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Metabolism and Target Organ Damage

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[1], this association is likely to

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.s

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[2].

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[3].

Increased glucose uptake by malignant tumors, mediated by increased levels of transporters, notably GLUT-1[4] 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[5].

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[3] and isocitrate dehydrogenase 1 in adult glioblastomas[6]. 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[3].

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[7].

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[8,9]. 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[10-12] as a consequence of increased Acetyl CoA levels[13].

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[14] 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[15,16].

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[15,16]. 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[16,17].

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[16,17] (a historical perspective of the topic is provided by Niklas *et al.*[18]). 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[19]. This phenomenon has been linked to an increased mutagenic rate resulting from higher basic metabolic rates, mediated by by-products of metabolism[16].

The finding that calorie restriction, which results in a reduced basic metabolic rate[20], is linked to reduced cancer incidence (further discussed in section IV) appears to corroborate this hypothesis[21,22]. 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[16].

The association between higher cancer risk and obesity appears paradoxical, based on the assumption that obesity is linked to a *reduced* basic metabolic rate[23]. Obesity is associated with higher energy expenditure[24]. 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[25], most studies do not confirm this finding[26], and some studies show an *increased* basic metabolic rate in obesity[27,23]. 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[28,29], 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[30]. 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[31], 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[32] and the fact that African hunter-gatherers have the same energy expenditure as westerners who live a sedentary life[31]. 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[32].

Obesity

Calle *et al.*[33], 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[33].

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 α (not Er β), and PR+ Her2- tumors[34]. In addition, obesity is inversely associated with premenopausal and directly with postmenopausal breast cancer[35]. 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)[34].

In a meta-analysis studying, the cancer burden attributable to increased BMI (defined as ≥ 25 kg/m^2) 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[36]. 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^2 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[36]. This study highlights that gender differences modulate the risk of BMI-associated malignancy and that the associations are incremental per 5 Kg/m^2 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[37]. 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

Obesity	
	↓ Premenopausal breast cancer[35]
	↑ Post menopausal breast cancer[35]
	Er, Pr + breast cancer[34]
	Cardias adenocarcinoma[34]
	Type I Endometrial Cancer[34]
	↓ Overall Prostate cancer incidence[58,148]
	↑ Prostate cancer aggressiveness[39,148-153]
T2DM	
	↓ Prostate cancer incidence[58]

histological grading at biopsy, PSA value, and estimated tumor size[38]. Many studies found that high BMI is associated with an increased incidence of exactly those subsets of prostate cancers that have higher aggressiveness[39]. Dickerman *et al.*[40] 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[41], also confer an increased risk of malignancy for cancers of the esophagus, stomach, pancreas, colon, thyroid, lung, urinary tract, female genital tract[41,42], and liver[43].

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[44-47]. 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[48]. Similarly, a higher waist circumference has been found to correlate with an increased risk of lung cancer[49,50] and visceral adipose tissue with a worse prognosis in patients undergoing chemotherapy[50]. 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.*[51] 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[52]. Donkers *et al.*[53] 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.*[54] 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[54]

Park *et al.*[55] 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.*[56] 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*"[57].

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[58]. In a large prospective study, Saydah *et al.*[59] 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[60]. 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[61].

The risk of prostate cancer is decreased by T2DM[58] [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[58].

In a meta-analysis, Zhu *et al.*[62] 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[63]. This finding constitutes yet another example of the ability of gender to modulate the biology of human diseases[64]. An association between the MetS and colon cancer was also found by Esposito[65]. In a series of 258 patients, Trabulo *et al.*[66] 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[67].

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[68,69].

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[70].

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[71]. 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[72]. The ability of bariatric surgery to reduce cancer incidence was confirmed in a recent meta-analysis[73].

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%[74-77]. Interestingly, physical activity reduces mortality even when started after diagnosis, in cancers of the colon[78,79] and breast[75,80]. While this reduction may be secondary to reduced incidence of cardiovascular events[81], 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[82,83].

Pre-incubation with the serum of exercise-conditioned animals reduces the clonogenic potential of cancer cells *in vitro* and their tumorigenicity *in vivo*[84-87] and increases the efficacy of chemotherapy[87,88]. 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)[86] and normalization of vascular supply[87,88], via modulation of the VEGF pathway and increased thromobospondin 1[88]. 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[89].

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[90].

D. Calorie restriction

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

E. Medical management of T2DM

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

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[68].

Molecular underpinnings

Hyperinsulinemia

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

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[107]. 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[110]. In addition, in transgenic mice with hyperinsulinemia, implanted breast tumors have increased aggressiveness[107]. Severe IGF-1 deficiency, linked to growth hormone receptor inactivating mutations, results in reduced cancer incidence in patients with the Laron syndrome[111,112]. In addition, in transgenic mice with hyperinsulinemia, implanted breast tumors have increased aggressiveness[107].

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

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

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

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[132]. By multivariate analysis, endometrial cancer appears to be linked predominantly to increased BMI, rather than diabetes[132]. 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[133-134].

Estrogen, upon binding to its receptors α and β, stimulates proliferation, rendering cells more amenable to accumulating mutations and affecting the transcription of genes involved in differentiation, apoptosis, and angiogenesis[135]. 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)[132], a pro-mutagenic vicious cycle is created.

Adipokines

In obesity, there are increased levels of pro-inflammatory cytokines, such as IL6, TNFα, 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[34].

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[34]. Low levels of adiponectin are associated with higher risks of the breast[136-138] and endometrial cancer[139-140], and in men, colorectal cancer[141].

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[142]. 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[143].

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[144] and this creates a milieu promoting cancer development. Contrariwise, calorie restriction reduces chronic inflammation[145].

Immune response

Obese patients have lower NK activity[146]. 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[147].

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 assisteancer 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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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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