World Journal of Surgical Research

Original Article

Open Access

High fat diet is not associated with stimulation of colorectal cancer liver metastases.

Jurstine Daruwalla, Andrew Hadj, Shu Wen Wen, Theodora Fifis, Eunice Yang, Linh Nguyen, Christopher Christophi, Mehrdad Nikfarjam

University of Melbourne Department of Surgery, Austin Health, Heidelberg, Victoria, Australia.

Abstract

***Background*:** A high fat diet induces fatty infiltration of visceral organs and has been associated with the development of some cancers and may influence the progression and spread of cancer. The impact of high fat diet on the growth and development colorectal liver metastases is uncertain.

***Methodology*:** Liver metastases were induced in CBA mice using a murine derived colon cancer cell line by intrasplenic injection. Mice were fed either a high fat (60% fat content) (n = 20) or low fat diet (5% fat content) (n = 20) for 6 weeks prior tumor induction and maintained on the same diet thereafter. Tumor volume and patterns of spread were assessed at day 21 post induction. Tumor necrosis, apoptosis and proliferation were assessed using immunohistochemistry.

***Results*:** No difference in liver metastases, tumor necrosis or apoptosis was observed between the two groups. There was a trend towards increased tumor proliferation in the high fat diet group.

***Conclusions*:** A high fat diet alone did not induce tumor stimulation and progression of colorectal liver metastases. Several studies have alluded to the deregulation of catabolic cytokines present in malignancy in the obese state and this may explain the negligible effects of a high fat diet.

Key Words: Obesity; colorectal cancer; tumor necrosis; proliferation; apoptosis

Introduction

Clinical and experimental studies have shown an association between obesity and increased incidence and progression of cancer [1-4]. Several epidemiological studies have implicated obesity as an independent risk factor for certain malignancies including endometrial [5], colorectal [6], breast cancer in postmenopausal women [7] and renal cell carcinoma in women [8] and men [9]. The effects of obesity have systemic and organ specific manifestations, the origins of which are no doubt multi-factorial. Liver dysfunction, in particular hepatic steatosis in obese patients, is recognised for its strong clinical association with hepatocellular carcinoma [9,10].

Address for correspondence and reprint requests to:
Mr Mehrdad Nikfarjam, Department of Surgery, University of Melbourne Austin Hospital, Level 8, Lance Townsend Building Studley Rd, Heidelberg, Victoria, 3084
Email: mehrdad.nikfarjam@gmail.com

Submitted Monday, March 24, 2014; Accepted: Sunday, April 13, 2014, Published: Wednesday, April 16, 2014

Colorectal cancer is the second leading cause of cancer related mortality with the majority of deaths attributable to liver metastases [11]. Obesity appears to confer an increased risk of developing colorectal cancer (CRC) [6,12]. It is associated with changes in the tumor microenvironment such as angiogenesis [13] and invasion [14,15] resulting in tumor spread [16]. Whether obesity itself is a risk factor for tumor development and progression or it is related to a high fat diet is undetermined. Studies with mice fed a high-calorie diet show increased proliferation in epithelial cells of the pancreas, prostate [17] and colon [18]. In contrast, numerous other studies demonstrate that restricted caloric intake inhibits tumor growth, particularly in breast cancer [19,20].

This study investigates the effect of a high caloric diet on colorectal liver metastases in an experimental model. We hypothesise a high fat diet leads to tumor stimulation and altered tumor cell kinetics.

Methodology

Experimental design

Six to eight week old CBA male mice (Laboratory Animal services, University of Adelaide, South Australia) were housed in standard cages with access to food and water *ad libitum*. All procedures were performed with ethics approval from the Austin Hospital animal ethics committee. Mice were divided into a high fat (n = 20) (19.4% protein, 20.6% carbohydrate and 60% fat, SF02-006) and control, low fat (n = 20) (19.4% protein, 75.6% carbohydrate and 5% fat, SF00-229) diet (Specialty Feeds, WA, Australia). Mice consuming the high fat diet are referred to as "HF" and mice consuming the low fat diet, "LF". Mice were maintained on the specified diets for 6 weeks prior to tumor induction

Liver Metastases Model

A dimethyl hydrazine (DMH) generated primary colon carcinoma murine derived cell line was utilized for induction of liver metastases This model of liver metastases has been previously established [21]. The cell line was maintained as solid tumors in the flanks of CBA mice. At the time of induction tumors were excised and a cell suspension was prepared as previously described [21]. Trypan

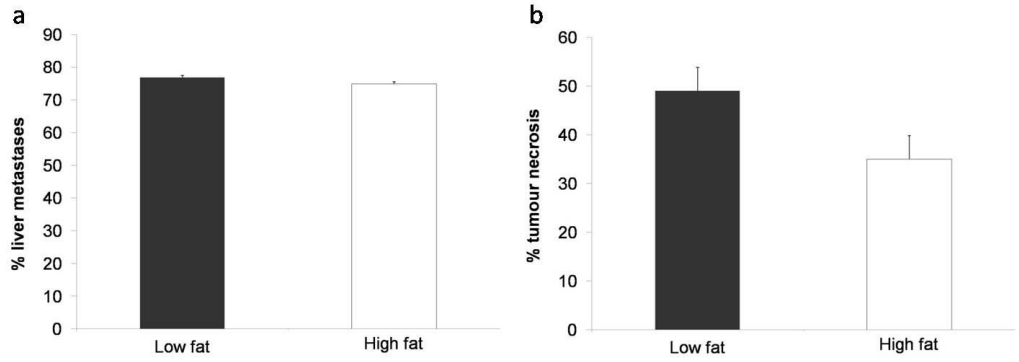


Figure 1 – A high fat diet does not induce tumor growth or have an effect on tumor necrosis. Mice were induced with colorectal liver metastases via intrasplenic injection. The effect of a high fat diet (60% fat) versus low fat diet on the percentage of liver metastases was investigated 3 weeks post tumor induction. a. A HF diet did not stimulate liver metastases 76.8% ± 0.61 versus low fat 74.9% ± 0.42 (p = 0.83). b. Percentage tumor necrosis was similar in the LF 49% ± 6.4 versus HF 35% ± 4.1 (p = 0.076).

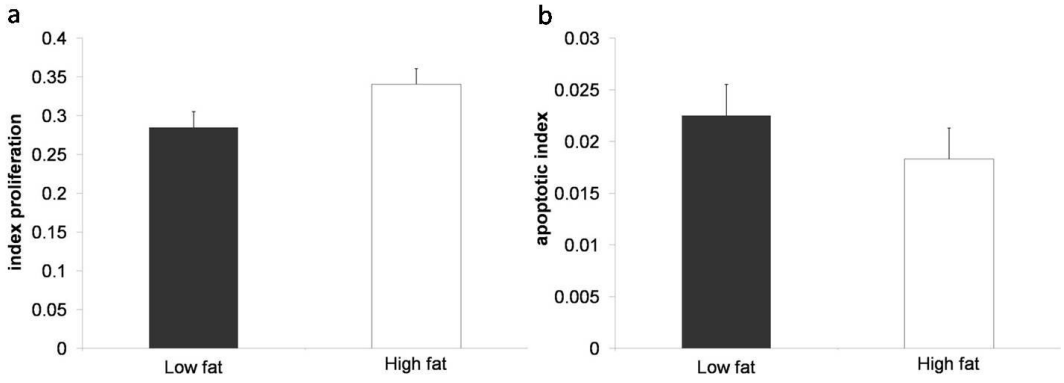


Figure 2 – High fat results in a trend towards increased tumor proliferation but has no effect on tumor apoptosis.
Tumor proliferation and apoptosis were assessed using immunohistochemistry for the nuclear proliferative marker, Ki-67 and caspase-3 respectively. Positive staining is demarcated by intense brown staining using the DAB method. a. There was a trend towards increased tumor proliferation in the high fat diet group 0.34 ± 0.02 compared to the low fat 0.29 ± 0.02 group (p = 0.061). b. Both groups demonstrated highly proliferative tumors with minimal apoptosis 0.03 ± 0.005 versus high fat 0.02 ± 0.003 (p = 0.23).

blue exclusion was used to attain a cell concentration of $1X10^6$ cells/ml. Mice were anaesthetized using a mixture of ketamine (100mg/kg, Pfizer, New Zealand) and xylazine (10mg/kg, Troy Laboratories, Australia). Liver metastases were induced via an 0.05 ml intrasplenic injection (50,000 cells). Time was allowed for passage of tumor cells from the spleen to the liver via the portal circulation after which a splenectomy was performed. In this model macroscopic liver tumors are evident by day 10 following induction. This is followed by a rapid exponential growth phase with fully established tumors by day 20 [21]. Animals were killed 21 days following tumor induction. The volume of tumor within the liver was determined by stereology using techniques previously described [21].

Histologic analysis

Tumor histology was examined using haematoxylin and eosin (H&E) staining using standard protocol [22]. Sections were examined using light microscopy to detect changes in tumor cell morphology and necrosis following treatment. The percentage of tumor necrosis was quantified using image analysis software.

Tumor cell kinetics

The effect of high and low calorie diet on tumor apoptosis and proliferation was quantified using immunohistochemistry of paraffin embedded sections. Detection was conducted using the Envision + horseradish peroxidase detection system (K4011) (DakoCytomation, Denmark). Antigen retrieval was performed using citrate buffer (1mM, pH=6) at 99°C for 20 minutes. Sections were then incubated with the primary antibody, Ki-67 (mAb DakoCytomation, Denmark) and caspase-3 (R&D Systems, USA). Endogenous peroxidase activity was quenched using peroxidase block (Envision+ kit, DakoCytomation, Denmark) for 30 minutes at room temperature. This was performed before (Ki-67) or after (caspase-3) incubation with the primary antibody. A secondary antibody (polyclonal rabbit anti-

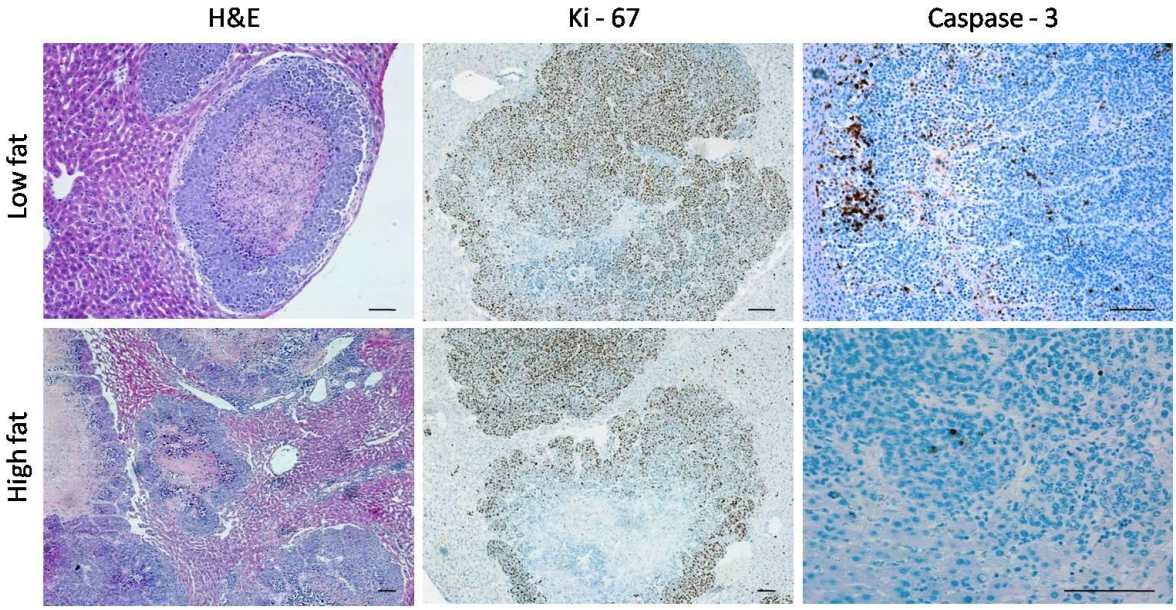


Figure 3 – Similar histologic features were demonstrated by low and high fat tumor specimens. Routine hematoxylin and eosin staining was performed on 3 μm sections and the percentage of tumor necrosis was quantified. Control tumors demonstrated poor-to-moderate differentiation. Tumors were cohesive with minimal central necrosis and displaced the surrounding normal liver. Ki-67 staining within tumors was heterogeneous, with features observed common to both control and high fat groups. Immunoreactivity within each specimen was variable with some tumors being highly proliferative, whilst others displayed minimal proliferation. Apoptotic cells were demarcated by intense brown staining using the DAB method and no real differences were observed between low and high fat specimens.

rat, E0468) was applied at a 1:200 dilution for 30 minutes (this step was omitted for caspase-3). Sections were then incubated with horseradish peroxidase (HRP)-complex for 30 minutes at room temperature. The substrate-chromogen, DAB (diaminobenzidine), was added and incubated for 10 minutes. Sections were counterstained with haematoxylin, dehydrated in ascending ethanol and mounted for viewing with light microscopy. Presence of the respective antigens was denoted by brown staining of the nuclei, (proliferation) or positively stained tumor cells (caspase-3).

For Ki-67 and caspase-3, a minimum of 10,000 cells per treatment group was counted. Immunohistochemically stained sections were captured using a digital light microscope (Nikon Coolscope®, Nikon Corporation, Japan) at a magnification between 40x and 400x. Images were captured for tumors from each liver sample using a pattern which ensured unbiased selection and no overlap between images. Expression was quantified in a blinded manner using ImagePro-Plus® (Cyber media, Version 4.5.1, Australia) and expressed as the number of positively stained cells per micrometre square area of tumor tissue over ten high-power fields.

Statistical analysis

All data is expressed as the mean ± standard error of the mean, (S.E.M) using a Statistical Package for the Social Sciences (SPSS 11.5®, Chicago, Illinois, USA). Pair-wise comparisons were analyzed using parametric (student T-test) or non-parametric (Mann-Whitney) tests where appropriate. All tests were two-sided and $P<0.05$ was considered statistically significant. Animal numbers were based on pilot studies, estimating a minimum requirement of 8-10 animals per study group to detect a 20-30 percent increase in tumor growth, each with a power of at least 0.8.

Results

Liver metastases

The two diet regimes were well tolerated by mice. Consumption of caloric intake was monitored by the number of food cubes. It was observed that mice in the high fat group did not consume as much quantity as the low fat group. Infact at the time of assessment, mice in the HF group weighed less than those in the LF group (23.5 g % ± 4.1 versus 30.0 g % ± 4.1; p<0.001). The overall percentage liver metastases were similar in both groups. A HF diet did not stimulate liver metastases 76.8% ± 0.61 versus low fat 74.9% ± 0.42 (p = 0.83) (Figure 1*a*). There was no difference in overall size of or number of tumors between the two groups. Extrahepatic metastases were not observed in either group.

Tumor necrosis

Percentage tumor necrosis was similar in the LF 49% ± 6.4 versus HF 35% ± 4.1 (p = 0.076) (Figure 1b). There was no evidence of hepatic steatosis in the normal liver and tumor morphology was not altered between the two groups.

Tumor cell kinetics

No effect on tumor cell kinetics was observed (Figure 2). Ki-67 staining within tumors was heterogeneous, with features observed common to both control and high fat groups. Immunoreactivity within each specimen was variable with some tumors being highly proliferative (Figure 3), whist others had minimal proliferation. Poorly differentiated tumors demonstrated a higher percentage of proliferating cells compared to well differentiate tumors. Proliferation of the normal liver was unaltered by caloric intake. Small sized tumors (1-200 μm in diameter) demonstrated the highest degree of proliferating cells. The same was observed in poorly differentiated large tumors (>500 μm in diameter). There was a trend towards increased tumor proliferation in the high fat diet group 0.34 ± 0.02 compared to the low fat 0.29 ± 0.02 group but this was not statistically significant, p = 0.061 (Figure 2a).

Both groups demonstrated highly proliferative tumors with minimal apoptosis 0.03 ± 0.005 versus high fat 0.02 ± 0.003 (p = 0.23) (Figure 2b).

Discussion

Obesity has been implicated as an independent factor associated with the risk of developing [1,23], risk of recurrence and mortality [24] from colorectal cancer compared to normal weight individuals. Accumulating epidemiologic evidence demonstrates an association between obesity and multiple other malignancies including cholangiocarcinoma (in females) [25], breast cancer (in post-menopausal women) [20,26], liver [27], colon [3,18], gastric [12] and pancreatic cancer [1,16]. It is also associated with increased mortality of oesophageal cancer [28] and renal cell carcinoma [1]. In a murine model of pancreatic cancer, Zyromski and colleagues observed that obese mice developed larger tumors and more metastases attributed to increased

proliferation relative to lean mice [4]. This study investigated the effect of a high fat diet on stimulation of colorectal cancer liver metastases. We found no difference in the percentage of liver metastases or extra-hepatic metastases, tumor volume or size of tumors in mice fed a HF diet (60% saturated fat) versus a LF diet. This has been observed in other studies using a HF diet [29,30].

The effect of HF diet has not been previously investigated in CBA mice for CRC liver metastasis. We found a HF diet (60% saturated fat) overall, did not result in weight gain compared to a LF diet. Previous studies investigating the effect of high fat diets have observed similar findings [30-32]. Certain strains of mice are relatively resistant to the obesity-promoting effects of a fat-rich diet [29-35] suggesting that propensity to obesity may be species specific. Another reason may be differences in duration of exposure to the diet. Suwit et al showed in C57BL6/J male mice fed a 58% fat diet for 8 months [35] were more obese than the same strain fed for 6 months [36]. The same study observed no difference in weight with HF diet at 5 months but a significant difference at 8 months [36]. The HF diet in our study contained 32.84% of saturated fat. Other studies have demonstrated obesity with 93% saturated fat content, but not with a saturated fat content of 35% [30]. We also observed that overall consumption in the HF diet group was less than the LF group. The HF diet contained 4.8% polyunsaturated fat as opposed to 15.9% used in another study that showed obesity with HF diet [36]. Several studies have observed that polyunsaturated fat particularly linoleic acid may increase satiety [37,38].

There is also the concept of obesity resistance where certain cytokines respond to feeding conditions to regulate energy metabolism [39,40]. In a study conducted on mice expressing a particular subunit, Cnot3 (involved in a complex critical to metabolic regulation) mice were lean with hepatic and adipose tissues containing reduced levels of lipids, and showed increased metabolic rates and enhanced glucose tolerance despite being on a HF diet [39]. Catabolic factors may also be increased in the presence of malignancy [41].

Adiposity has both systemic effects and local effects resulting in fatty infiltration of visceral organs [42]. Hepatic steatosis is established in the development and progression to hepatocellular carcinoma [43]. Similarly, fat in the gall bladder can alter function leading to cholelithiasis, inflammation, fibrosis and ultimately cancer [25]. Patel *et al*., demonstrated that central obesity is a risk factor for pancreatic cancer independent of BMI [2] and this has been observed in breast [19], colon [3], prostate [44], endometrial [45], liver [10] and gastrointestinal cancer [12]. On histologic examination of the normal liver and tumors we did not observe evidence of steatosis in the HF specimens. This is in contrast to other studies demonstrating increased fatty infiltration in both the tumor and host tissue [4,27]. The absence of hepatic steatosis in our study is however, likely due to the fact animals were not obese. HF diet did however, tend to increase tumor proliferation compare to LF diet, but this was not statistically significant. Some studies have reported a reduction in apoptosis in the obese state [46,47]. In our study there was no difference in apoptotic index and similar findings have been observed previously [4,48].

In this study, CBA mice induced with CRC liver metastases were not susceptible to obesity when fed a HF diet and consequently a HF diet did not result in tumor stimulation. The vast proportion of literature implicates the metabolic syndrome and systemic and local organ changes directly associated with obesity as contributing factors to metastases

and poor prognosis. A HF diet in itself is therefore not a risk factor for tumor stimulation. Further studies could analyze the effect in CBA mice exposed to a prolonged HF diet to determine whether this is the case.

Learning Points

- A high fat diet associated with obesity has been connected with carcinogenesis.
- We demonstrate that high fat diet alone, in a non-obese murine model does not appear to alter the growth.
- A high fat diet does not alter the spread and tumour kinetics of colorectal cancer liver metastases.

Authors Contribution

JD, CC, MN: study design, conception and interpretation of data

JD, MN: animal surgery, literature review, writing and critical revision of article, guarantor of integrity of the work as a whole, from inception to published article

JD, SWW, LN, MN: analysis and interpretation of data, stereology, statistical analysis

JD, SWW: final approval of the version to be published

All authors: experimental setup and overlooking experiment, acquisition of specimens and data, (tumour sampling, specimen sectioning, stereology, and immunohistochemistry), revision of article

Conflict of Interests

The authors declare that there are no conflict of interests.

Ethical Considerations

The study was approved by the Institute animal ethics committee.

Funding

None declared

Acknowledgement

None

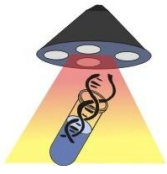
References

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.[pubmKed]
2. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE: Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. Cancer Epidemiol Biomarkers Prev 2005;14:459-66.[pubmed]
3. Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C: Obesity is an independent prognostic variable in colon cancer survivors. Clin Cancer Res 2010;16:1884-93.[pubmed]
4. Zyromski NJ, Mathur A, Pitt HA, Wade TE, Wang S, Nakshatri P, Swartz-Basile DA, Nakshatri H: Obesity potentiates the growth and dissemination of pancreatic cancer. Surgery 2009;146:258-63.[pubmed]
5. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS: Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 2007;86:s858-66.[pubmed]
6. Potter JD: Nutrition and colorectal cancer. Cancer Causes Control 1996;7:127-46.[pubmed]
7. Hunter DJ, Willett WC: Nutrition and breast cancer. Cancer Causes Control 1996;7:56-68.[pubmed]
8. .Wolk A, Lindblad P, Adami HO: Nutrition and renal cell cancer. Cancer Causes Control 1996;7:5-18.[pubmed]
9. Bergstrom A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A: Obesity and renal cell cancer--a quantitative review. Br J Cancer 2001; 85:984-90.[pubmed]
10. Qian Y, Fan JG: Obesity, fatty liver and liver cancer. Hepatobiliary Pancreat Dis Int 2005;4:173-7.[pubmed]
11. Aihw Aiohaw: Cancer In Australia: An Overview, 2006. Australian Institute Of Health And Welfare, 2006.
12. Kitayama J, Tabuchi M, Tsurita G, Ishikawa M, Otani K, Nagawa H: Adiposity and gastrointestinal malignancy. Digestion 2009;79 Suppl 1:26-32.[pubmed]

13. Sierra-Honigmann MR, Nath AK, Murakami C, Garcia-Cardena G, Papapetropoulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ, Flores-Riveros JR: Biological action of leptin as an angiogenic factor. Science 1998;281:1683-6.[pubmed]
14. Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? Lancet 2001;357:539-45.[pubmed]
15. Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, Flanagan L, Tenniswood MP, Guha C, Lisanti MP, Pestell RG, Scherer PE: Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization. Oncogene 2003;22:6408-23.
16. Mathur A, Zyromski NJ, Pitt HA, Al-Azzawi H, Walker JJ, Saxena R, Lillemoe KD: Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009;208:989-94; discussion 94-6.[pubmed]
17. Xue L, Yang K, Newmark H, Lipkin M: Induced hyperproliferation in epithelial cells of mouse prostate by a Western-style diet. Carcinogenesis 1997;18:995-9.[pubmed]
18. Newmark HL, Yang K, Lipkin M, Kopelovich L, Liu Y, Fan K, Shinozaki H: A Western-style diet induces benign and malignant neoplasms in the colon of normal C57Bl/6 mice. Carcinogenesis 2001;22:1871-5.
19. Rose DP, Komninou D, Stephenson GD: Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev 2004;5:153-65.[pubmed]
20. van Noord PA: Breast cancer and the brain: a neurodevelopmental hypothesis to explain the opposing effects of caloric deprivation during the Dutch famine of 1944-1945 on breast cancer and its risk factors. J Nutr 2004;134:3399S-406S.[pubmed]
21. Kuruppu D, Christophi C, Bertram JF, O'Brien PE: Characterization of an animal model of hepatic metastasis. J Gastroenterol Hepatol 1996;11:26-32.[pubmed]
22. Daruwalla J, Nikfarjam M, Malcontenti-Wilson C, Muralidharan V, Christophi C: Effect of thalidomide on colorectal cancer liver metastases in CBA mice. J Surg Oncol 2005;91:134-40.[pubmrd]
23. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec G, Bergmann MM: Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920-31.[pubmed]
24. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, O'Connell MJ, Wolmark N: Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647-54.[pubmed]
25. Pitt HA: Hepato-pancreato-biliary fat: the good, the bad and the ugly. HPB (Oxford) 2007;9:92-7.[pubmed]
26. Garofalo C, Koda M, Cascio S, Sulkowska M, Kanczuga-Koda L, Golaszewska J, Russo A, Sulkowski S, Surmacz E: Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli. Clin Cancer Res 2006;12:1447-53.[pubmed]
27. Yakar S, Nunez NP, Pennisi P, Brodt P, Sun H, Fallavollita L, Zhao H, Scavo L, Novosyadlyy R, Kurshan N, Stannard B, East-Palmer J: Increased tumor growth in mice with diet-induced obesity: impact of ovarian hormones. Endocrinology 2006;147:5826 34.[pubmed]
28. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, Dubrow R, Schoenberg JB, Mayne ST, Farrow DC, Ahsan H, West AB: Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1998;90:150-5.[pubmed]
29. Parekh PI, Petro AE, Tiller JM, Feinglos MN, Surwit RS: Reversal of diet-induced obesity and diabetes in C57BL/6J mice. Metabolism 1998;47:1089-96.[pubmed]
30. Surwit RS, Petro AE, Parekh P, Collins S: Low plasma leptin in response to dietary fat in diabetes- and obesity-prone mice. Diabetes 1997;46:1516-20.[pubmed]
31. Bergen HT, Mizuno T, Taylor J, Mobbs CV: Resistance to diet-induced obesity is associated with increased proopiomelanocortin mRNA and decreased neuropeptide Y mRNA in the hypothalamus. Brain Res 1999;851:198-203.[pubmed]
32. Black BL, Croom J, Eisen EJ, Petro AE, Edwards CL, Surwit RS: Differential effects of fat and sucrose on body composition in A/J and C57BL/6 mice. Metabolism 1998;47:1354-9.[pubmed]
33. Jiang T, Wang Z, Proctor G, Moskowitz S, Liebman SE, Rogers T, Lucia MS, Li J, Levi M: Diet-induced obesity in C57BL/6J mice causes increased renal lipid accumulation and glomerulosclerosis via a sterol regulatory element-binding protein-1c-dependent pathway. J Biol Chem 2005;280:32317-25.
34. Prpic V, Watson PM, Frampton IC, Sabol MA, Jezek GE, Gettys TW: Differential mechanisms and development of leptin resistance in A/J versus C57BL/6J mice during diet-induced obesity. Endocrinology 2003;144:1155-63.[pubmed]
35. Surwit RS, Feinglos MN, Rodin J, Sutherland A, Petro AE, Opara EC, Kuhn CM, Rebuffe-Scrive M: Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. Metabolism 1995;44:645-51.[pubmed]
36. Gallou-Kabani C, Vige A, Gross MS, Rabes JP, Boileau C, Larue-Achagiotis C, Tome D, Jais JP,

Junien C: C57BL/6J and A/J mice fed a high-fat diet delineate components of metabolic syndrome. Obesity (Silver Spring) 2007;15:1996-2005.[pubmed]
37. Lawton CL, Delargy HJ, Brockman J, Smith FC, Blundell JE: The degree of saturation of fatty acids influences post-ingestive satiety. Br J Nutr 2000;83:473-82.[pubmed]
38. Westerterp-Plantenga MS: Fat intake and energy-balance effects. Physiol Behav 2004;83:579-85.[pubmed]
39. Morita M, Oike Y, Nagashima T, Kadomatsu T, Tabata M, Suzuki T, Nakamura T, Yoshida N, Okada M, Yamamoto T: Obesity resistance and increased hepatic expression of catabolism-related mRNAs in Cnot3+/- mice. EMBO J 2011;30:4678-91.[pubmed]
40. Yamamoto T, Habata Y, Matsumoto Y, Yasuhara Y, Hashimoto T, Hamajyo H, Anayama H, Fujii R, Fuse H, Shintani Y, Mori M: Apelin-transgenic mice exhibit a resistance against diet-induced obesity by increasing vascular mass and mitochondrial biogenesis in skeletal muscle. Biochim Biophys Acta 2011;1810:853-62.[pubmed]
41. Tisdale MJ: Mechanisms of cancer cachexia. Physiol Rev 2009; 89: 381-410.[pubmed]
42. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol 2003;14:281-7.[pubmed]
43. McCullough AJ: Pathophysiology of nonalcoholic steatohepatitis. J Clin Gastroenterol 2006;40 Suppl 1:S17-29.[pubmed]
44. Barb D, Neuwirth A, Mantzoros CS, Balk SP: Adiponectin signals in prostate cancer cells through Akt to activate the mammalian target of rapamycin pathway. Endocr Relat Cancer 2007;14:995-1005.[pubmed]
45. Dal Maso L, Augustin LS, Karalis A, Talamini R, Franceschi S, Trichopoulos D, Mantzoros CS, La Vecchia C: Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab 2004;89:1160-3.[pubmed]
46. Hoda MR, Popken G: Mitogenic and anti-apoptotic actions of adipocyte-derived hormone leptin in prostate cancer cells. BJU Int 2008;102:383-8.[pubmed]
47. Hoda MR, Keely SJ, Bertelsen LS, Junger WG, Dharmasena D, Barrett KE: Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. Br J Surg 2007;94:346-54.[pubmed]
48. Korner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, Bullen J, Neuwirth A, Tseleni S, Mitsiades N, Kiess W, Mantzoros CS: Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. J Clin Endocrinol Metab 2007;92:1041-8.[pubmed]

World Journal of Surgical Research



Published by Narain Publishers Pvt. Ltd. (NPPL)
The **Open Access** publishers of **peer reviewed** journals. All articles are immediately published online on acceptance.
All articles published by NPPL are available **free** online