non-users of HRT, obese women (BMI >30) compared with normal weight women (BMI <25) had a similar prognosis (hazard ratio (HR) 1.1, 95% confidence interval (CI) 0.8-1.6), despite larger tumours found in obese women. Obese HRT users had less favourable tumour characteristics and poorer prognosis compared with normal weight women (HR 3.7, 95% CI 1.9-7.2). The influence of BMI on breast cancer prognosis was similar whether diagnosed by mammographic screening or not. We found a similar prognosis of postmenopausal breast cancer-specific death regardless of BMI in non-users of HRT, but among HRT users obesity was associated with a poorer breast cancer prognosis.

Ross, J. A., K. C. Oeffinger, et al. (2004). "Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study." J Clin Oncol **22**(17): 3558-62.

PURPOSE: Overweight (body mass index [BMI] 25 to 29 kg/m2) and obesity (BMI > or = 30 kg/m2) frequently follow treatment for childhood acute lymphoblastic leukemia (ALL). Recent studies

suggest that risk is most apparent in females treated with cranial radiation at a younger age. Because radiation at a young age may affect the hypothalamus causing leptin receptor insensitivity, we hypothesized that a polymorphism in the leptin receptor (LEPR) gene, Gln223Arg, might influence susceptibility to obesity in survivors of childhood ALL. PATIENTS AND METHODS: We genotyped 600 non-Hispanic white adult ALL survivors enrolled onto the Childhood Cancer Survivor Study. BMI was compared between those with two copies of the Arg allele to those who had at least one copy of the Gln allele. RESULTS: Female survivors with BMI > or = 25 kg/m2 were more likely Arg homozygous than those with BMI less than 25 kg/m2 (24% v 12%; P =.007). This difference was not observed in males. Moreover, among females treated with > or = 20 Gy cranial radiation, Arg/Arg individuals had six times higher odds of having BMI > or = 25 kg/m2 (95% CI, 2.1 to 22.0) than those with a Gln allele (P =.04 for interaction). CONCLUSION LEPR polymorphism may influence obesity in female survivors of childhood ALL, particularly those exposed to cranial radiation. Because obesity is associated with increased morbidity and mortality in later life, identification of children at high risk might allow for early targeted interventions.

Sakamoto, K., S. Niwa, et al. (2007). "Influence of obesity on the short-term outcome of laparoscopic colectomy for colorectal cancer." J Minim Access Surg **3**(3): 98-103.

PURPOSE: Obesity has been generally associated with increased surgical risk. However, data on the outcome of laparoscopic colectomy in obese and non-obese patients are controversial. The aim of this study is to assess the short-term outcome of laparoscopic colectomy for colorectal cancer (CRC) in obese patients as compared with non-obese patients. MATERIALS AND METHODS: Sixty-nine patients who underwent laparoscopic anterior resection for CRC during the past six years were retrospectively evaluated. The patients with CRC involving the sigmoid or rectosigmoid colon and subjected to intracorporeal anastomosis were included in this study. They were divided into three groups according to body mass index (BMI): obese (BMI >/= 28.0 kg/m(2)), pre-obese (BMI: 25.0-27.9 kg/m(2)) and non-obese (BMI < 25.0 kg/m(2)). RESULTS: Nine patients (13.0%) were obese, 11 patients (15.9%) were pre-obese and 49 patients (71.1%) were non-obese. Patient characteristics, such as age, gender, tumor location, previous laparotomy, were similar among the three groups. There were no significant differences in operative time, blood loss, intraoperative complications and conversion rates. Postoperative complications and duration of postoperative hospital stay were also similar among the three groups. However, two of the three patients in the pre-obese group had to be operated on again due to incarceration of the small bowel into a port site. CONCLUSIONS: Laparoscopic colectomy can be safely performed in obese patients with short-term results similar to those obtained in non-obese and pre-obese patients.

Samanic, C., G. Gridley, et al. (2004). "Obesity and cancer risk among white and black United States veterans." Cancer Causes Control **15**(1): 35-43.

BACKGROUND: Obesity has been linked to excess risk for many cancers, but the evidence remains tenuous for some types. Although the prevalence of obesity varies by race, few studies of obesity-related cancer risk have included non-white subjects. METHODS: In a large cohort of male US veterans (3,668,486 whites; 832,214 blacks) hospitalized with a diagnosis of obesity between 1969 and 1996, we examined risk for all major cancer sites and subsites. Person-years accrued from the date of first obesity diagnosis until the occurrence of a first cancer, death, or the end of the observation period (September 30, 1996). We calculated age- and calendar-year adjusted relative risks (RR) and 95% confidence intervals (CI) for cancer among white and black veterans, comparing obese men to men hospitalized for other reasons, with obesity status as time-dependent. For selected cancers, we performed additional analyses stratified by specific medical conditions related to both obesity and risk of those cancers. To determine whether obesity-related cancer risks differed significantly between white and black men, we evaluated heterogeneity of risk for each cancer site. RESULTS: Among white veterans, risk was significantly elevated for several cancers, including cancers of the lower esophagus, gastric cardia, small intestine, colon, rectum, gallbladder and ampulla of vater, male breast, prostate, bladder, thyroid, and connective tissue, and for malignant melanoma, multiple myeloma, chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML). Excess risks initially observed for cancers of the liver and pancreas persisted among men without a history of diabetes or alcoholism. Among black veterans, risks were significantly elevated for cancers of the colon, extrahepatic bile ducts, prostate, thyroid, and for malignant melanoma, multiple myeloma, CLL and AML. CONCLUSIONS: Obese men are at increased risk for several major cancers as well as a number of uncommon malignancies, a pattern generally similar for white and black men. Due to the increasing prevalence of obesity and overweight worldwide, it is important to clarify the impact of excess body weight on cancer and to elucidate the mechanisms involved.

Sauter, E. R., S. Scott, et al. (2008). "Biomarkers associated with breast cancer are associated with obesity." Cancer Detect Prev **32**(2): 149-55.

BACKGROUND: Obesity is linked to the development of postmenopausal breast cancer, and some studies indicate obesity predicts a worse prognosis for premenopausal women who develop the disease. It was our hypothesis that proteins associated with breast cancer would be associated with body mass index (BMI). METHODS: We searched our database of women enrolled in breast health translational research trials for information on BMI and markers predictive of breast cancer (basic fibroblast growth factor (bFGF), prostate-specific antigen (PSA), human kallikrein (hK)2, and urinary plasminogen activator (uPA). Information on BMI and one or more nipple aspirate fluid (NAF) or serum biomarkers was available from 382 women. RESULTS: In this data set, NAF and serum levels of PSA (nPSA and sPSA), and NAF levels hK2, bFGF and uPA were each associated with pre- and/or postmenopausal breast cancer. sPSA was inversely associated with BMI in both pre- (r=-.56, p=.001) and postmenopausal women (r=-.62, p=.0035) without breast cancer. This association was lost when controlling for plasma volume. In women without breast cancer, NAF bFGF (p=.07, premenopausal subjects) and NAF hK2 (p=.09, postmenopausal subjects) were borderline associated with BMI. In women with breast cancer, nPSA was inversely (r=-.53, p=.049) associated with BMI in premenopausal women and directly associated with BMI in postmenopausal women (r=.37, p=.017). nPSA trended higher in hormone sensitive cancers, especially those that expressed progesterone receptor (p=.059). CONCLUSIONS: sPSA was inversely associated with BMI in all pre- and postmenopausal women and specifically in pre- and postmenopausal women without breast cancer. NAF PSA was associated with BMI in pre- and postmenopausal women with breast cancer. Evaluating the change in PSA with changes in weight may provide clues regarding a subject's breast cancer risk.

Schaub, N. P., K. J. Jones, et al. (2009). "Serum proteomic biomarker discovery reflective of stage and obesity in breast cancer patients." J Am Coll Surg **208**(5): 970-8; discussion 978-80.

BACKGROUND: Currently no standardized blood test exists for breast cancer screening or staging purposes. The goals of this study were to use proteomic mass spectrometry approaches for profiling, fractionation, and identification of serum proteins from breast cancer patients for discovery of new biomarkers of stage and nodal status. STUDY DESIGN: Samples from 150 patients were collected preoperatively for patients undergoing breast biopsy. Serum was processed using weak cation exchange (WCX) fractionation and analyzed with matrix-assisted laser desorption ionization time of flight mass spectrometry. Spectra were processed and group profiles, peak statistics, and cross-validation scores were determined using a k-nearest neighbor genetic algorithm. Pools of subgroups based on stage, race, and obesity were processed with WCX fractionation followed by trypsin digestion. Differentially expressed proteins and peptides were identified by tandem mass spectrometry. RESULTS: Matrix-assisted laser desorption ionization time of flight proteomic profiling using WCX capture of serum proteins resulted in correct cancer stage classifications ranging from 72% to 84%. Nodal status was classified correctly with 88% cross-validation scores. Levels of endogenous low mass peptide fragments derived from kininogen, fibrinogen, plasminogen, and inter-alpha-trypsin inhibitor heavy chain 4 protein were increased in cancer stage III and stage IV samples. Adding trypsin digestions with WCX capture indicated increased levels of alpha-2-HS-glycoprotein, prothrombin, and serum amyloid A in stage IV samples. Obesity, but not race, was a factor in the relative levels of detected proteins/peptides. CONCLUSIONS: WCX fractionation alone or with trypsin digestion of serum suggest it can be possible to use a panel of proteins to predict breast cancer stage and nodal status. Additional study is required on the role of inflammatory molecules in breast cancer development.

Siviero-Miachon, A. A., A. M. Spinola-Castro, et al. (2009). "Adiposity in childhood cancer survivors: insights into obesity physiopathology." Arq Bras Endocrinol Metabol **53**(2): 190-200.

As childhood cancer treatment has become more effective, survival rates have improved, and a number of complications have been described while many of these patients reach adulthood. Obesity is a well-recognized late effect, and its metabolic effects may lead to cardiovascular disease. Currently, studies concerning overweight have focused on acute lymphocytic leukemia and brain tumors, since they are at risk for hypothalamic-pituitary axis damage secondary to cancer therapies (cranial irradiation, chemotherapy, and brain surgery) or to primary tumor location. Obesity and cancer have metabolic syndrome features in common. Thus, it remains controversial if overweight is a cause or consequence of cancer, and to date additional mechanisms involving adipose tissue and hypothalamic derangements have been considered, comprising premature adiposity rebound, hyperinsulinemia, leptin regulation, and the role of

peroxisome proliferator-activated receptor gamma. Overall, further research is still necessary to better understand the relationship between adipogenesis and hypothalamic control deregulation following cancer therapy.

Skirnisdottir, I. and B. Sorbe (2008). "Prognostic impact of body mass index and effect of overweight and obesity on surgical and adjuvant treatment in early-stage epithelial ovarian cancer." Int J Gynecol Cancer **18**(2): 345-51.

The present study was performed to find out if the body mass index (BMI) was associated with clinical and pathologic features (age, histology, tumor grade, and substages) and prognosis in early stages (FIGO I-II) of epithelial ovarian cancer. Further aims of the study were to evaluate if overweight or obesity affected the feasibility of optimal surgery and postoperative adjuvant therapy. A total of 635 patients were included in this study. Four percent of the patients were underweight (BMI <18.5), 53% were of ideal body weight (BMI 18.5-25), 31% were overweight (BMI 25-30), and 12% were obese (BMI >30). Overweight and obese patients were significantly (P = 0.006) older than underweight and ideal body weight patients. Tumor grade and histologic type distributions were not different across the BMI strata. FIGO stage (P = 0.011) and presence of ascites (P = 0.007) at primary surgery were associated with the BMI status. A history of cardiovascular disease was significantly (P = 0.006) more common in overweight and obese patients. Survival analyses in the four BMI subgroups did not show any significant differences with regard to recurrence-free survival. The 5-year recurrence-free survival of the complete series was 72%. Overweight and obese patients did not have worse survival than normal weight and underweight patients. Perioperative or postoperative morbidity and adjuvant oncologic treatment were not affected by the BMI. In a multivariate Cox analysis, FIGO substage and tumor grade, but not BMI, were independent and significant prognostic factors with regard to all types of survival rates.

Smith, M. R. (2004). "Osteoporosis and obesity in men receiving hormone therapy for prostate cancer." J Urol **172**(5 Pt 2): S52-6; discussion S56-7.

PURPOSE: A presentation on osteoporosis, obesity and obesity related disease at the Conference on Innovations and Challenges in Prostate Cancer: Prevention, Detection and Treatment is summarized. MATERIALS AND METHODS: A focused literature review was done. RESULTS: Gonadotropin-releasing hormone (GnRH) agonists decrease bone mineral density and increase fracture risk. GnRH agonists also increase weight and fat mass, and decrease lean body mass. Treatment related changes in body composition may contribute to fatigue and fracture risk. The phenotype of men with GnRH agonist shares some features with the insulin resistance syndrome, raising the possibility that GnRH may also increase the risk of diabetes mellitus and cardiovascular disease. CONCLUSIONS: The routine use of GnRH agonists in men with long life expectancy increases the importance of understanding and preventing the unintended adverse effects of treatment. Some adverse effects have the potential to impact not only quality of life, but also noncancer mortality. Additional research is needed to characterize better the unintended effects of androgen deprivation therapy and develop optimal strategies to prevent osteoporosis, obesity and obesity related disease.

Smith, M. R. (2007). "Obesity and sex steroids during gonadotropin-releasing hormone agonist treatment for prostate cancer." Clin Cancer Res **13**(1): 241-5.

PURPOSE: To evaluate effects of obesity on sex steroid levels during treatment with a gonadotropin-releasing hormone agonist in men with prostate cancer. EXPERIMENTAL DESIGN: Forty-nine hormone-naive men with recurrent or locally advanced prostate cancer were included in the analyses. All subjects were treated with leuprolide 3-month depot for 48 weeks. Serum levels of estradiol, sex hormone-binding globulin, total testosterone, and free testosterone were assessed at baseline, 24 weeks, and 48 weeks. Subjects were categorized by body mass index (BMI) and percent body fat. RESULTS: Pretreatment serum sex hormone-binding globulin and total testosterone levels were significantly lower in overweight and obese men than in men with normal BMI. In the overall study population, mean serum testosterone concentrations decreased from 372 +/- 18 ng/dL at baseline to 13 +/- 1 ng/dL at week 48 (P < 0.001). Free testosterone decreased from 6.75 +/- 0.33 ng/dL at baseline to 0.21 +/- 0.02 ng/dL at week 48 (P < 0.001). During treatment with leuprolide, obese men had significantly higher total and free testosterone levels than men with normal BMI. Compared with normal men, total and free testosterone levels during treatment were 1.8-fold and 2.3-fold higher in obese men. Similar results were observed when subjects were categorized by body fat. CONCLUSIONS: Despite lower pretreatment serum testosterone levels, obese men have higher total and free testosterone levels during leuprolide treatment than men with normal BMI. These differences may contribute to the association between obesity and increased prostate cancer mortality.

Smith, M. R., H. Lee, et al. (2008). "Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer." Urology **71**(2): 318-22.

OBJECTIVES: Gonadotropin-releasing hormone agonists increase fat mass, decrease insulin sensitivity, and increase serum triglycerides. To better characterize the metabolic effects of gonadotropin-releasing hormone agonist treatment, we prospectively evaluated the changes in body composition, insulin sensitivity, and levels of adiponectin, resistin, C-reactive protein (CRP), and plasminogen activator inhibitor type 1 (PAI-1). We also assessed the relationships among changes in adipocytokines, body composition, and insulin sensitivity. METHODS: In this prospective, 12-week study, 25 nondiabetic men with locally advanced or recurrent prostate cancer and no radiographic evidence of metastases were treated with leuprolide depot and bicalutamide. The outcomes studied included changes from baseline to week 12 in body composition, insulin sensitivity, and levels of adiponectin, resistin, CRP, and PAI-1. RESULTS: The mean +/- standard error percentage of fat body mass increased by 4.3% +/- 1.3% from baseline to week 12 (P = 0.002). The insulin sensitivity index decreased by 12.9% +/- 7.6% (P = 0.02). The serum adiponectin levels increased by 37.4% +/- 7.2% from baseline to week 12 (P <0.001). In contrast, the resistin, CRP, and PAI-1 levels did not change significantly. Changes in body composition tended to be associated with changes in adiponectin, but not insulin sensitivity. CONCLUSIONS: Combined androgen blockade with leuprolide and bicalutamide significantly increased fat mass and adiponectin levels and decreased insulin sensitivity but did not alter the resistin, CRP, or PAI-1 levels. This pattern of metabolic changes appears distinct from the classic metabolic syndrome.

Smith, P. W., H. Wang, et al. (2007). "Obesity does not increase complications after anatomic resection for non-small cell lung cancer." Ann Thorac Surg **84**(4): 1098-105; discussion 1105-6.

BACKGROUND: The effect of obesity on complications after resection for lung cancer is unknown. We hypothesized that obesity is associated with increased complications after anatomic resections for non-small cell lung cancer. METHODS: A review of our prospective general thoracic database identified 499 consecutive anatomic resections for non-small cell lung cancer from November 2002 to May 2006. Body mass index (BMI) was used to group patients as nonobese (BMI > 18.5 to < 30) and obese (BMI > or = 30). Patient characteristics and oncologic and operative variables were compared between groups. Multivariable logistic regression models were fit with BMI included at every level. Outcomes examined included in-hospital morbidity, mortality, length of stay, and readmission. RESULTS: Seventy-five percent (372 of 499) were nonobese, and 25% (127 of 499) were obese. Preoperative variables were similar, except for a greater incidence of diabetes mellitus (p < 0.0001) in the obese group. Overall mortality was 1.4% (7 of 499) and was not different between groups (p = 0.85). Thirty-day readmission rates (p = 0.76) and length of stay (p = 0.30) were similar. Obese patients had a higher incidence of acute renal failure (p = 0.001). A complication occurred in 33% (124 of 372) of nonobese and 31% (39 of 127) of obese patients (p = 0.59). Respiratory complications occurred in 22% (81 of 372) of nonobese and 14% (18 of 127) of obese patients (p = 0.06). Significant predictors of any complication include performance status, diffusing capacity, and tumor stage. Significant predictors of respiratory complications include performance status, diffusing capacity, chronic renal insufficiency, prior thoracic surgery, and chest wall resection. CONCLUSIONS: In contrast to our hypothesis, obesity does not increase the incidence of perioperative complications, mortality, or length of stay after anatomic resection for non-small cell lung cancer.

Soliman, P. T., R. L. Bassett, Jr., et al. (2008). "Limited public knowledge of obesity and endometrial cancer risk: what women know." Obstet Gynecol **112**(4): 835-42.

OBJECTIVE: To estimate if women in the general population are aware of the relationship between obesity and cancer risk, and to identify groups who may benefit from educational programs. METHODS: A self-administered survey was distributed to women in the Houston community. The questions were taken from a bank of validated questions published by the Center for Disease Control, Behavioral Risk Factor Surveillance System, and the Harvard Forums on Health Survey. Demographic information and participant knowledge of obesity-related cancer risk was collected. Logistic regression and Cochran-Armitage tests for trend were use to assess the association between predictor variables and knowledge. RESULTS: One thousand five hundred forty-five women completed the survey; 28% were normal weight (body mass index [BMI] less than 25 kg/m(2)), 24% were overweight (BMI 25-30 kg/m(2)), and 45% were obese (BMI at least 30 kg/m(2)). Fifty-eight percent (95% confidence interval 56-61%) were not aware that obesity increased risk for endometrial cancer. There was no difference in knowledge of endometrial cancer risk associated with any of the demographic characteristics studied. Black women were the most likely to respond that they did not know

about the relationship between obesity and cancer. There was no association between personal weight and knowledge of obesity-associated risk. CONCLUSION: There is limited knowledge of the relationship between obesity and cancer risk, particularly among black women. Patient education regarding these risks may increase awareness of the relationship between obesity and endometrial cancer among women.

Sonestedt, E., B. Gullberg, et al. (2007). "Both food habit change in the past and obesity status may influence the association between dietary factors and postmenopausal breast cancer." Public Health Nutr **10**(8): 769-79.

OBJECTIVE: Valid dietary data are essential when trying to identify whether or not one or more dietary exposures are responsible for disease. We examined diet composition in women who reported dietary change in the past compared with non-changers, and how the associations between dietary factors and postmenopausal breast cancer are influenced by dietary change, obesity status and misreporting of energy. DESIGN: A population-based prospective cohort study. Data were obtained by a diet history method, anthropometrical measurements and an extensive lifestyle questionnaire including items on past food habit change. SETTING: The Malmo Diet and Cancer (MDC) study, conducted in Malmo, Sweden. SUBJECTS: A subsample of 12,781 women from the MDC cohort recruited from 1991 to 1996. A total of 428 postmenopausal women were diagnosed with incident breast cancer, during 9.2 years of follow-up. RESULTS: Past food habit changers reported healthier food habits and lower energy intake compared with non-changers, a finding that raises issues regarding possible reporting biases. When excluding diet changers, the trend of increased breast cancer risk across omega-6 fatty acid quintiles was stronger, and a tendency of decreased risk emerged for 'fruit, berries and vegetables'. When excluding individuals with non-adequate reports of energy intake, risk estimates were similar to that of the whole sample. In women with body mass index < 27 kg m-2, significant trends of increased breast cancer risk were seen for total fat and omega-6 fatty acids, and of decreased risk for 'fruit, berries and vegetables'. CONCLUSIONS: This study indicates that both obesity and self-reported past food habit change may be important confounders of diet-breast cancer relationships. The study demonstrates that sensitivity analysis, through stratification, may facilitate interpretation of risk relationships and study results.

Sonestedt, E., E. Wirfalt, et al. (2005). "Past food habit change is related to obesity, lifestyle and socio-economic factors in the Malmo Diet and Cancer Cohort." Public Health Nutr **8**(7): 876-85.

OBJECTIVES: To examine if obesity status and socio-economic and lifestyle factors are associated with self-reported past food habit change, and also whether the level of obesity depends on the reason for change. DESIGN: Cross-sectional analysis within the Malmo Diet and Cancer (MDC) study using data from the baseline examination and the extensive socio-economic and lifestyle questionnaire including questions of past food habit change. The risk of having changed food habits in the past was examined using logistic regression. Mean differences in obesity status across categories of reasons for past food habit change were examined using analysis of variance. SETTING: Malmo, the third largest city in Sweden. SUBJECTS: A sub-sample (15 282 women and 9867 men) from the MDC cohort recruited from 1992 to 1996. RESULTS: Individuals with body mass index (BMI) >30 kg m(-2) had an increased risk of having reported past food habit change compared with individuals with BMI <25 kg m(-2) (odds ratio (OR) = 1.63, 95% confidence interval (CI) = 1.48-1.83 for women; OR = 1.53, 95% CI = 1.32-1.76 for men). The highest level of obesity was observed among individuals who had changed their diet due to reasons related to the metabolic syndrome. Changers were more likely to be highly educated and to live alone, be retired, ex-smokers and non-drinkers at baseline. CONCLUSIONS: Because past food habit change is related to obesity and other lifestyle and socio-economic factors, a complex confounding situation may exist that could seriously influence observed relationships between diet and disease. Studies need to collect information on past food habit change and take this information into account in the analysis and when interpreting study outcomes.

Song, Y. M., J. Sung, et al. (2008). "Obesity and risk of cancer in postmenopausal Korean women." J Clin Oncol **26**(20): 3395-402.

PURPOSE: To evaluate an association between obesity, measured by body mass index (BMI; kg/m(2)), and risk of cancer at individual and all sites in postmenopausal women. METHODS: A cohort of 170,481 postmenopausal Korean women who were age 40 to 64 years at baseline measurement of BMI was observed prospectively from 1994 to 2003 for cancer incidence. Multivariable adjusted proportional hazard models were used for evaluating the association. RESULTS: Women with a BMI of 30 kg/m(2) or higher had a 23% higher risk of cancer than women with a BMI between 21.0 and 22.9 kg/m(2) (hazard ratio = 1.23; 95% CI, 1.08 to 1.41). According to the increase in BMI level, significant positive trends existed in cancers of colon, breast,

corpus uteri, and kidney with hazard ratios of 1.05 (95% CI, 1.02 to 1.08), 1.07 (95% CI, 1.05 to 1.10), 1.13 (95% CI, 1.07 to 1.20), and 1.08 (95% CI, 1.02 to 1.15), respectively, for the increase of BMI by 1 kg/m(2). When the analysis was limited to never-smokers, women with a BMI of 25 kg/m(2) or higher showed a significantly increased risk of cancers of the colon, breast, corpus uteri, and kidney and leukemia compared with the normal BMI (18.5 to 22.9 kg/m(2)) group. CONCLUSION: Although variations exist between the individual cancer sites, obesity was associated with an overall increased risk of cancer in postmenopausal Korean women. To reduce the risk of cancer, active strategies to prevent obesity should be implemented in postmenopausal women.

Spangler, E., C. M. Zeigler-Johnson, et al. (2007). "Association of obesity with tumor characteristics and treatment failure of prostate cancer in African-American and European American men." J Urol **178**(5): 1939-44; discussion 1945.

PURPOSE: The impact of body mass index on tumor characteristics and treatment failure in prostate cancer is not well understood in diverse ethnic groups. We evaluated the effect of body mass index in African-American and European American patients from a radical prostatectomy cohort between 1995 and 2004 with regard to tumor histopathological characteristics and biochemical relapse-free survival. MATERIALS AND METHODS: A total of 924 patients were studied to evaluate whether obese men (body mass index greater than 30) had different preoperative and postoperative tumor characteristics or biochemical relapse-free survival compared to nonobese men. There were 784 European American and 140 African-American patients analyzed using failure time models, adjusted for age, preoperative prostate specific antigen, tumor stage and race. RESULTS: Mean and median followup was 42 and 36 months, respectively. African-American men were significantly more obese than European American men. Mean body mass index was 29.0 in African-American and 28.1 in European American men (p = 0.003). African-American men (OR 2.30, 95% CI 1.04-5.1) were more likely to have higher tumor stage on final pathology. Obesity was a risk factor for biochemical failure in African-American men (adjusted hazard ratio 5.49, 95% CI 2.16-13.9) but not in European American men (HR 1.41, 95% CI 0.96-2.08), and this difference was statistically significant (p value for interaction 0.036). CONCLUSIONS: Obesity is associated with poorer tumor prognostic characteristics and decreased biochemical relapse-free survival, particularly in African-American men. These data suggest that obesity may in part explain the poorer prostate cancer prognosis seen in African-American men compared to other racial and ethnic groups.

Stamatiou, K. N., A. G. Alevizos, et al. (2007). "Associations between coronary heart disease, obesity and histological prostate cancer." Int Urol Nephrol **39**(1): 197-201.

OBJECTIVE: The present study investigates the possible associations between coronary heart disease and histological prostate carcinoma in autopsy material. MATERIAL AND METHOD: The material of our study, were 116 men between 55 years and 98 years of age, who died in the period of August 2002-January 2005. The initial segment of the aorta and the prostate glands of all cadavers were removed while the initial 30 mm of the left and right coronary arteries and the peripheral zone of the prostate gland underwent pathologic examination. RESULTS: Of all subjects examined 71.8% had pathological findings suggesting advanced coronary heart disease. Twenty out of 116 cadavers were found with histological carcinoma in their prostate specimen. Among subjects positive for prostate cancer, 12 had died of cardiovascular diseases, while 16 had macroscopic evidence of advanced coronary artery obstructive disease, a finding that was confirmed on pathologic examination. Although most of the subjects had atheromatous lesions on the coronary arteries, the percentage of men with prostate cancer, which had advanced atheromatosis, was greater when compared to those of subjects without prostate cancer. The relation between the coronary artery obstructive disease severity and the presence of latent prostate cancer was statistically significant (P = 0.02). No statistically significant correlation was obtained between body mass index and the presence of prostate cancer. CONCLUSIONS: Our results indicate that there could be an association between coronary artery obstructive disease and prostate cancer, however due to the relatively low sample further studies are needed in order to confirm such findings.

Stark, A., D. Schultz, et al. (2009). "Obesity and risk of the less commonly diagnosed subtypes of breast cancer." Eur J Surg Oncol **35**(9): 928-35.

OBJECTIVES: A set of common epidemiologic risk factors have been associated with the risk of breast cancer despite of its molecular sub-classifications. We implemented a case series study with the primary objective of evaluating if obesity is associated with the diagnostic risk of "ER+ and/or PR+, HER2+", "ER-/PR-, HER2-", or "ER-/PR-, HER2+" relative to the most commonly diagnosed subtype of breast carcinoma, "ER+ and/or PR+, HER2-". METHODS: Demographic, clinical and pathologic data were collected from existing

databases. The statuses of HER2/neu biomarker and hormone receptors were dichotomized as either positive or negative. Immunohistochemical staining was used to assess the prevalence of different subtypes. Body mass index was calculated from weight and height data collected at the time of consultation. CONCLUSIONS: Findings from the present study suggest that excess body weight decreases the diagnostic risk of "ER-/PR-, HER2-", or "ER-/PR-, HER2-" relative to "ER+ and/or PR+, HER2-". Obese and overweight women are more likely to be diagnosed with to "ER+ and/or PR+, HER2-", the subtype that has best prognosis and mostly associated with personal lifestyle. Weight gain with the population attributable-risk factor of 21.3% contributes the most to the incidence of invasive post menopausal breast cancer. Younger pre-menopausal women were more likely to be diagnosed with "ER+ and/or PR+, HER2+". In younger women biology of breast cancers with positive expression for hormone receptors and epidermal growth factor is a complex that extends beyond the currently assessed prognostic markers.

Stattin, P., A. Lukanova, et al. (2004). "Obesity and colon cancer: does leptin provide a link?" Int J Cancer **109**(1): 149-52.

Obesity, a risk factor for colorectal cancer, is associated with elevated serum levels of leptin, the adipocyte-derived hormone, and insulin. Experimental and epidemiologic studies have indicated a role for insulin in the pathogenesis of colon cancer, and recent experimental studies have suggested a similar role for leptin. In a case-control study nested in the Janus Biobank, Norway, we measured serum levels of leptin and C-peptide (a marker of pancreatic insulin secretion) in cryopreserved prediagnostic sera from men (median age, 45 years) who were diagnosed with cancer of the colon (n = 235) or rectum (n = 143) after blood collection (median time, 17 years), and among 378 controls matched for age and date of blood collection. Conditional logistic regression analyses showed an approximately 3-fold increase in colon cancer risk with increasing concentrations of leptin up to an odds ratio (OR) of 2.72 (95% CI = 1.44-5.12) for top vs. bottom quartile (p(trend) = 0.008). The corresponding OR for C-peptide was 1.81 (95% CI = 0.67-4.86; p(trend) = 0.19). The risk estimates remained unchanged after mutual adjustment. No association of hormone levels with rectal cancer risk was found. Reproducibility of hormone measurements assessed by intraclass coefficients (ICCs) for paired samples taken 1 year apart was high for leptin (ICC = 0.82) but lower for C-peptide (ICC = 0.30). Our results suggest that leptin is a risk factor for colon cancer, and that leptin may provide a link between obesity and colon cancer. Leptin may be directly involved in colon tumorigenesis or it may serve as a sensitive and robust marker of an obesity-induced adverse endocrine environment. Only weak support for an association of insulin with colon cancer was found.

Strom, S. S., A. M. Kamat, et al. (2006). "Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer." Cancer **107**(3): 631-9.

BACKGROUND: Several reports have shown that obesity is associated with increased risk of biochemical failure after radical prostatectomy. However, limited information is available regarding the impact of obesity on prostate cancer progression after radiotherapy. The current study sought to determine whether obesity was an independent predictor of biochemical failure (BF) and clinical recurrence (CF) among patients treated with external-beam radiotherapy (EBRT). METHODS: A retrospective analysis was performed on 873 patients receiving EBRT as the sole treatment for localized prostate cancer between 1988 and 2001. The Kaplan-Meier method, log-rank test, and Cox proportional hazards analyses were performed. RESULTS: Of the 873 patients, 18% were mildly obese and 5% were moderately to severely obese. Obesity was related to younger age at diagnosis ($P < .001$), more recent year of diagnosis ($P = .03$), and race ($P = .03$), with African-American men having the highest obesity rates. During a mean follow-up of 96 months, 295 patients experienced BF and 127 had CF. On multivariate analysis, controlling for clinical and treatment characteristics, increased body mass index (BMI) significantly predicted BF (hazards ratio [HR] = 1.04; 95% confidence interval [95% CI], 1.02-1.07) with a positive trend by BMI category ($P = .001$). Similar results were found when the outcome was CF; BMI remained an independent predictor of progression (HR = 1.05; 95% CI, 1.01-1.09), with a statistically significant trend by increased BMI category ($P = .03$). CONCLUSIONS: The current findings validate the important role of obesity, not only on BF but also on CF, and suggest a link to the biologic basis of tumor progression that can be therapeutically exploited.

Strom, S. S., X. Wang, et al. (2005). "Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy." Clin Cancer Res **11**(19 Pt 1): 6889-94.

PURPOSE: Several lines of evidence suggest that diet and weight gain may be important environmental factors implicated in prostate carcinogenesis, especially in tumor progression. The

purpose of this study was to evaluate obesity at different ages in a well-characterized cohort of prostate cancer patients treated with prostatectomy and to develop a prognostic model that incorporates body mass index (BMI) as a measure of obesity. EXPERIMENTAL DESIGN: We carried out a prospective study of 526 patients registered at the M.D. Anderson Cancer Center from 1992 to 2001. Kaplan-Meier and Cox proportional hazard analyses were done. RESULTS: During an average follow-up of 54 months, 97 (18%) post-prostatectomy patients experienced biochemical failure. Patients who were obese (BMI > or = 30 kg/m2) at diagnosis had a higher rate of biochemical failure than nonobese men (P = 0.07). Those obese at 40 years had an even greater rate of biochemical failure (P = 0.001). Higher BMI at diagnosis [hazard ratio (HR), 1.07; P = 0.01] and Gleason score = 7(4 + 3) and > or =8 (HR, 3.9; P = 0.03 and HR, 10.0; P < or = 0.001, respectively) remained significant independent predictors of biochemical failure in multivariate analysis. Men who gained weight at the greatest rate (>1.5 kg/y) between 25 years and diagnosis progressed significantly sooner (mean time, 17 months) than those who exhibited a slower weight gain (mean time, 39 months; P(trend) = 0.005). The inclusion of obesity to the clinical nomogram improved performance. CONCLUSIONS: Our findings validate the importance for a role of obesity in prostate cancer progression and suggest a link to the biological basis of prostate cancer progression that can be therapeutically exploited.

Stroup, S. P., J. Cullen, et al. (2007). "Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition." Cancer **110**(5): 1003-9.

BACKGROUND: Given the limited data regarding the impact of obesity on treatment outcomes after external beam radiation therapy (EBRT) for the definitive treatment of prostate cancer, the authors sought to evaluate the effect of obesity as measured by body mass index (BMI) on biochemical disease recurrence (BCR) using the most current 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition (prostate-specific antigen [PSA] nadir + 2 ng/mL). METHODS: A retrospective cohort study identified men who underwent primary EBRT for localized prostate cancer between 1989 and 2003 using the Center for Prostate Disease Research (CPDR) Multi-center National Database. BMI was calculated (in kg/m(2)) and the data were analyzed. Univariate and multivariate Cox proportional hazards regression analyses were used to determine whether BMI significantly predicted BCR. RESULTS: Of the 1868 eligible patients, 399 (21%) were obese. The median age of the patients and pretreatment PSA level were 70.2 years and 8.2 ng/mL, respectively. Of 1320 patients for whom data were available with which to calculate PSA recurrence (PSA nadir + 2 ng/mL), a total of 554 men (42.0%) experienced BCR. On univariate analysis, BMI was found to be an independent predictor of PSA recurrence (P = .02), as was race, pretreatment PSA level, EBRT dose, clinical T classification, Gleason score, PSA nadir, and the use of androgen-deprivation therapy (ADT). On multivariate analysis, BMI remained a significant predictor of BCR (P = .008). CONCLUSIONS: To the authors' knowledge, this is the first study to report the association between obesity and BCR after EBRT for localized prostate cancer as measured by the updated 2006 RTOG-ASTRO definition. A higher BMI is associated with greater odds of BCR after undergoing definitive EBRT.

Surmacz, E. (2007). "Obesity hormone leptin: a new target in breast cancer?" Breast Cancer Res **9**(1): 301.

Leptin is a multifunctional hormone produced mainly by the adipose tissue and involved in the regulation of food intake and energy balance. In addition, leptin can stimulate mitogenic and angiogenic processes in peripheral organs. Because leptin levels are elevated in obese individuals and excess body weight has been shown to increase breast cancer risk in postmenopausal women, attempts have been made to evaluate whether leptin can promote breast cancer. Data obtained in cell and animal models and analyses of human breast cancer biopsies indeed suggest such an involvement. Furthermore, a recent report clearly shows that targeting leptin signaling may reduce mammary carcinogenesis. Thus, leptin should become a new attractive target in breast cancer.

Tenesa, A., H. Campbell, et al. (2009). "Common genetic variants at the MC4R locus are associated with obesity, but not with dietary energy intake or colorectal cancer in the Scottish population." Int J Obes (Lond) **33**(2): 284-8.

BACKGROUND: Common single-nucleotide polymorphism (SNP) variants around the melanocortin 4 receptor (MC4R) gene have recently been associated with obesity risk and insulin resistance. Obesity is a known risk factor for colorectal cancer (CRC) and we hypothesized that there might be a common inherited genetic component. METHODS AND RESULTS: Four of the variants reported earlier were genotyped and tested for association with body mass index (BMI), waist

circumference (WC), dietary energy intake (DEI) and CRC. Using a case-control genetic association study, we replicated the association with BMI (P=0.0001, additive genetic effect=0.37 kg/m(2)) and WC (P=0.005, additive genetic effect=0.70 cm) using over 3800 individuals. However, there was no association between these variants and CRC risk. Rare (highly penetrant) variants within the MC4R gene have been shown to influence eating behaviour and hyperphagia. We hypothesized that the newly identified common variants might also influence hyperphagia. Using DEI data recorded from a validated food frequency questionnaire, we found no significant genetic association between MC4R SNPs and DEI. CONCLUSIONS: As the MC4R locus explains only 0.28% of the BMI and 0.14% of the WC phenotypic variance in the Scottish population, most of the genetic contribution to obesity remains to be identified.

Tsujinaka, S., F. Konishi, et al. (2008). "Visceral obesity predicts surgical outcomes after laparoscopic colectomy for sigmoid colon cancer." Dis Colon Rectum **51**(12): 1757-65; discussion 1765-7.

PURPOSE: This study was designed to assess whether visceral obesity is a more useful predictor of surgical outcomes compared with body mass index after laparoscopic colectomy. METHODS: A total of 133 consecutive patients who underwent elective laparoscopic colectomy for sigmoid colon cancer between April 2001 and April 2007 were included. Obesity was defined by visceral fat area > or = 130 cm(2) or body mass index > or = 25 kg/m(2), and the variables were compared for obese and nonobese patients. RESULTS: There were 68 (51.1 percent) obese patients according to visceral fat area and 27 (20.3 percent) according to body mass index. Using either definition, obese patients had a significantly longer operative time compared with nonobese patients. Patients classified as obese by visceral fat area had a significantly higher incidence of wound infection (20.6 vs. 4.6 percent; P = 0.006) and overall complication rates (32.4 vs. 12.3 percent, P = 0.006) compared with nonobese patients, whereas there was no significant difference when classified by body mass index. Postoperative hospital stay was significantly longer in obese patients compared with nonobese patients classified by visceral fat area (median 10.5 vs. 9 days; P = 0.007), whereas it was not statistically different when classified by body mass index. CONCLUSION: Visceral fat area is a more useful parameter than body mass index in predicting surgical outcomes after laparoscopic colectomy for sigmoid colon cancer.

van Roermund, J. G. and J. A. Witjes (2007). "The impact of obesity on prostate cancer." World J Urol **25**(5): 491-7.

Increasing prevalence of obesity in many parts of the world emphasizes the importance of learning more about the relationship between obesity and prostate cancer (PC). The present paper reviews the impact of obesity on PC using knowledge obtained from the available literature. Search of published literature in PUBMED database. Adipose tissue constitutes an active endocrine and metabolic organ which may be relevant in the development and progression of PC by different potential mechanisms. Furthermore, obesity could have an impact on the outcome of different treatment modalities for PC, both functionally as anatomically. Obesity is a growing problem, however, the exact role in the development and progression of PC has not been elucidated. Regarding the optimal treatment of PC in obese patients, comparative prospective studies are needed.

Vanamala, J., C. C. Tarver, et al. (2008). "Obesity-enhanced colon cancer: functional food compounds and their mechanisms of action." Curr Cancer Drug Targets **8**(7): 611-33.

Obesity is rapidly becoming a global phenomenon. This is more than a cosmetic issue as obesity is associated with several life-threatening diseases, including colon cancer. Insulin resistance and inflammation, underlying factors in obesity-related diseases, promote colonocyte proliferation and suppress programmed cell death, or apoptosis, by activating the insulin-like growth factor (IGF) and prostaglandin pathways. These pathways converge on the Wnt pathway, which is implicated in colon carcinogenesis. Despite tremendous advances in our understanding of the molecular mechanisms involved in colon carcinogenesis, mortality due to colon cancer world-wide is unacceptably high. Even though conventional therapies can prolong a patient's life-span a few years, they cause serious side effects. Thus, there is growing interest in functional foods and dietary bioactive compounds with chemopreventive properties. This search is fueled by the epidemiological studies indicating that plant-based diets are protective against several types of cancers. This review provides a brief summary of the IGF and prostaglandin pathways, which are implicated in obesity-enhanced colon cancer, and some of the functional foods/dietary compounds that target these pathways. It is essential to understand the molecular mechanisms involved in chemoprevention before providing appropriate science-based dietary recommendations to prevent colon cancer in both obese and non-obese individuals.

Vona-Davis, L., D. P. Rose, et al. (2008). "Triple-negative breast cancer and obesity in a rural Appalachian population." Cancer Epidemiol Biomarkers Prev **17**(12): 3319-24.

BACKGROUND: Our objective was to determine the clinicopathologic features of triple-negative (estrogen receptor, progesterone receptor, and human epidermal growth factor-2 receptor negative) breast cancer and their relationship to obesity in women drawn from a population with one of the highest obesity rates in the United States. METHODS: This retrospective study involved 620 White patients with invasive breast cancer in West Virginia. Hospital tumor registry, charts, and pathology records provided age at diagnosis, tumor histologic type, size, nodal status, and receptor status. Body mass index was calculated and a value of > or = 30 was considered indicative of obesity. RESULTS: Triple-negative tumors occurred in 117 (18.9%) of the 620 patients, most often in association with invasive ductal carcinomas. Patients with triple-negative tumors were younger than those with other receptor types, 44.5% and 26.7%, respectively, being diagnosed at age <50 years (P = 0.0004). The triple-negative tumors were larger (P = 0.0003), most notably in the younger women, but small tumors (<2.0 cm) were more often accompanied by lymph node metastases. Obesity was present in 49.6% of those with triple-negative tumors but in only 35.8% of those with non-triple-negative tumors (P = 0.0098). Lymph node metastases were more frequently associated with T(2) tumors in obese patients (P = 0.032) regardless of their receptor status. CONCLUSIONS: Triple-negative breast cancers within a White, socioeconomically deprived, population occurred in younger women, with later stage at diagnosis, and in association with obesity, which itself has been associated with a poor prognosis in breast cancer.

Wang, S. S., L. M. Morton, et al. (2007). "Genetic variation in catechol-O-methyltransferase (COMT) and obesity in the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial." Hum Genet **122**(1): 41-9.

Catechol-O-methyltransferase (COMT) is an important modulator in the catabolism of extraneural dopamine, which plays an important role in drug reward mechanisms. It is hypothesized that genetic variations in the COMT gene, which can result in a three to fourfold difference in COMT enzyme activity, may be associated with several reward-motivated behaviors. The aim of our study was to examine the relationship between COMT polymorphisms with smoking, obesity and alcohol. Three single nucleotide polymorphisms (SNPs) in COMT were genotyped in 2,371 participants selected randomly from the screening arm of the PLCO Cancer Screening Trial after stratifying by sex, age, and smoking status. Smoking, obesity, and alcohol consumption were assessed by questionnaire. SNP and haplotype associations were estimated using odds ratios (ORs) and 95% confidence intervals (CIs) derived from conditional logistic regression models, adjusted for race/ethnicity. The COMT Ex4-76C > G (Leu136Leu) polymorphism was statistically significantly associated with individuals who had >30% increases in BMI from ages 20 to 50 years, compared to those with 0-5% increase in BMI (0-5%) over the same age period: (CC is referent; OR(CG)= 1.42, OR(GG)= 1.46, P (trend)= 0.06). By sex, the increased risk was further pronounced among females (OR(CG)= 1.50, OR(GG)= 2.10, P (trend)= 0.03). Consistent with our analyses of single polymorphisms, individuals whose BMI increased >30% from ages 20 to 50 years were more likely than individuals with 0-5% increases in BMI to possess COMT haplotypes [COMT Ex3-104C > T-COMT Ex4-76 C > G-COMT Ex4-12 A > G] that included the variant allele for COMT Ex4-76 C > G: C-G-G (T-C-A is referent: OR(C-G-G)= 1.33, 95% CI 1.01-1.77) and C-G-A (OR(C-G-A)= 1.79, 95% CI 0.72-4.49). We observed no association between any of the COMT polymorphisms with smoking behavior or alcohol intake. The COMT Ex4-76C > G (Leu136Leu) polymorphism appears to play a role in large increases in BMI. The null association with smoking and alcohol and the pronounced association with increasing BMI among women further implicates COMT's role in estrogen metabolism as a potentially culpable pathway. Our results support a need for comprehensive evaluation of COMT variations and their functional relevance as COMT may be an important molecular target to evaluate for new treatments regarding obesity.

Wasserman, L., S. W. Flatt, et al. (2004). "Correlates of obesity in postmenopausal women with breast cancer: comparison of genetic, demographic, disease-related, life history and dietary factors." Int J Obes Relat Metab Disord **28**(1): 49-56.

BACKGROUND: Obesity in women has been associated with a variety of factors, including genetic predisposition, social class, early age at menarche, exercise, alcohol consumption and diet. Obesity is a risk factor for the occurrence and the recurrence of breast cancer in postmenopausal women, perhaps because of increased exposure to estrogen, insulin and insulin-like growth factors (IGFs). The progesterone receptor (PR) and the steroid hormone receptor coactivator pCIP/ACTR/AIB1/TRAM1/RAC3 (AIB1) are hypothesized to mediate signaling crosstalk between these hormonal pathways. Polymorphisms in both

genes have been described and their association with breast cancer risk reported. If genetic factors contribute to obesity, and the PR and AIB1 genes influence estrogenic, insulin and IGF pathways, then genetic patterns resulting from PR and AIB1 polymorphisms may be associated with obesity in postmenopausal women. OBJECTIVE: We compared the PR and AIB1 genotypes of postmenopausal women with breast cancer with demographic, disease-related, reproductive, lifestyle and dietary variables in terms of the strength of their relationship with obesity (BMI> or =30 kg/m2). SUBJECTS: A total of 301 postmenopausal women previously diagnosed with Stage I, II or IIIA breast cancer, who are enrolled in the Women's Healthy Eating and Living (WHEL) study (age: 34.5-70.8 y, BMI: 17.8-54.6 kg/m2). MEASUREMENTS: The PR polymorphism PROGINS was identified by PCR. The length of the AIB1 polyglutamine repeat was determined by PCR and nondenaturing gel electrophoresis or DNA sequencing. BMI was obtained at the baseline clinic visit upon entry into the WHEL study. Information about date of diagnosis, stage of disease, tumor hormone receptor status and adjuvant treatment received were obtained from medical records. Reproductive, menstrual history, demographic, family history of cancer, smoking history and exercise frequency and intensity information were obtained from questionnaires. Dietary and alcohol intake data came from four 24-h telephone recalls of food intake obtained at the study entry. RESULTS: The combined inheritance of PROGINS A1/A1 and AIB1 28/29, 28/30, 28/31, 29/29 or 29/30 (AIB1 LG) genotypes (adjusted odds ratio (OR)=2.22 (95% confidence interval 1.25-3.93)) and early age at menarche (<12 y) (adjusted OR=2.34 (1.12-4.86)) were each associated with the risk for obesity. Current use of tamoxifen (adjusted OR=0.49 (0.28-0.87)) and an alcohol intake > or =10 g/day (adjusted OR=0.28 (0.11-0.77)) were inversely associated with BMI > or =30 kg/m2. CONCLUSION: Early age at menarche and a PROGINS A1/A1+AIB1 LG genetic pattern had comparable levels of association with obesity in this cross-sectional sample of postmenopausal women with breast cancer. Since this was a cross-sectional rather than a case-control design, the association between PROGINS and AIB1 genotype and obesity found in this sample should be considered preliminary, and must be re-evaluated with a new and larger sample.

Wee, C. C., A. Huang, et al. (2008). "Obesity and the likelihood of sexual behavioral risk factors for HPV and cervical cancer." Obesity (Silver Spring) **16**(11): 2552-5.

Obesity is associated with higher cervical cancer mortality, but its relationship with sexual behavioral risk factors that predispose women to human papilloma virus (HPV) and cervical cancer is unclear. We used data from 3,329 women participants, aged 20-59 years, of the 1999-2004 National Health and Nutrition Examination Survey, to analyze the relationship between BMI and age at first intercourse, number of sexual partners, condom use during sexual activity, history of sexually transmitted disease (STD), herpes simplex virus 2 (HSV-2) seropositivity, and HPV prevalence. BMI was not associated with the prevalence of HPV. Mildly obese women (BMI 30.0-34.9 kg/m(2)) were least likely to report a STD history (9% vs. 13% in normal weight) and >or=2 sexual partners in the previous year (8% vs. 13%) while overweight women (BMI 25.0-29.9 kg/m(2)) were least likely to report >or=10 lifetime partners; among those with multiple partners, BMI was not associated with sexual activity without condoms in the past month. After adjustment for age, race/ethnicity, and education, women with higher BMI were less likely to report sexual behavioral risk factors than normal-weight women; however, odds ratios were only significant for mildly obese women for reporting a STD history (0.74, 95% confidence interval 0.55-0.99) and having >or=2 sexual partners in the last year (0.57, 0.39-0.85). Higher BMI was not associated with HSV-2 seropositivity after adjustment. HPV and sexual behavioral risk factors for HPV and cervical cancer are not more prevalent in obese than normal-weight women and unlikely to account for higher-observed cervical cancer mortality in obese women.

Wee, C. C., E. P. McCarthy, et al. (2004). "Obesity and breast cancer screening." J Gen Intern Med **19**(4): 324-31.

BACKGROUND: Compared to normal weight women, women with obesity have higher mortality from breast cancer but are less often screened. OBJECTIVES: To examine the relation between mammography use and weight category and to examine the influence of race, illness burden, and other factors on this relationship. DESIGN AND SETTING: The 1998 National Health Interview Survey, a U.S. civilian population-based survey. PARTICIPANTS: Five thousand, two hundred, and seventy-seven women ages 50 to 75 years who responded to the Sample Adult and Prevention questionnaires. MEASUREMENTS: Mammogram use in the preceding 2 years. RESULTS: Among 5277 eligible women, 72% reported mammography use. The rate was 74% among white women and 70% among black women. Among white women, mammogram use was lowest in women with a body mass index (BMI) greater than 35 kg/m(2) (64% to

67%). After adjusting for sociodemographic factors, health care access, medical conditions, hospitalizations, and mobility status, higher BMI was associated with lower screening among white women, P =.02 for trend; the relative risk (RR) for screening in moderately obese white women (BMI, 35 to 40 kg/m(2)) was 0.83 (95% confidence interval [CI], 0.68 to 0.96) compared to normal weight white women. Compared to normal weight black women, mammography use was similar or higher in overweight (BMI, 25 to 30 kg/m(2); RR, 1.19; 95% CI, 1.01 to 1.32), mildly obese (BMI, 30 to 35 kg/m(2); RR, 1.22; 95% CI, 0.98 to 1.39), and moderately obese black women (RR, 1.37; 95% CI, 1.37 to 1.50) after adjustment. The P value for the race-BMI interaction was.001. Results for white and black women were unchanged after additional adjustment for psychological functioning and health habits. CONCLUSION: Among white women, those with higher BMI were less likely to undergo breast cancer screening than normal weight women. This relationship was not seen in black women. Our findings were not explained by differences in sociodemographic factors, health care access, illness burden, or health habits. More research is needed to determine the reasons for these disparities so that appropriate efforts can be made to improve screening.

Wen, W., Q. Cai, et al. (2008). "The modifying effect of C-reactive protein gene polymorphisms on the association between central obesity and endometrial cancer risk." Cancer **112**(11): 2409-16.

BACKGROUND: Obesity is a major risk factor for endometrial cancer. Obesity, particularly central obesity, is considered as a systemic inflammatory condition and is related strongly to insulin resistance. C-reactive protein (CRP) is the most recognized biologic marker of chronic systematic inflammation, and it is conceivable that the CRP gene may work together with obesity in the development of endometrial cancer. METHODS: On the basis of a population-based case-control study in a Chinese population, the authors obtained obesity measurements and data on 6 CRP single-nucleotide polymorphisms (SNPs) from 1046 patients with newly diagnosed endometrial cancer (cases) and from 1035 age frequency-matched controls. The association of the CRP SNPs with endometrial cancer risk and their modification on the association between obesity and endometrial cancer risk were evaluated. RESULTS: Although CRP SNPs alone were not associated with endometrial cancer, the associations of endometrial cancer with central obesity, measured as the waist-to-hip ratio (WHR) and the waist circumference, seemed to be stronger in women who were homozygous for the major allele of reference SNP (rs)1130864 (cytidine [C]/C) than in women who had the C/thymidine (T) and T/T genotypes (interaction test: P = .013 for WHR; P = .083 for waist circumference). When the women were stratified further by menopausal status, the observed interactions persisted mainly in premenopausal women (interaction test: P < .001 for WHR; P = .002 for waist circumference). CONCLUSIONS: The current results suggested that, in the Chinese population that was studied, obesity-related insulin resistance and proinflammatory effects may play an important role in endometrial cancer risk, and these effects were modified significantly by the CRP SNP rs1130864.

Wolfberg, A. J., F. J. Montz, et al. (2004). "Role of obesity in the surgical management of advanced-stage ovarian cancer." J Reprod Med **49**(6): 473-6.

OBJECTIVE: To assess whether obese women with advanced-stage ovarian cancer undergoing primary cytoreduction surgery were at increased risk of suboptimal cytoreduction and complications during the operative and postoperative period as compared to nonobese women. STUDY DESIGN: A retrospective, case-control study of all cases of advanced-stage epithelial ovarian cancer managed surgically at Johns Hopkins Hospital between January 1, 1990, and December 31, 1999. RESULTS: Obese patients were as likely as nonobese patients to undergo optimal cytoreduction at surgery. Obese patients were more likely than nonobese patients to be high-risk anesthesia candidates and more likely than nonobese patients to have tumors >20 cm at surgery. Obese patients were not at greater risk of surgical or postoperative complications than were nonobese patients. CONCLUSION: Obesity is not a risk factor for suboptimal surgical management of advanced-stage ovarian cancer.

Zhang, C., K. M. Rexrode, et al. (2008). "Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women." Circulation **117**(13): 1658-67.

BACKGROUND: Accumulating evidence indicates that abdominal adiposity is positively related to cardiovascular disease (CVD) risk and some other diseases independently of overall adiposity. However, the association of premature death resulting from these diseases with abdominal adiposity has not been widely studied, and findings are inconsistent. METHODS AND RESULTS: In a prospective cohort study of 44,636 women in the Nurses' Health Study, associations of abdominal adiposity with all-cause and cause-specific mortality were examined. During 16 years of follow-up, 3507 deaths were identified, including 751 cardiovascular deaths and 1748 cancer deaths. After adjustment for body mass index and

potential confounders, the relative risks across the lowest to the highest waist circumference quintiles were 1.00, 1.11, 1.17, 1.31, and 1.79 (95% confidence interval [CI], 1.47 to 1.98) for all-cause mortality; 1.00, 1.04, 1.04, 1.28, and 1.99 (95% CI, 1.44 to 2.73) for CVD mortality; and 1.00, 1.18, 1.20, 1.34, and 1.63 (95% CI, 1.32 to 2.01) for cancer mortality (all P<0.001 for trend). Among normal-weight women (body mass index, 18.5 to < 25 kg/m(2)), abdominal obesity was significantly associated with elevated CVD mortality: Relative risk associated with waist circumference > or = 88 cm was 3.02 (95% CI, 1.31 to 6.99) and for waist-to-hip ratio > 0.88 was 3.45 (95% CI, 2.02 to 6.92). After adjustment for waist circumference, hip circumference was significantly and inversely associated with CVD mortality. CONCLUSIONS: Anthropometric measures of abdominal adiposity were strongly and positively associated with all-cause, CVD, and cancer mortality independently of body mass index. Elevated waist circumference was associated with significantly increased CVD mortality even among normal-weight women.

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a. Many investigators suggested that obesity predisposes to adverse prostate cancer characteristics and outcomes. We tested the effect of obesity on the rate of aggressive prostate cancer at either prostate biopsy or radical prostatectomy (RP). Clinical and pathological data were available for 1,814 men. Univariable and multivariable logistic regression models addressed the rate of high grade prostate cancer (HGPCa) at either biopsy or final pathology. Clinical stage, prostate-specific antigen (PSA), percentage of free PSA and prostate volume were the base predictors. All models were fitted with and without body mass index (BMI), which quantified obesity. BMI and its reciprocal (InvBMI) were coded as cubic splines to allow nonlinear effects. Predictive accuracy (PA) was quantified with area under curve estimates, which were subjected to 200 bootstrap re-samples to reduce overfit bias. Gains in PA related to the inclusion of BMI were compared using the Mantel-Haenszel test. HGPCa at biopsy was detected in 562 (31%) and HGPCa at RP pathology was present in 931 (51.3%) men. In either univariable or multivariable models predicting HGPCa at biopsy, BMI or InvBMI failed to respectively reach statistical significance or add to multivariable PA (BMI gain = 0%, p = 1.0; InvBMI gain = -0.2%, p = 0.9). Conversely, in models predicting HGPCa at RP, BMI and InvBMI represented independent predictors but failed to increase PA (BMI gain = 0.7%, p = 0.6; InvBMI gain = 0.5, p = 0.7%). Obesity does not predispose to more aggressive prostate cancer at biopsy. Similarly, obesity does not change the ability to identify those who may harbor HGPCa at RP.
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