

Review

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## Metabolism and cancer-select topics

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### Abstract

Metabolism and cancer intersect in multiple ways. Cancer has unique metabolic properties, including an inordinate reliance on anaerobic glycolysis (the Warburg effect). From an evolutionary standpoint, increased cancer incidence is associated with increased metabolic rates across species. Epidemiological data prove that a group of overlapping metabolic alterations, including obesity, type 2 diabetes Mellitus, nonalcoholic fatty liver disease, and metabolic syndrome, constitute predisposing risk factors for cancer development in multiple anatomical sites. The molecular pathways underpinning this association involve hyperinsulinemia, hyperglycemia, sex hormones, adipokines, chronic inflammation, oxidative stress, and altered immune response.

**Keywords:** Cancer, metabolism, type 2 diabetes Mellitus (T2DM), obesity

### INTRODUCTION

The existence of an association between metabolic alterations and cancer is multifaceted. Cancer cells have long been known to have unique metabolic properties, including a preference for aerobic glycolysis (the so-called Warburg effect). Yet, an association between obesity, type 2 Diabetes Mellitus (T2DM), their associated and partly overlapping metabolic syndrome (MetS), and nonalcoholic fatty liver disease (NAFLD) and cancer development has also been unveiled relatively recently. Since these diseases have a high prevalence, which is expected to rise even further in the near future<sup>[1]</sup>, this association is likely to



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continue to exact a high toll in terms of financial and human burden for years to come. However, the extent of this association remains poorly appreciated, even among physicians, and its molecular basis is incompletely understood.

## METHODS

We searched Pub med data base using the key words ([“metabolism”], [“obesity”], [“diabetes”], [“NAFLD”], [“Met S”], [“calorie restriction”], [“bariatric surgery”], [“hyperinsulinemia”], [“hyperglycemia”], [“exercise”], [“adipokines”], [“metformin”]) and [“cancer”]; [“Warburg effect”].

## AIMS

In this review, we endeavored to cover select topics relating to metabolism and cancer with the following aims: (1) provide a general biological frame of reference for the topic; (2) sketch out the main epidemiological and clinical data proving this association; (3) identify molecular pathways that underpin it and that point to future lines of research. Outside the scope of this study are changes induced in the host by cancer, the most notable of which is cancer cachexia<sup>[2]</sup>.

### **Cancer has unique metabolic features: the Warburg effect**

Warburg and Cory demonstrated in the 1920s that cancer cells have high rates of glucose uptake and of conversion of glucose to lactate and bypass mitochondrial oxidative phosphorylation, even in the presence of oxygen. This phenomenon, also called aerobic glycolysis, has been consistently confirmed by modern studies<sup>[3]</sup>.

Increased glucose uptake by malignant tumors, mediated by increased levels of transporters, notably GLUT-1<sup>[4]</sup> constitutes the biological basis for the use of positive emission tomography scans, after the administration of radiolabeled glucose tracer, in the detection of malignancy. This metabolic abnormality is regarded as one of the fundamental hallmarks of cancer<sup>[5]</sup>.

Further proof of the principle of the crucial role of energy metabolism in the development of cancer is constituted by the occurrence of mutations in succinate dehydrogenase in pheochromocytomas and paragangliomas<sup>[3]</sup> and isocitrate dehydrogenase 1 in adult glioblastomas<sup>[6]</sup>. However, it is currently appreciated that, when it comes to energy metabolism, tumors are more heterogeneous and flexible than originally appreciated and are also capable of oxidative phosphorylation<sup>[3]</sup>.

The biological rationale for the Warburg effect and for its selection by cancer cells remains unclear. Proposed mechanisms include the satisfaction of increased energy requirements of tumor cells by the quick generation of ATP and the generation of NADPH and NADH for the de novo synthesis of lipids and nucleotides<sup>[7]</sup>.

It has also been noted that high levels of lactate in the tumor microenvironment as a consequence of the Warburg effect inhibit cytotoxic immune cells while leaving T-reg lymphocytes unaffected, thus effectively dampening the antineoplastic activity of the immune system<sup>[8,9]</sup>. Another proposed consequence of the Warburg effect is the direct promotion of growth at the transcriptional level, secondary to the chromatin remodeling induced by histone acetylation<sup>[10-12]</sup> as a consequence of increased Acetyl CoA levels<sup>[13]</sup>.

It is currently believed that multiple metabolic alterations characterize cancer cells and represent both the basis for possible novel tumor classification schemes and novel treatment modalities. This topic is covered in depth in other papers<sup>[14]</sup> and remains beyond the scope of this review.

## Metabolism modulates the risk of cancer development and progression

Several lines of evidence point to a relation between metabolism and cancer development.

### *Peto's paradox.*

The current model of cancer development postulates that cancer arises from the accumulation of mutations in key genes that are crucial in the development and progression of malignant cell clones, such as those controlling cell growth and tissue invasion. Richard Peto made seminal observations on carcinogenesis, pointing out that the probability of cancer development is proportional to the length of exposure to carcinogens, as it is to be expected if the probability of carcinogen-induced mutation were a stochastic event. Based on this model, it would be expected that an increased number of cells would result in higher cancer incidence, by increasing the number of possible targets of mutagenic agents. Paradoxically, Peto noted that, across species, an increased organ size does not only result in an increased cancer incidence but in a lower incidence<sup>[15,16]</sup>.

Different explanations exist for this paradox. One is the evolution of increased cancer suppressor mechanisms in larger animals. Elephants, for instance, that are known to have a very low cancer incidence, are endowed with multiple copies of the tumor suppressor gene p53<sup>[15,16]</sup>. Another explanation, which does not exclude the first but could constitute a compounding risk factor, is that a direct relationship exists between cancer incidence and metabolic rate, and both are comparatively higher in smaller than in larger animals<sup>[16,17]</sup>.

The discovery of the relationship between metabolic rate and body size is credited to Kleiber, who observed in the 1930s that per unit of body weight, smaller animals have a much higher basic metabolic rate than larger animals<sup>[16,17]</sup> (a historical perspective of the topic is provided by Niklas *et al.*<sup>[18]</sup>). Indeed, a large European prospective study including ~140,000 men and 317,000 women found an association between increased metabolic rate and increased risk of multiple cancer types, independent of obesity<sup>[19]</sup>. This phenomenon has been linked to an increased mutagenic rate resulting from higher basic metabolic rates, mediated by by-products of metabolism<sup>[16]</sup>.

The finding that calorie restriction, which results in a reduced basic metabolic rate<sup>[20]</sup>, is linked to reduced cancer incidence (further discussed in section IV) appears to corroborate this hypothesis<sup>[21,22]</sup>. This reduced cancer incidence has been linked to inhibition of mTOR, since pharmacological or (in transgenic mice) knockout of mTOR is linked to prolonged lifespan. Presumably, decreased energy demands reduce mitochondrial activity. In support of this hypothesis is the fact that metformin also inhibits mitochondrial activity<sup>[16]</sup>.

The association between higher cancer risk and obesity appears paradoxical, based on the assumption that obesity is linked to a *reduced* basic metabolic rate<sup>[23]</sup>. Obesity is associated with higher energy expenditure<sup>[24]</sup>. However, it is not clear whether the basic metabolic rate in obesity, when adjusted for fat-free mass is reduced. Although some studies do show a reduced basic metabolic rate associated with higher BMI<sup>[25]</sup>, most studies do not confirm this finding<sup>[26]</sup>, and some studies show an *increased* basic metabolic rate in obesity<sup>[27,23]</sup>. Methodological differences may be, at least in part, responsible for these differences.

Some studies show that physical activity may increase basic metabolic rate, secondary to increased energy expenditure and increased fat-free mass<sup>[28,29]</sup>, which in turn is associated with reduced cancer risk (discussed later). However, some studies have failed to show a similar effect after long-term training<sup>[30]</sup>. Thus, the relation between physical activity and basal metabolic rate is complex. The validity of an additive model,

which postulates a direct and linear correlation between energy expenditure and metabolism, has been questioned. A constrained total energy expenditure model has been proposed<sup>[31]</sup>, which envisions an increase of energy expenditure with physical activity at low activity, and a plateau at a higher activity level, with the adaptation of the basic metabolic rate to maintain total energy expenditure within a narrow range. Many data support this model, including the fact that long-term exercise may cause a *reduction* of the basic metabolic rate in humans<sup>[32]</sup> and the fact that African hunter-gatherers have the same energy expenditure as westerners who live a sedentary life<sup>[31]</sup>. Animal models have further shown that the body maintains constant energy expenditures in response to increased physical activity, by reducing growth, basic metabolic rate, and lactation, even at the cost of cannibalizing nursing offspring<sup>[32]</sup>.

### *Obesity*

Calle *et al.*<sup>[33]</sup>, in their seminal prospective study of > 900,000 US adults, found obesity (defined as a BMI > 40) to confer a 52% higher mortality for malignancy to men and 62% to women, compared with individuals of normal weight. Malignant tumors involved were cancers of the esophagus, colorectum, liver, gallbladder, pancreas, and kidney, non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). Obesity was a significant risk factor overall in ~5%-20% of tumors, with the lowest risks found in the presence of smoking, the higher in its absence<sup>[33]</sup>.

It has been further shown that specific histological types of cancers are associated with increased BMI. So, the rate of Estrogen Receptor and Progesterone Receptor (ER and PR)+, but not ER and PR- and Er+ and Pr- breast cancers is increased in patients with increased BMI. Similarly, patients in the highest quartile of BMI, in a large Swedish cohort had a higher incidence of grade 2, low proliferative rate, Er  $\alpha$  (not Er  $\beta$ ), and PR+ Her2- tumors<sup>[34]</sup>. In addition, obesity is inversely associated with premenopausal and directly with postmenopausal breast cancer<sup>[35]</sup>. Increased BMI is associated with increased incidence of papillary thyroid carcinoma and cardias but not non-cardias adenocarcinomas of the stomach and of endometrial adenocarcinoma, endometrioid type (type I endometrial cancer)<sup>[34]</sup>.

In a meta-analysis studying, the cancer burden attributable to increased BMI (defined as  $\geq 25$  kg/m<sup>2</sup>) in 30 European countries, the population attributable risk was 2.5 and 4% for men and women, respectively, with 65% of cancers represented by endometrial, postmenopausal breast and colorectal cancer<sup>[36]</sup>. This study confirmed the association with increased BMI of cancers of the colo-rectum, gallbladder, esophagus (adenocarcinoma), kidney, endometrium and postmenopausal breast, NHL, MM and also found an increased risk for prostate cancer and MM. The same authors found, in a meta-analysis of 221 prospective data sets, including 282,137 individuals, that, in men, a 5 Kg/m<sup>2</sup> increase in BMI was strongly associated with esophageal adenocarcinoma, thyroid, colon, and kidney cancer; in women with endometrial, gallbladder and esophageal adenocarcinoma. A weaker association was found for rectal cancer and malignant melanoma in men, postmenopausal breast cancer, thyroid pancreatic and colon cancer in women and, in both genders, leukemia, multiple myeloma, and NHL<sup>[36]</sup>. This study highlights that gender differences modulate the risk of BMI-associated malignancy and that the associations are incremental per 5 Kg/m<sup>2</sup> increases in weight and broadly consistent across geographic differences, pointing to an etiological, rather than incidental relation between the two conditions.

In the case of prostate cancer, the association with obesity is quite nuanced and exemplifies how global epidemiological data need to be examined in great detail to allow for all the clinical and pathological variables of the disease to be accounted for [Table 1]. Prostate cancer's incidence is much higher than its overall mortality<sup>[37]</sup>. The realization of such disparity is indeed the basis for an "active surveillance" approach to this disease, relying on the identification of tumors that most likely will behave aggressively, based on

**Table 1. Association of cancer with obesity and T2D can be complex and histotype specific**

|                |   |
|----------------|---|
| <b>Obesity</b> | <ul style="list-style-type: none"> <li>↓ Premenopausal breast cancer<sup>[35]</sup></li> <li>↑ Post menopausal breast cancer<sup>[35]</sup></li> <li>Er, Pr + breast cancer<sup>[34]</sup></li> <li>Cardias adenocarcinoma<sup>[34]</sup></li> <li>Type I Endometrial Cancer<sup>[34]</sup></li> <li>↓ Overall Prostate cancer incidence<sup>[58,148]</sup></li> <li>↑ Prostate cancer aggressiveness<sup>[39,148-153]</sup></li> </ul> |
| <b>T2DM</b>    | <ul style="list-style-type: none"> <li>↓ Prostate cancer incidence<sup>[58]</sup></li> </ul>  |

histological grading at biopsy, PSA value, and estimated tumor size<sup>[38]</sup>. Many studies found that high BMI is associated with an increased incidence of exactly those subsets of prostate cancers that have higher aggressiveness<sup>[39]</sup>. Dickerman *et al.*<sup>[40]</sup> likewise found an association between increases in visceral fat and thigh subcutaneous fat and the risk of advanced and fatal disease.

Not surprisingly, NAFLD and nonalcoholic Steato Hepatitis (NASH), which are tightly related to obesity and to the MetS<sup>[41]</sup>, also confer an increased risk of malignancy for cancers of the esophagus, stomach, pancreas, colon, thyroid, lung, urinary tract, female genital tract<sup>[41,42]</sup>, and liver<sup>[43]</sup>.

An apparent exception to the association existing between cancer and obesity exists for lung cancer, since a negative correlation exists between BMI and lung cancer's incidence and mortality<sup>[44-47]</sup>. This apparent paradox is explained by a retrospective study of 513 resected non-small cell lung cancer, showing an association between visceral fat (determined by CT scan) and increased aggressiveness for these limited-stage tumors<sup>[48]</sup>. Similarly, a higher waist circumference has been found to correlate with an increased risk of lung cancer<sup>[49,50]</sup> and visceral adipose tissue with a worse prognosis in patients undergoing chemotherapy<sup>[50]</sup>. An association between visceral adiposity and cancer incidence and/or prognosis has been unveiled in other organs as well. In a cohort of 106 patients, Iwase *et al.*<sup>[51]</sup> found that breast cancer patients in the upper tertile for upper body obesity had shorter disease-free survival after neoadjuvant chemotherapy. In a cohort of 1257 hepatocellular carcinoma patients, a high ratio of visceral to subcutaneous fat (assessed by CT scans) predicted increased mortality, independent of cancer stage and Child-Pugh class, and by multivariate analysis, this association was found to be independent of BMI<sup>[52]</sup>. Donkers *et al.*<sup>[53]</sup> found in a cohort of 176 patients with high-grade endometrial cancer, that high visceral fat constituted an independent predictor of poor prognosis in type II (non-endometrioid-type) cancers.

Many studies specifically link visceral adiposity to the incidence and prognosis of colon cancer. Lee *et al.*<sup>[54]</sup> studied a cohort of 1290 postmenopausal women with colon cancer, matched with 670 postmenopausal women without colon cancer that had undergone a screening colonoscopy. After identifying a study cohort that included a group of 199 pairs of colon cancer-healthy Korean patients, well balanced for BMI and smoking status, patients with visceral adiposity volumes in the 67th percentile or higher had an increased incidence of colorectal cancer<sup>[54]</sup>

Park *et al.*<sup>[55]</sup> demonstrated in a cohort of 472 stage III colorectal cancer patients, that both higher visceral to total adipose tissue (VT) and visceral to subcutaneous adipose tissue ratios were associated with poor survival and that a higher VT at the L3-L4 level was associated with a higher risk of peritoneal seeding and tumor recurrence. In a review of 4722 NAFLD patients, Allen *et al.*<sup>[56]</sup> found that NAFLD was associated

with an increased risk of hepatic and non-hepatic cancers, prompting the hypothesis that “*the presence of NAFLD works as a reliable marker of predominantly visceral obesity*”<sup>[57]</sup>.

These collective data paint a more nuanced scenario of the interaction between obesity and cancer, pointing out that the anatomical pattern of fat distribution and particularly, the extent of accumulation of visceral fat plays an important role in this association.

### *T2DM*

T2DM confers an increased risk for the development of endometrial cancer, intrahepatic cholangiocarcinoma, colon, liver, pancreas, and breast cancer<sup>[58]</sup>. In a large prospective study, Saydah *et al.*<sup>[59]</sup> using a cohort of close to 23,000 patients, found that patients within the highest quartile of HbA1c had a higher risk for colorectal cancer; a similar association with glycalbumin was also found by others<sup>[60]</sup>. An increased risk for colorectal cancer was identified in a meta-analysis by Yukhara, independent of other risk factors, i.e., smoking, obesity, and physical exercise<sup>[61]</sup>.

The risk of prostate cancer is decreased by T2DM<sup>[58]</sup> [Table 1], a fact possibly explained by the lower androgen levels associated with T2DM, resulting in reduced stimulation of androgen receptor sensitive prostate cancer cells<sup>[58]</sup>.

In a meta-analysis, Zhu *et al.*<sup>[62]</sup> found including 2.2 million patients, that DM is associated with a reduction in survival at 5 years ranging from 16% to 19% respectively for colorectal, colonic and rectal cancers. Interestingly, some authors have found that T2DM confers to women a higher risk of colorectal cancer than men<sup>[63]</sup>. This finding constitutes yet another example of the ability of gender to modulate the biology of human diseases<sup>[64]</sup>. An association between the MetS and colon cancer was also found by Esposito<sup>[65]</sup>. In a series of 258 patients, Trabulo *et al.*<sup>[66]</sup> found an association between the MetS and adenomas and colorectal cancer.

Both long-term and new onset (< 3 years) T2DM increase the risk of pancreatic ductal adenocarcinoma<sup>[67]</sup>.

T2DM and the Met S confer an increased risk of hepatocellular carcinoma, (HCC), thought to be secondary to NAFLD and particularly to NASH, which is blunted by metformin<sup>[68,69]</sup>.

An increased risk for gastric cancer in patients with T2DM has been described in most studies and deemed to be secondary to hyperglycemia and hyperinsulinemia, as well as an increased propensity to develop persistent *H. pylori* infection. Interestingly this effect appears to be more marked in women and in Asian populations<sup>[70]</sup>.

### *Targeting metabolism to reduce cancer risk*

Additional proof of the principle of the etiological relationship existing between increased BMI T2DM and, at large, the Met S and cancer is provided by the beneficial effect of therapeutic interventions and lifestyle changes in reducing such risk.

### *Bariatric surgery*

A. Swedish prospective study showed that bariatric surgery reduces cancer incidence<sup>[71]</sup>. This reduction appears limited to women and involves predominantly cancers thought to be hormone-mediated, i.e., endometrial and postmenopausal breast. It has been speculated that this lack of association for men may be

due to the different types of tumors linked to obesity in men and women and differences in follow-up times needed to demonstrate an association for different cancer types<sup>[72]</sup>. The ability of bariatric surgery to reduce cancer incidence was confirmed in a recent meta-analysis<sup>[73]</sup>.

## B. Physical exercise

### B1. Exercise prevents cancer development: epidemiological evidence.

Physical activity reduces the incidence of cancers of the bladder, breast, colon, endometrium, esophagus (adenocarcinoma), kidney, and stomach, with relative risk reductions ranging from 10% to 20%<sup>[74-77]</sup>. Interestingly, physical activity reduces mortality even when started after diagnosis, in cancers of the colon<sup>[78,79]</sup> and breast<sup>[75,80]</sup>. While this reduction may be secondary to reduced incidence of cardiovascular events<sup>[81]</sup>, there is experimental evidence that physical activity directly affects tumor biology.

### B2. Exercise reduces cancer incidence and improves prognosis: experimental evidence. Experimental models have shown in rodents that exercise reduces the development and progression of cancer<sup>[82,83]</sup>.

Pre-incubation with the serum of exercise-conditioned animals reduces the clonogenic potential of cancer cells *in vitro* and their tumorigenicity *in vivo*<sup>[84-87]</sup> and increases the efficacy of chemotherapy<sup>[87,88]</sup>. These effects have been linked to multiple effects, including decreased EGF and increased IGF-1 Binding Protein 1 (which modulates the bioavailability of IGF-1)<sup>[86]</sup> and normalization of vascular supply<sup>[87,88]</sup>, via modulation of the VEGF pathway and increased thrombospondin 1<sup>[88]</sup>. In a mice model of hepatic carcinogenesis, the number of hepatic dysplastic foci and cancers induced by Diethylnitrosamine was drastically reduced by physical exercise in genetically modified, obese, insulin-resistant mice, thus proving that the antineoplastic effect of exercise is independent of weight control<sup>[89]</sup>.

## C. Diet

It is known that a diet rich in vegetables, fresh fruit, and whole grains while poor in red meat has a protective effect against cancer. However, it is unclear to what extent this protective effect is independent of its protective effect against the development of T2DM and increased BMI<sup>[90]</sup>.

## D. Calorie restriction

An abundance of nutrients promotes cell proliferation, while a lack of nutrients activates pathways protecting against oxidative stress<sup>[91,92]</sup>. In *S. Cerevisiae*, lack of nutrients is associated with increased resistance to oxidative stress and increased life span<sup>[93]</sup>. In eukaryotic organisms, calorie restriction increases lifespan and reduces the incidence of chronic diseases, including cancer<sup>[91,94,95]</sup>. This anti-cancer effect may be modulated by the type of calorie restriction, i.e., intermittent vs. chronic and may vary in chemical vs. transgenic models of cancer<sup>[95]</sup>. In animal models, calorie restriction also increases the efficacy of chemotherapy<sup>[91]</sup>. The anti-cancer activity of calorie restriction is thought to be mediated by the Insulin/IGF-1 pathway, leptins and adiponectin<sup>[96]</sup>.

## E. Medical management of T2DM

Metformin treatment, compared to other glucose-lowering treatments<sup>[97,98]</sup>, has been particularly associated with reduced cancer risk and mortality in many organs, in most<sup>[99-104]</sup>, but not all studies<sup>[105,106]</sup>.

The protective effect metformin has on the development of hepatocellular carcinoma has been causally linked to the reduction in hepatic accumulation of fatty acids, inhibition of oxidative damage, and cancer-inhibiting changes induced in the immune system, including CD8 lymphocytes<sup>[68]</sup>.

## Molecular underpinnings

### *Hyperinsulinemia*

Hyperinsulinemia is associated with increased risks of breast, colorectal, pancreatic and endometrial cancer<sup>[107,108]</sup>. Insulin levels in diabetic patients are tightly linked to the duration of the disease and treatment<sup>[109]</sup>. In a large study, hyperinsulinemia was associated with a doubling of cancer mortality, independent of obesity<sup>[109]</sup>.

Cancer promoting effect of hyperinsulinemia is thought to be mediated primarily by increased levels of IGF-1, which are caused by increased levels of IGF-1 binding proteins, since IGF-1 has higher growth-promoting activity of insulin<sup>[107]</sup>. Several lines of evidence, including the increased incidence of colon cancer in patients with acromegaly, point to IGF-1 as a key factor in the development of colon cancer<sup>[110]</sup>. In addition, in transgenic mice with hyperinsulinemia, implanted breast tumors have increased aggressiveness<sup>[107]</sup>. Severe IGF-1 deficiency, linked to growth hormone receptor inactivating mutations, results in reduced cancer incidence in patients with the Laron syndrome<sup>[111,112]</sup>. In addition, in transgenic mice with hyperinsulinemia, implanted breast tumors have increased aggressiveness<sup>[107]</sup>.

### *Hyperglycemia*

Hyperglycemia modulates multiple pathways that are crucial to cancer development and progression. These include: (1) cell proliferation; (2) invasion; (3) apoptosis; (4) inflammation; (5) chemotherapy resistance.

Hyperglycemia stimulates cell proliferation *in vitro* in breast<sup>[113]</sup> and pancreatic cancer<sup>[114]</sup> cell lines, possibly secondary to repression of p21 and SMAD4<sup>[115]</sup>. It promotes invasion and migration through STAT3<sup>[116]</sup>, Heme Oxygenase -1, via upregulation of the TGFβ 1/PI3K/Akt pathway<sup>[117]</sup>, TGFβ secretion<sup>[118,119]</sup>, inhibition of metalloproteinases MMP2 and MMP9<sup>[120]</sup>, increased production of u-PA<sup>[121]</sup>, and upregulation of superoxide dismutase, resulting in activation of the extracellular signal-regulated kinase and the mitogen-activated protein kinases (MAPK)<sup>[122,123]</sup>.

Hyperglycemia affects apoptosis via the p53 pathway, reducing p53 activity, by reducing its phosphorylation on Serine 46<sup>[124]</sup> or p53 levels, via the HIPK2 protein<sup>[125]</sup>.

Hyperglycemia promotes an inflammatory state via cytokines, such as TNFα, IFNγ and IL-6<sup>[126]</sup>. Interestingly the same cytokines are also involved in insulin resistance<sup>[127]</sup>. Hyperglycemia is linked to chemotherapy resistance in multiple tumor cell lines *in vitro*<sup>[128-131]</sup>. This effect is associated with reduced apoptosis in prostate cancer cells after docetaxel treatment<sup>[130]</sup>.

### *Sex hormones*

One of the tumors where the etiologic association between increased BMI and cancer development is best understood at the molecular level is endometrial cancer.



Increased estrogen stimulation is regarded as the principal factor promoting the development of type I endometrial cancer and its precursor lesion, atypical endometrial hyperplasia/Endometrial Intraepithelial Neoplasia<sup>[132]</sup>. By multivariate analysis, endometrial cancer appears to be linked predominantly to increased BMI, rather than diabetes<sup>[132]</sup>. In postmenopausal women, the main source of estrogen is the adipose tissue, where aromatase converts androgens to estrogens. A reduction in levels of sex hormone-binding globulin induced by obesity and mediated by adipokines, further increases levels of bioactive estrogen<sup>[133-134]</sup>.

Estrogen, upon binding to its receptors  $\alpha$  and  $\beta$ , stimulates proliferation, rendering cells more amenable to accumulating mutations and affecting the transcription of genes involved in differentiation, apoptosis, and angiogenesis<sup>[135]</sup>. Considering that up to 40% of endometrial cancers arise in the setting of mismatch repair enzyme deficiency, as a result of somatic and less commonly inherited mutations (i.e., in the Lynch syndrome)<sup>[132]</sup>, a pro-mutagenic vicious cycle is created.

#### *Adipokines*

In obesity, there are increased levels of pro-inflammatory cytokines, such as IL6, TNF $\alpha$ , and PAI, and reduced levels of beneficial mediators, such as adiponectin, which can be secreted directly by adipose cells or by fat-infiltrating inflammatory cells<sup>[34]</sup>.

Adiponectin levels are inversely correlated with BMI, cancer incidence, and stage. Adiponectin has antiapoptotic activity, stimulating p53 and Bax expression and reducing Bcl-2 expression<sup>[34]</sup>. Low levels of adiponectin are associated with higher risks of the breast<sup>[136-138]</sup> and endometrial cancer<sup>[139-140]</sup>, and in men, colorectal cancer<sup>[141]</sup>.

Leptin is produced by adipocytes and breast cancer cells. Leptin deficiency caused by homozygous inactivation in humans and in mice models causes hyperphagia and obesity, which is reverted by leptin administration<sup>[142]</sup>. However, obese subjects with normal leptin genes show a much less dramatic response, secondary to the occurrence of leptin resistance (142). Leptin acts at different levels, modulating cell proliferation, apoptosis, angiogenesis, and ER signaling<sup>[143]</sup>.

#### *Chronic inflammation and oxidative stress*

Obesity and energy accumulation are associated with a low-grade inflammatory state, highlighted by increased levels of C-reactive protein<sup>[144]</sup> and this creates a milieu promoting cancer development. Contrariwise, calorie restriction reduces chronic inflammation<sup>[145]</sup>.

#### *Immune response*

Obese patients have lower NK activity<sup>[146]</sup>. In an *in vivo* model obesity, caused by high fat diet in mice, resulted in accelerated growth of implanted tumors. This effect was more pronounced for implanted tumors with higher immunogenicity and was caused by a reduction in the tumor infiltrating lymphocytes and particularly, CD8 cells<sup>[147]</sup>.

## **CONCLUSIONS**

In summary, strong evidence links the development of multiple cancer types to T2DM and obesity and their associated and partially overlapping conditions Mets and NAFLD. This association is mediated by molecular pathways affecting multiple aspects of cancer biology. Medical management and/or prevention of these dysmetabolic conditions have the added benefit of reducing the excess cancer incidence and mortality with which they are associated.

## DECLARATIONS

### Authors' contributions

Designed, wrote and edited the manuscript: Lonardo F  
Provided assistance in managing references: Ballouk C

### Availability of data and materials

All the data provided in the manuscript were taken from papers identified through a MedLine search or books.

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None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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## REFERENCES

1. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008;32:1431-7. [DOI PubMed](#)
2. Porporato PE. Understanding cachexia as a cancer metabolism syndrome. *Oncogenesis* 2016;5:e200. [DOI PubMed PMC](#)
3. Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. *Biochem Soc Trans* 2016;44:1499-505. [DOI PubMed PMC](#)
4. Zambrano A, Molt M, Uribe E, Salas M. Glut 1 in cancer cells and the inhibitory action of resveratrol as a potential therapeutic strategy. *Int J Mol Sci* 2019;20:3374. [DOI PubMed PMC](#)
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74. [DOI PubMed](#)
6. Huang J, Yu J, Tu L, Huang N, Hang L, Luo Y. Isocitrate dehydrogenase mutations in glioma: from basic discovery to therapeutics development. *Front Oncol* 2019;9:506. [DOI PubMed PMC](#)
7. Liberti MV, Locasale JW. The Warburg Effect: how does it benefit cancer cells? *Trends Biochem Sci* 2016;41:211-8. [DOI PubMed PMC](#)
8. Angelin A, Gil-de-Gómez L, Dahiya S, et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. *Cell Metab* 2017;25:1282-1293.e7. [DOI PubMed PMC](#)
9. Grzes KM, Field CS, Pearce EJ. Treg cells survive and thrive in inhospitable environments. *Cell Metab* 2017;25:1213-5. [DOI PubMed](#)
10. Shen F, Boccuto L, Pauly R, Srikanth S, Chandrasekaran S. Genome-scale network model of metabolism and histone acetylation reveals metabolic dependencies of histone deacetylase inhibitors. *Genome Biol* 2019;20:49. [DOI PubMed PMC](#)
11. Lu C, Thompson CB. Metabolic regulation of epigenetics. *Cell Metab* 2012;16:9-17. [DOI PubMed PMC](#)
12. Evertts AG, Zee BM, Dimaggio PA, Gonzales-Cope M, Collier HA, Garcia BA. Quantitative dynamics of the link between cellular metabolism and histone acetylation. *J Biol Chem* 2013;288:12142-51. [DOI PubMed PMC](#)
13. Cluntun AA, Huang H, Dai L, Liu X, Zhao Y, Locasale JW. The rate of glycolysis quantitatively mediates specific histone acetylation sites. *Cancer Metab* 2015;3:10. [DOI PubMed PMC](#)
14. Monferrer E, Vieco-Martí I, López-Carrasco A, et al. Metabolic classification and intervention opportunities for tumor energy dysfunction. *Metabolites* 2021;11:264. [DOI PubMed PMC](#)
15. Tollis M, Boddy AM, Maley CC. Peto's paradox: how has evolution solved the problem of cancer prevention? *BMC Biol* 2017;15:60. [DOI PubMed PMC](#)
16. Dang CV. A metabolic perspective of Peto's paradox and cancer. *Philos Trans R Soc Lond B Biol Sci* 2015;370:20140223. [DOI PubMed PMC](#)

17. Dang CV. Links between metabolism and cancer. *Genes Dev* 2012;26:877-90. DOI PubMed PMC
18. Niklas KJ, Kutschera U. Kleiber's Law: How the fire of life ignited debate, fueled theory, and neglected plants as model organisms. *Plant Signal Behav* 2015;10:e1036216. DOI PubMed PMC
19. Kliemann N, Murphy N, Viallon V, et al. Predicted basal metabolic rate and cancer risk in the European prospective investigation into cancer and nutrition. *Int J Cancer* 2020;147:648-61. DOI PubMed
20. Redman LM, Ravussin E. Caloric restriction in humans: impact on physiological, psychological, and behavioral outcomes. *Antioxid Redox Signal* 2011;14:275-87. DOI PubMed PMC
21. Meynet O, Ricci JE. Caloric restriction and cancer: molecular mechanisms and clinical implications. *Trends Mol Med* 2014;20:419-27. DOI PubMed
22. Hursting SD, Smith SM, Lashinger LM, Harvey AE, Perkins SN. Calories and carcinogenesis: lessons learned from 30 years of calorie restriction research. *Carcinogenesis* 2010;31:83-9. DOI PubMed
23. Bray GA. Obesity: basic considerations and clinical approaches. *Disease-a-Month* 1989;35:454-537. DOI PubMed
24. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995;332:621-8. DOI PubMed
25. Miller WM, Spring TJ, Zalesin KC, et al. Lower than predicted resting metabolic rate is associated with severely impaired cardiorespiratory fitness in obese individuals. *Obesity (Silver Spring)* 2012;20:505-11. DOI PubMed
26. Carneiro IP, Elliott SA, Siervo M, et al. Is obesity associated with altered energy expenditure? *Adv Nutr* 2016;7:476-87. DOI PubMed PMC
27. Bessard T, Chutz Y, Jéquier E. Energy expenditure and postprandial thermogenesis in obese women before and after weight loss. *Am J Clin Nutr* 1983;38:680-93. DOI PubMed
28. Lemmer JT, Ivey FM, Ryan AS, et al. Effect of strength training on resting metabolic rate and physical activity: age and gender comparisons. *Med Sci Sports Exerc* 2001;33:532-41. DOI PubMed
29. Pannemans DL, Westerterp KR. Energy expenditure, physical activity and basal metabolic rate of elderly subjects. *Br J Nutr* 1995;73:571-81. DOI PubMed
30. Speakman JR, Selman C. Physical activity and resting metabolic rate. *Proc Nutr Soc* 2003;62:621-34. DOI PubMed
31. Pontzer H, Durazo-Arvizu R, Dugas LR, et al. Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. *Curr Biol* 2016;26:410-7. DOI PubMed PMC
32. Westerterp KR, Meijer GA, Janssen EM, Saris WH, Ten Hoor F. Long-term effect of physical activity on energy balance and body composition. *Br J Nutr* 1992;68:21-30. DOI PubMed
33. 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. DOI PubMed
34. Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes* 2013;2013:291546. DOI
35. Lega IC, Lipscombe LL. Review: diabetes, obesity, and cancer-pathophysiology and clinical implications. *Endocr Rev* 2020;41:33-52. DOI PubMed
36. Renehan AG, Soerjomataram I, Tyson M, et al. Incident cancer burden attributable to excess body mass index in 30 European countries. *Int J Cancer* 2010;126:692-702. DOI PubMed
37. Rawla P. Epidemiology of prostate cancer. *World J Oncol* 2019;10:63-89. DOI PubMed PMC
38. Kinsella N, Helleman J, Bruinsma S, et al. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. *Transl Androl Urol* 2018;7:83-97. DOI PubMed PMC
39. Golabek T, Bukowczan J, Chłosta P, Powroźnik J, Dobruch J, Borówka A. Obesity and prostate cancer incidence and mortality: a systematic review of prospective cohort studies. *Urol Int* 2014;92:7-14. DOI PubMed
40. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, et al. Midlife metabolic factors and prostate cancer risk in later life. *International Journal of Cancer* 2018;142:1166-73. DOI
41. Lonardo A, Roncucci L. The "obese liver" and gastrointestinal cancer risk. *Transl Gastroenterol Hepatol* 2020;5:44. DOI PubMed PMC
42. Mantovani A, Petracca G, Beatrice G, et al. Nonalcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. *Gut* 2022;71:778-88. DOI PubMed
43. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology* 2021;73 Suppl 1:4-13. DOI PubMed PMC
44. Smith L, Brinton LA, Spitz MR, et al. Body mass index and risk of lung cancer among never, former, and current smokers. *J Natl Cancer Inst* 2012;104:778-89. DOI PubMed PMC
45. ten Haaf K, Jeon J, Tammemägi MC, et al. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. *PLoS Med* 2017;14:e1002277. DOI PubMed PMC
46. Dahlberg SE, Schiller JH, Bonomi PB, et al. Body mass index and its association with clinical outcomes for advanced non-small-cell lung cancer patients enrolled on Eastern Cooperative Oncology Group clinical trials. *J Thorac Oncol* 2013;8:1121-7. DOI PubMed PMC
47. Leung CC, Lam TH, Yew WW, Chan WM, Law WS, Tam CM. Lower lung cancer mortality in obesity. *Int J Epidemiol* 2011;40:174-82. DOI PubMed
48. Barbi J, Patnaik SK, Pabla S, et al. Visceral obesity promotes lung cancer progression-toward resolution of the obesity paradox in

- lung cancer. *J Thorac Oncol* 2021;16:1333-48. DOI PubMed
49. Yu D, Zheng W, Johansson M, et al. Overall and central obesity and risk of lung cancer: a pooled analysis. *J Natl Cancer Inst* 2018;110:831-42. DOI PubMed PMC
50. Nattenmüller J, Wochner R, Muley T, et al. Prognostic impact of CT-quantified muscle and fat distribution before and after first-line-chemotherapy in lung cancer patients. *PLoS One* 2017;12:e0169136. DOI PubMed PMC
51. Iwase T, Sangai T, Fujimoto H, et al. Quality and quantity of visceral fat tissue are associated with insulin resistance and survival outcomes after chemotherapy in patients with breast cancer. *Breast Cancer Res Treat* 2020;179:435-43. DOI PubMed
52. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* 2015;63:131-40. DOI PubMed
53. Donkers H, Fasmer KE, Mcgrane J, et al. The role of sarcopenic obesity in high-grade endometrial cancer. *Int J Gynaecol Obstet* 2021;154:248-55. DOI PubMed
54. Lee JY, Lee HS, Lee DC, et al. Visceral fat accumulation is associated with colorectal cancer in postmenopausal women. *PLoS One* 2014;9:e110587. DOI PubMed PMC
55. Park JW, Chang SY, Lim JS, et al. Impact of visceral fat on survival and metastasis of stage III colorectal cancer. *Gut Liver* 2022;16:53-61. DOI PubMed PMC
56. Allen AM, Hicks SB, Mara KC, Larson JJ, Therneau TM. The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity - a longitudinal cohort study. *J Hepatol* 2019;71:1229-36. DOI PubMed PMC
57. Marchesini G, Petroni ML, Cortez-Pinto H. Adipose tissue-associated cancer risk: Is it the fat around the liver, or the fat inside the liver? *J Hepatol* 2019;71:1073-5. DOI PubMed
58. Fernandez CJ, George AS, Subrahmanyam NA, Pappachan JM. Epidemiological link between obesity, type 2 diabetes mellitus and cancer. *World J Methodol* 2021;11:23-45. DOI PubMed PMC
59. Saydah SH, Platz E, Rifai N, Pollak M, Brancati F, Helzlsouer K. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2003;12:412-8. PubMed
60. Ozasa K, Ito Y, Suzuki K, et al; JACC Study Group. Glucose intolerance and colorectal cancer risk in a nested case-control study among Japanese people. *J Epidemiol* 2005;15 Suppl 2:S180-4. DOI PubMed PMC
61. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol* 2011;106:1911-21; quiz 1922. DOI PubMed PMC
62. Zhu B, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: a meta-analysis based on the cohort studies. *PLoS One* 2017;12:e0176068. DOI PubMed PMC
63. Krämer HU, Müller H, Stegmaier C, Rothenbacher D, Raum E, Brenner H. Type 2 diabetes mellitus and gender-specific risk for colorectal neoplasia. *Eur J Epidemiol* 2012;27:341-7. DOI PubMed
64. Mauvais-jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *The Lancet* 2020;396:565-82. DOI PubMed PMC
65. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Giugliano D. Metabolic syndrome and endometrial cancer: a meta-analysis. *Endocrine* 2014;45:28-36. DOI PubMed
66. Trabulo D, Ribeiro S, Martins C, et al. Metabolic syndrome and colorectal neoplasms: An ominous association. *World J Gastroenterol* 2015;21:5320-7. DOI PubMed PMC
67. Kaleru T, Vankeshwaram VK, Maheshwary A, Mohite D, Khan S. Diabetes mellitus in the middle-aged and elderly population (> 45 years) and its association with pancreatic cancer: an updated review. *Cureus* 2020;12:e8884. DOI PubMed PMC
68. Zhang Y, Wang H, Xiao H. Metformin actions on the liver: protection mechanisms emerging in hepatocytes and immune cells against NASH-related HCC. *Int J Mol Sci* 2021;22:5016. DOI PubMed PMC
69. Zampaglione L, Ferrari J, Pedica F, Goossens N. HCC in metabolic syndrome: current concepts and future directions. *Hepatoma Res* 2021;7:55. DOI
70. Tseng CH. The Relationship between diabetes mellitus and gastric cancer and the potential benefits of metformin: an extensive review of the literature. *Biomolecules* 2021;11:1022. DOI PubMed PMC
71. Sjöström L, Narbro K, Sjöström CD, et al; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741-52. DOI PubMed
72. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *The Lancet* 2008;371:569-78. DOI PubMed
73. Wiggins T, Guidozi N, Welbourn R, Ahmed AR, Markar SR. Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: a systematic review and meta-analysis. *PLoS Med* 2020;17:e1003206. DOI PubMed PMC
74. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al; 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE\*. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc* 2019;51:1252-61. DOI PubMed PMC
75. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479-86. DOI PubMed
76. Van Blarigan EL, Fuchs CS, Niedzwiecki D, et al. Association of survival with adherence to the american cancer society nutrition and physical activity guidelines for cancer survivors after colon cancer diagnosis: The CALGB 89803/alliance trial. *JAMA Oncol*

- 2018;4:783-90. DOI PubMed PMC
77. Lugo D, Pulido AL, Mihos CG, et al. The effects of physical activity on cancer prevention, treatment and prognosis: a review of the literature. *Complement Ther Med* 2019;44:9-13. DOI PubMed
78. Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24:3527-34. DOI PubMed
79. Haydon AM, Macinnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* 2006;55:62-7. DOI PubMed PMC
80. Irwin ML, Smith AW, McTiernan A, et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol* 2008;26:3958-64. DOI PubMed PMC
81. Jones LW, Habel LA, Weltzien E, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. *J Clin Oncol* 2016;34:2743-9. DOI PubMed PMC
82. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: a critical systematic review of in vivo preclinical data. *Cancer Res* 2016;76:4032-50. DOI PubMed PMC
83. Pedersen L, Christensen JF, Hojman P. Effects of exercise on tumor physiology and metabolism. *Cancer J* 2015;21:111-6. DOI PubMed
84. Kurgan N, Tsakiridis E, Kouveliotti R, Moore J, Klentrou P, Tsiani E. Inhibition of human lung cancer cell proliferation and survival by post-exercise serum is associated with the inhibition of Akt, mTOR, p70 S6K, and Erk1/2. *Cancers (Basel)* 2017;9:46. DOI PubMed PMC
85. Dethlefsen C, Hansen LS, Lillelund C, et al. Exercise-induced catecholamines activate the hippo tumor suppressor pathway to reduce risks of breast cancer development. *Cancer Res* 2017;77:4894-904. DOI PubMed
86. Rundqvist H, Augsten M, Strömberg A, et al. Effect of acute exercise on prostate cancer cell growth. *PLoS One* 2013;8:e67579. DOI PubMed PMC
87. Betof AS, Lascola CD, Weitzel D, et al. Modulation of murine breast tumor vascularity, hypoxia and chemotherapeutic response by exercise. *J Natl Cancer Inst* 2015;107:djv040. DOI PubMed PMC
88. Schadler KL, Thomas NJ, Galie PA, et al. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. *Oncotarget* 2016;7:65429-40. DOI PubMed PMC
89. Arfianti A, Pok S, Barn V, et al. Exercise retards hepatocarcinogenesis in obese mice independently of weight control. *J Hepatol* 2020;73:140-8. DOI PubMed
90. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33:1674-85. DOI PubMed PMC
91. Brandhorst S, Longo VD. Fasting and caloric restriction in cancer prevention and treatment. *Recent Results Cancer Res* 2016;207:241-66. DOI PubMed PMC
92. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 1996;273:59-63. DOI PubMed PMC
93. Longo VD, Fabrizio P. Chronological aging in *Saccharomyces cerevisiae*. *Subcell Biochem* 2012;57:101-21. DOI PubMed PMC
94. Ibrahim EM, Al-Foheidi MH, Al-Mansour MM. Energy and caloric restriction, and fasting and cancer: a narrative review. *Support Care Cancer* 2021;29:2299-304. DOI PubMed PMC
95. Chen Y, Ling L, Su G, et al. Effect of intermittent versus chronic calorie restriction on tumor incidence: a systematic review and meta-analysis of animal studies. *Sci Rep* 2016;6:337379. DOI PubMed PMC
96. Nencioni A, Caffa I, Cortellino S, Longo V. Fasting and cancer: molecular mechanisms and clinical applications. *Nat Rev Cancer* 2018;18:707-19. DOI PubMed PMC
97. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin: Response to Farooki and Schneider. *Diabetes Care* 2006;29:1990-1. DOI PubMed
98. Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012;17:813-822. DOI PubMed PMC
99. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ* 2005;330:1304-5. DOI PubMed PMC
100. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* 2010;33:322-6. DOI PubMed PMC
101. Feng Z, Zhou X, Liu N, Wang J, Chen X, Xu X. Metformin use and prostate cancer risk: A meta-analysis of cohort studies. *Medicine (Baltimore)* 2019;98:e14955. DOI PubMed PMC
102. Zhang K, Bai P, Dai H, Deng Z. Metformin and risk of cancer among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Prim Care Diabetes* 2021;15:52-8. DOI PubMed
103. Wang Z, Lai S, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2014;106:19-26. DOI PubMed
104. Winston Ng CA, Jiang AA, Shuen Toh EM, et al. Metformin and colorectal cancer: a systematic review, meta-analysis and meta-regression. *Int J Colorectal Dis* 2020;35:1501-12. DOI PubMed
105. Hu J, Chen JB, Cui Y, et al. Association of metformin intake with bladder cancer risk and oncologic outcomes in type 2 diabetes mellitus patients: A systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11596. DOI PubMed PMC

106. Chu D, Wu J, Wang K, et al. Effect of metformin use on the risk and prognosis of endometrial cancer. *BMC Cancer* 2018;18:438. DOI PubMed PMC
107. Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. *Physiol Rev* 2015;95:727-48. DOI PubMed PMC
108. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. *Arch Physiol Biochem* 2008;114:63-70. DOI PubMed
109. Tsujimoto T, Kajio H, Sugiyama T. Association between hyperinsulinemia and increased risk of cancer death in nonobese and obese people: a population-based observational study. *Int J Cancer* 2017;141:102-11. DOI PubMed PMC
110. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr* 2001;131:3109S-20S. DOI PubMed
111. Guevara-Aguirre J, Bautista C, Torres C, et al. Insights from the clinical phenotype of subjects with Laron syndrome in Ecuador. *Rev Endocr Metab Disord* 2021;22:59-70. DOI PubMed
112. 10.1007/s11154-020-096024112. Steuerman R, Shevah O, Laron Z. Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. *Eur J Endocrinol* 2011;164:485-9. DOI
113. Hou Y, Zhou M, Xie J, Chao P, Feng Q, Wu J. High glucose levels promote the proliferation of breast cancer cells through GTPases. *Breast Cancer (Dove Med Press)* 2017;9:429-36. DOI PubMed PMC
114. Han L, Ma Q, Li J, et al. High glucose promotes pancreatic cancer cell proliferation via the induction of EGF expression and transactivation of EGFR. *PLoS One* 2011;6:e27074. DOI PubMed PMC
115. Li W, Zhang X, Sang H, et al. Effects of hyperglycemia on the progression of tumor diseases. *J Exp Clin Cancer Res* 2019;38:327. DOI PubMed PMC
116. Saengboonmee C, Seubwai W, Pairojkul C, Wongkham S. High glucose enhances progression of cholangiocarcinoma cells via STAT3 activation. *Sci Rep* 2016;6:18995. DOI PubMed PMC
117. Kang X, Kong F, Wu X, et al. High glucose promotes tumor invasion and increases metastasis-associated protein expression in human lung epithelial cells by upregulating heme oxygenase-1 via reactive oxygen species or the TGF- $\beta$ 1/PI3K/Akt signaling pathway. *Cell Physiol Biochem* 2015;35:1008-22. DOI PubMed
118. Alisson-Silva F, Freire-de-Lima L, Donadio JL, et al. Increase of O-glycosylated oncofetal fibronectin in high glucose-induced epithelial-mesenchymal transition of cultured human epithelial cells. *PLoS One* 2013;8:e60471. DOI PubMed PMC
119. Rahn S, Zimmerman V, Viol F, Knaack H, et al. Diabetes as a risk factor for pancreatic cancer: hyperglycemia promotes epithelial-mesenchymal-transition and stem cell properties in pancreatic ductal epithelial cells. *Cancer Lett* 2018;415:129-50. DOI PubMed
120. Sun XF, Shao YB, Liu MG, et al. High-concentration glucose enhances invasion in invasive ductal breast carcinoma by promoting Glut1/MMP2/MMP9 axis expression. *Oncol Lett* 2017;13:2989-95. DOI PubMed PMC
121. Flores-López LA, Martínez-Hernández MG, Viedma-Rodríguez R, Díaz-Flores M, Baiza-Gutman LA. High glucose and insulin enhance uPA expression, ROS formation and invasiveness in breast cancer-derived cells. *Cell Oncol (Dordr)* 2016;39:365-78. DOI PubMed
122. Li W, Ma Z, Ma J, et al. Hydrogen peroxide mediates hyperglycemia-induced invasive activity via ERK and p38 MAPK in human pancreatic cancer. *Oncotarget* 2015;6:31119-33. DOI PubMed PMC
123. Cao L, Chen X, Xiao X, Ma Q, Li W. Resveratrol inhibits hyperglycemia-driven ROS-induced invasion and migration of pancreatic cancer cells via suppression of the ERK and p38 MAPK signaling pathways. *Int J Oncol* 2016;49:735-43. DOI PubMed
124. Baldari S, Garufi A, Granato M, et al. Hyperglycemia triggers HIPK2 protein degradation. *Oncotarget* 2017;8:1190-203. DOI PubMed PMC
125. Garufi A, Pistrutto G, Baldari S, Toietta G, Cirone M, D'Orazi G. p53-dependent PUMA to DRAM antagonistic interplay as a key molecular switch in cell-fate decision in normal/high glucose conditions. *J Exp Clin Cancer Res* 2017;36:126. DOI PubMed PMC
126. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 2002;106:2067-72. DOI PubMed
127. Ramteke P, Deb A, Shepal V, Bhat MK. Hyperglycemia associated metabolic and molecular alterations in cancer risk, progression, treatment, and mortality. *Cancers (Basel)* 2019;11:1402. DOI PubMed PMC
128. Ma YS, Yang IP, Tsai HL, Huang CW, Juo SH, Wang JY. High glucose modulates antiproliferative effect and cytotoxicity of 5-fluorouracil in human colon cancer cells. *DNA Cell Biol* 2014;33:64-72. DOI PubMed PMC
129. Zhao W, Chen R, Zhao M, Li L, Fan L, Che XM. High glucose promotes gastric cancer chemoresistance in vivo and in vitro. *Mol Med Rep* 2015;12:843-50. DOI PubMed PMC
130. Biernacka KM, Uzoh CC, Zeng L, et al. Hyperglycaemia-induced chemoresistance of prostate cancer cells due to IGFBP2. *Endocr Relat Cancer* 2013;20:741-51. DOI PubMed
131. Qahtani A, Holly J, Perks C. Hypoxia negates hyperglycaemia-induced chemo-resistance in breast cancer cells: the role of insulin-like growth factor binding protein 2. *Oncotarget* 2017;8:74635-48. DOI PubMed PMC
132. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet* 2016;387:1094-108. DOI PubMed
133. Simó R, Sáez-López C, Barbosa-Desongles A, Hernández C, Selva DM. Novel insights in SHBG regulation and clinical implications. *Trends Endocrinol Metab* 2015;26:376-83. DOI PubMed
134. Simó R, Barbosa-Desongles A, Hernandez C, Selva DM. IL1 $\beta$  down-regulation of sex hormone-binding globulin production by decreasing HNF-4 $\alpha$  via MEK-1/2 and JNK MAPK pathways. *Mol Endocrinol* 2012;26:1917-27. DOI PubMed PMC

135. Bhardwaj P, Au CC, Benito-Martin A, et al. Estrogens and breast cancer: Mechanisms involved in obesity-related development, growth and progression. *J Steroid Biochem Mol Biol* 2019;189:161-70. DOI PubMed PMC
136. Yu Z, Tang S, Ma H, Duan H, Zeng Y. Association of serum adiponectin with breast cancer: a meta-analysis of 27 case-control studies. *Medicine (Baltimore)* 2019;98:e14359. DOI PubMed PMC
137. Mantzoros C, Petridou E, Dessypris N, et al. Adiponectin and breast cancer risk. *J Clin Endocrinol Metab* 2004;89:1102-7. DOI PubMed
138. Tworoger SS, Eliassen AH, Kelesidis T, et al. Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metab* 2007;92:1510-6. DOI PubMed
139. Dal Maso L, Augustin LS, Karalis A, et al. Circulating adiponectin and endometrial cancer risk. *J Clin Endocrinol Metab* 2004;89:1160-3. DOI PubMed
140. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab* 2007;92:255-63. DOI PubMed
141. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst* 2005;97:1688-94. DOI PubMed
142. Candia P, Praticchizzo F, Garavelli S, Alviggi C, La Cava A, Matarese G. The pleiotropic roles of leptin in metabolism, immunity, and cancer. *J Exp Med* 2021;218:e20191593. PubMed
143. Crean-Tate KK, Reizes O. Leptin regulation of cancer stem cells in breast and gynecologic cancer. *Endocrinology* 2018;159:3069-80. DOI PubMed PMC
144. Slattery ML, Curtin K, Poole EM, et al. Genetic variation in C-reactive protein in relation to colon and rectal cancer risk and survival. *Int J Cancer* 2011;128:2726-34. DOI PubMed PMC
145. Ye J, Keller JN. Regulation of energy metabolism by inflammation: a feedback response in obesity and calorie restriction. *Aging (Albany NY)* 2010;2:361-8. DOI PubMed PMC
146. Moulin CM, Rizzo LV, Halpern A. Effect of surgery-induced weight loss on immune function. *Expert Rev Gastroenterol Hepatol* 200;2:617-9. DOI PubMed
147. Ringel AE, Drijvers JM, Baker GJ, et al. Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity. *Cell* 2020;183:1848-1866.e26. DOI PubMed PMC
148. Allot EH, Masko EM, Freeland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol* 2013;63:800-9. DOI PubMed PMC
149. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. *Cancer* 2019;125:2877-85. DOI PubMed PMC
150. Møller H, Roswall N, Van Hemelrijck M, et al. Prostate cancer incidence, clinical stage and survival in relation to obesity: a prospective cohort study in Denmark. *Int J Cancer* 2015;136:1940-7. DOI PubMed
151. Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL Jr, Freedland SJ. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. *Cancer Epidemiol Biomarkers Prev* 2014;23:2936-42. DOI PubMed PMC
152. Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate cancer mortality. *Obes Res Clin Pract* 2014;8:e374-81. DOI PubMed PMC
153. Yamoah K, Zeigler-Johnson CM, Jeffers A, et al. The impact of body mass index on treatment outcomes for patients with low-intermediate risk prostate cancer. *BMC Cancer* 2016;16:557. DOI PubMed PMC