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Research Article

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Reduction of Chronic Hyperinsulinemia (Insulin Resistance) for the Prevention and Treatment of Cancerous Disease: The Crucial Role of Caloric Restriction

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Abstract

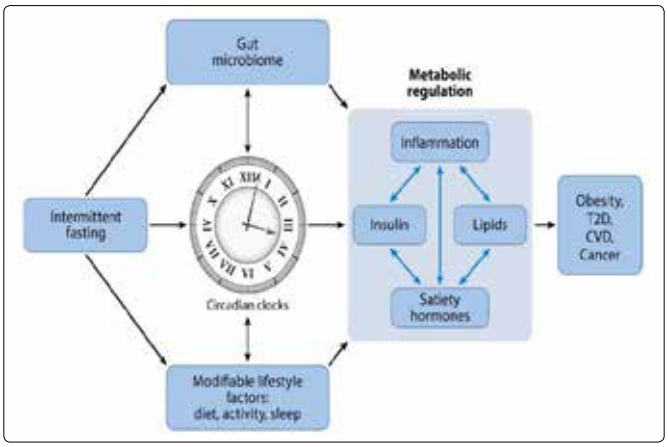
Gene's expression changes with nutrition and physical activity and hormones signaling like insulin. A Western lifestyle may increase cancer risk through alterations in the metabolism of insulin and insulin-like growth factors. The anabolic signals by insulin or IGF-I can promote tumour development by inhibiting apoptosis, and by stimulating cell proliferation. ***There is dynamic change in gene expression in response to nutritional availability [1]****. A clear association between adiposity, physical inactivity and Western diet, and the risk of incident cancer, cancer recurrence and mortality after "curative" surgery is increasing. Insulin Resistance Status characterized by hyperinsulinemia is associated with an excessive increased risk for a number of malignancies. An increasing clinical, biological and epidemiological evidence sustain that Insulin-IGFs System has been implicated in breast, prostate, pediatric, colon-recto and gynecological cancers, including sarcomas, epithelial cancers, multiple myeloma and melanoma. Chronic hyperinsulinaemia may be a cause of cancers of the colon, pancreas, endometrium, breast, prostate, ovarium, and possibly of the lung, and may predispose strongly to melanoma development; reducing the hormone-vitamin D anticancerigen action [2].*

Caloric Restriction slows down May age-related diseases, notably cancer and heart disease, because lowers blood insulin [3]. (1) And reduce oxidative stress directly and by lowering glucose concentrations. Caloric Restriction is a powerful protective therapy in Cancer. Prevention has been known for some time: the mechanism of intermittent caloric restriction that provides greater protection in mammary, colonic and pancreatic tumors is the sustained reduction in insulin excess /insulin resistance. "Mechanism of the increased cancer risk reflects the consequences of the hyperinsulinaemia" [4]. Thus, increased glucose uptake activates known oncogenic pathways to induce malignant phenotype and promotes oncogenesis [5]. A possible primary cause of cancer lies on insulin released from beta pancreatic cells [6]. Recently, the kinase signaling-insulin-dependent is a modulator of expression of microRNAs, the molecular link between the disturb in metabolism and the oncogenic process [7, 8].

On the contrary, the oncogenic process doesn´t occur during the aging in the Insulin- IGF-1 deficiency due to GH insensitivity and developmental GH/IGF-1 deficiency also exhibit significantly decreased cancer, cellular resistance to genotoxic stressors and marked resistance to chemically induced carcinogenesis [9]. ***The metabolic dependencies of cancer cells may be exploited for an optimal cancer treatment****. Thus, a carbohydrate-restricted diet will slow cancer growth in patients by decreasing the secretion and circulating levels of insulin [10].* ***Accumulative evidence demonstrated a causal role of higher fasting insulin levels in the etiology of cancer risk [11, 12]****. It is only when the stem cells are destroyed that a full recovery is possible. Increasing evidence points to the ability of both anti-insulin drugs and bioactive food components to modify the self-renewal capabilities of cancer stem cells [13].*

Chronic inflammation contribute to cancer development in hyperinsulinemic patients: in white fat, immune cells and macrophages are continuously activated to secrete proinflammatory factors, which can initiate, promote, and sustain tumorigenesis, by further enhancing, hyperinsulinemia [14]. Targeting cancer cell metabolism has emerged as a novel approach to prevent or treat cancers, and patient's hormonal context plays a crucial role in determining cancer outcome [15]. On the contrary, the more the insulin signaling in cancer cell, (that increase hypoxia and glucogen accumulation), the more invasion, motility and proliferation of cancer [16]. The master oncogene in cancer biology, the hypoxia-inducible-factor HIF-1 is strogly regulated in a positive manner by insulin - the hyperinsulinemia/HIF-1α/oxidative stress cascade – [17-19]. Cancer is linked to metabolic disruption [20].

Reducing levels of insulin thoughout fasting ameliorated endogenous circadian clock to ensure physiological processes that support an optimal health:
Improves gut microbiome and metabolic regulation, increasing sleep quality and society, reducing systemic and tissue inflammation, adipocyte size, cell proliferation and tumour growth. Reducing chronic insulin excess is therapeutic arm for Cancer, diabetes and cardiovascular diseases.



Introduction

When does cancer appear?

At present, it becomes increasingly evident, according to increasing experimental and preclinical evidence and currently clinical and epidemiological, that the root of cell transformation and malignancy (oncogenesis) is the alteration of cellular metabolism, as noted Warburg over 90 years ago [21]. The immortality of neoplastic (precancerous) cell lines occurs when there are multiple signalings (genetic and environmental) that stimulate "eternally" (only) Growth; without a subsequent step (in the physiological cell cycle) to specialization (cell differentiation); therefore, said in simple words, there will be an uncontrolled, disorderly and perpetual growth of the cell, which has become "selfish" and only multiplies in an environment of chaos. This constitutes the deadly invasive cancer. And it is that the transformed cell groups, those that only receive multiple signals that order them to proliferate, proliferate and not specialize, have completely lost the inhibitory (anticancer) signals that prevent them from proliferating that growth without control. These cancer cells are cells without physiological contact inhibition (neighboring cells that inhibit uncontrolled growth by humoral signals); that is, they are "selfish" cells (Dr. Trezguerres, Department of Physiology and Endocrinology, Universidad Complutense de Madrid). But, for cancer to manifest itself, it is imperative that there are at least two genetic mutations; and this is achieved with the chronic stimulation of growth factors by themselves mutagenic, such as Insulin. When there is, in this genetic imprint, a permanent hormonal environment that stimulates cell growth, together with the preferred energy "foods" for the nutrition of the cancer cell (glucose and iron), the "cancer is triggered" [22, 23].

Well, well: the chronic excess of the main anabolic hormone Insulin, generated in response to its deficient biological action (Insulin Resistance syndrome, metabolic syndrome, syndrome X ..), has long been an epidemic silent in today's western world; and today it is known that it is accompanied by the presence of prostate cancer, one of the cancers with the highest lethality: and this is not a "coincidence": for more than 50 years, researchers have known that the main hormone that "Immortalizes cancer cells" is insulin [24, 25]. Thus, in addition to the Axis Insulin-IGF-1, Insulin is the hormone that physiologically, (in addition to stimulating cell growth) inhibits programmed cell death: apoptosis, a process of cell death without inflammation, and that is physiologically protective by eliminating unwanted cells, and, with them, altered DNA.

Bluntly, abdominal (upper) obesity is the greatest risk for human cancer, and this, regardless of total weight; that is, a superior obesity (neck, trunk) or abdominal proper is enough to confer the highest risk for future cancer acquisition (http://dx.doi.org/10.1155/2013/291546). Independent of the superior obesity, which is a favorable cause of cancer and neoplasms, the excess of caloric energy ingested causes resistance to the positive metabolic, vascular and anti-inflammatory effects of Insulin (Insulin Resistance) (IR), directly, through a numbing of its receptor (in liver, muscle and adipose tissue), or through a permanent excess of Insulin, altered in its sensitivity (Figure 1).

There is growing evidence that Tyrosine-Kinase receptors are the key to the formation and progression of human cancer, that is, the receptors for insulin (IR) and those for ILGF-1 (insulin-like growth factor); and this even, at physiological levels [25]: The hormones play a transcendental role in the progression (extension of the primary tumor) and the distant extension (metastasis) of most cancers [26]. The proliferative effect of Insulin and stimulant of cell mitosis has been known for more than 5 years; since it is an anabolic hormone and as such, a powerful stimulant of tumor metastases (Figure 2) [25-27]. Thus, when insulin is in optimal quantity, and its optimal biological action is conserved, the cell (eg the smooth muscle cell) is maintained in a quiescent state, and due to its multiple anti-inflammatory effects; on the other hand, when there is resistance to its effects - being in excess - insulin strongly promotes cell migration [27, 28].

Hyperinsulinemia and Cancer As?

The cell is biologically programmed; but its structure and function will depend on the surrounding environment; that is to say, it will change according to the balance and the constant dynamics of the messages that she (and her environment receives); then, its function will depend on the constant change of its micro-environment: signals from the same cell (autocrine), from neighboring cells (paracrine) and from the hormones themselves (endocrine). The greater the proliferation of a cell; the smaller its differentiation; thus, insulin, the most pleomorphic hormone that stimulates cell growth, promotes proliferation from fibroblasts in vitro, to the neoplastic cell [24, 27]. Physiologically in a normal state, the Insulin-IGFs system (Insulin-like factors) perfectly regulates cell and tissue growth and differentiation: growth is achieved by hypertrophy (increase in size) and hyperplasia (increase in number) of the cell; while its Differentiation usually implies the EESC of growth with the Function Specialization. Overgrowth implies a powerful stimulus for the appearance of Malignancy [29]. All epithelial cancers, including those of greater lethality such as small-cell lung cancer have over-activation of insulin-like factor receptors: IGF-1 (Insulin-growth-factor-1), which, today they consider themselves strongly involved in the pathogenesis of cancer [30].

A chronic inflammatory state has been demonstrated in Insulin Resistance, where insulin, when secreted in excess, loses its anti-inflammatory and modulating action of cell proliferation; thus, excessive insulin induces tumor proliferation because it is itself a powerful growth factor; and for stimulating a series of growth factors, particularly IGF-1 (see figure 3); In addition, the excess of insulin, acts deeply enhancing the proliferative effect of other hormones such as estrogens [31-34]. Apart from increasing atherosclerosis, due to greater endothelial vascular dysfunction (and favor iron deposition), excess energy promotes various types of neoplastic transformation,

in vitro and in vivo; and any nutritional state that exacerbates the chronic increase in insulin, progressively (and cumulatively) increases the risk of cancer, in particular by generating the over activation of the inflammatory nuclear transcription factor Nf-kB, a potent promoter of cell survival cancerous by deeply inhibiting your programmed cell death: apoptosis [35-39]. A commonly forgotten evidence; and that every minute increases overwhelmingly: Overweight and excess energy ingested as dietary calories increase the risk of acquiring a malignant neoplasm, particularly derived from chronic non-antagonized inflammation [36-40]. It is known, for example, that the risk of breast cancer is reduced with lactation (and its energy released), but in particular, the increased risk of malignancy decreases with the total duration of breastfeeding. In this regard, it is established conclusively, (Italian Group Capri Workshop Group) which are the hormonal influences that increase the growth speed of the gland breast, those that powerfully increase the risk of breast cancer - like a first early menstruation (menarche). The visceral (android) distribution of female fat is a marker of Insulin Resistance, and of increased risk of Breast Cancer, which starts from puberty, since it causes greater adipocyte-dependent inflammation and Above all, it perpetuates the chronic excess of insulin. However, even if the overweight subject does not voluntarily reduce weight - which would reduce their systemic inflammatory and adipose tissue status - frequent aerobic exercise - can control and reduce cancer, a particular fact and of great relevance in breast cancer [41-44].

In concert with the chronic and unbalanced excessive action of steroid hormones and / or the inflammatory action of Leptin (generated in adipose tissue), insulin greatly enhances its cellular effects; and, conversely, its excess increases the oncogenic power of exogenous estrogens in concert with leptin: this synergistic action directly promotes and exacerbates the excessive growth of the uterus, prostate, type 2 diabetes; and in particular, breast cancer, prostate, and probably lung cancer. But, in the absence of excess or resistance to the biological effects of insulin, the appearance of malignant neoplasia, its risk and prognosis would be greatly reduced. The more accumulation of android adipose tissue, greater bioavailability of non-esterified fatty acids-, greater secretion of inflammatory cytokines and TNF alpha; FFAs are potent insulin tropic agents, that is, powerful stimulants of post-prandial insulin secretion, and also inducers of their tissue resistance (when competing with the hormone); these and adipocyte inflammatory peptides directly increase insulin resistance: all this aggravates and perpetuates hyperinsulinemia; and the higher the cellular exposure to Insulin, the greater the growth tumor: insulin increases the free fraction and bioactivity of IGF-1 by decreasing its transport protein [45].

Insulin: The Hormone That Allows and Aggresses Cancer

The Insulin-IGFs axis is in intimate connection with the growth hormone GH, since the cellular response of the permanent growth of a tissue depends on it. Insulin becomes the pivot hormone that allows (permissive action) the survival of the paraneoplastic, neoplastic and cancerous cells, supporting and nourishing, along with glucose, oncogenic molecular signaling (Figures 3, 4, 5, 6, 7, 8). Insulin signaling controls the transcription of many genes; and it is, physiologically determinant (regulator) of tissue blood flow, at rest and exercise. And we all know that the growth rate of any tumor tissue is accelerated the higher its degree of blood supply (tissue flow). Very particularly in post-menopausal women, android obesity is a proven risk factor for breast cancer, directly, and through an increase - in particular - of leptin, an inflammatory hormone-cytokine; which rises in accordance with the speed in the increase in fat mass: it is the hormone that directly modulates the growth of tumor cells [24]. Permanent, chronic, non-pause stimulation of many hormonal receptors causes alteration in their conformation and response; In addition to altering its tissue density. And this occurs when a chronic excess of the greater anabolic is secreted and that stimulates cell proliferation: Insulin and the Insulin-IGF-1 axis; favored significantly in its signaling, by the permissive action of GH Growth Hormone. It has been proven in vivo that the insulin receptor is a potential oncogene for mammary epithelial cells: its density is very high in the vast majority of breast CA [25, 26]. Because the receptors for Insulin and ILGF-1 are homologous, Insulin regulates and activates the ILGF-1 receptor. Insulin receptors are overexpressed in the vast majority of malignant tumors, especially IR-A; and they also stimulate the receptors for IGF-1 (hybrid receptors), thus constituting the Insulin-IGFs axis in the major human cancer stimulant [46, 47]. As oncogenes products, aberrant receptors that transform normal cells into cancer cells can be expressed: certain oncogenic products (Ros and ErbB) are activated and uncontrolled forms of insulin receptors that enhance cell proliferation.

For more than half a century, it has been shown that high fats have been promoters of cancer, especially breast and prostate, by chronically generating very high levels of insulin and a receptor over activity in the Insulin axis - IGFs; which, activates the expression of the aberrant receptor for insulin (IR type A) and the consequent mutagenic over activation of IGF2 [18-20]. Insulin-like factor Insulin-like growth factor-1 (IGF-1) is a potent physiological and pathophysiological inhibitor of apoptosis and powerful stimulant of cell proliferation and tumor development; thus, numerous researchers confirm that both ILGFs are powerful mitogenic agents for epithelial cancers, constituting ILGF-II, the most powerful promoter of epithelial carcinogenesis, such as lung and breast CA. In addition, ILGF-1 is committed to the maintenance -in vitro-of Immortalized human bronchial epithelial cells, and in prostate, along with hyperinsulinemia [48-56].

A larger final size reached by a subject, particularly in the face of rapid childhood growth (higher speed or catch-up) due to greater tissue signaling of permissible growth factors (GH / IGFs) for greater cell and tissue proliferation ; The greater the risk for human cancer. Specifically, in many neoplasms, particularly in prostate cancer, the aggressiveness is greater, because the final size of a man reflects increased activity during the pre-adulthood of the Insulin-IGF-1 Axis [57]. The definitive role that abdominal obesity plays (regardless of body mass index) in the development of human cancer is decisive, as was recently corroborated for prostate cancer: thus, a benign biopsy can transform - in five years - into established malignancy especially if it is "fed" by high concentrations of exogenous fatty acids [58].

In the absence of any genetic alteration or mutation, human normal prostate epithelial cells proliferate markedly with 5 micrograms of insulin / ml. A direct association between insulin levels and prostate Ca risk has been demonstrated, regardless of the degree of total and abdominal adiposity. Thus, hyperinsulinemia (overweight or abdominal obesity) is what can predispose to a neoplasm - more than obesity itself [58]. And this is corroborated in particular in Asian and American populations, where, due to the existence of a greater fatty liver, the overweight abdominal obesity confers greater risk for malignant neoplasms [58].

The proliferation and survival of cancer cell lines can only occur when the proliferative signaling of the Insulin-IGF-1 system and its receptor are intact, because apoptosis cascades are deeply inhibited that would prevent the appearance of cancer cells Moreover, the permanent stimulation of IGF-1 promoted by growth hormone and insulin (both in coordination), are key to planting. Distance from cancer cells - metastasis. And its reduction with the improvement in its sensitivity has shown to improve the aggressiveness of cancer, as in the case of anti-hyperglycemic drugs that reduce insulin resistance, such as Metformin (Figure 1). If, experimentally, the activity or signaling of IGF-1 is decreased - by increasing the levels of its ILGF-binding protein-1- linker protein, we will achieve a very effective antineoplastic strategy by improving insulin sensitivity [49]. And this is achieved, effectively with regular aerobic exercise.

Permanent Excess of Insulin

When the Metabolic Requirements of the Cancerous Cell are provided

The insulin-like factor-1-IGF-1- is a powerful factor required by the cell for cell cycle progression (from the G1 phase to the S phase). The Insulin-IGFS axis increases the risk of cell transformation by increasing cell turnover, as they are powerful antiapoptotic and mitogenic agents (Figure 2) [60]. Thus, numerous clinical, experimental and epidemiological evidence indicates that the increase in IGF-1, even relative (together with a decrease in the IGFB-3 linker protein) is independently associated with an increased risk of prostate cancer, colon -straight; of breast in premenopausal women; and probably from the lung: this evidence derives mainly from the Physicians 'Health Study and the Nurses' Health Study [17, 37].

Animal fats are powerful stimulants of the nutrition of cancer cells by strongly increasing their vascular irrigation, by promoting the formation of neo-vessels around the tumor; that is, saturated fats are angiogenic, directly favoring lung metastases from colon cancer [61]. And, being the powerful insulinotrophic free fatty acids - stimulants of insulin secretion - and having fats Inflammatory (Saturated and TRANS) plus calories per gram (9 Kilocalories instead of 4 kilocalories generated by carbohydrates or proteins), powerfully stimulate the growth of malignant cells (see below). Thus, insulin is a permissive hormone for the development of Cancer, even without genetic predisposition; which, de novo, can initiate the process of Carcinogenesis (in collaboration with the stimulated excess of other hormones, such as leptin, GH, estrone, etc). Both in vitro and in vivo, it is sufficiently demonstrated that endogenous Insulin promotes greater activity and tumor growth.

In a magnificent cohort study between almost 4,000 children and pubertals, for 50 years in Europe (England-Scotland) - The Boyd Orr Cohort Study - a powerful association between ingested energy and the occurrence of subsequent cancer (not related to to smoke); results that remained after adjusted socioeconomic variables [62]. Why does excess insulin always directly promote latent cancer? For the Warburg Effect: causes aerobic glycolysis, which is preferred by rapidly growing cells; this deeply fuels the replication of these cancer cells (more than normal cells, which prefer the energy of oxidative phosphorylation [63, 64].

Excess Caloric Energy as a Generator of Neoplasia

The tumor cell has much greater avidity for glucose, compared to a normal cell (Aerobic Glycolysis). If we raise the intake of ingested energy, we will be nourishing, preferably, the transformed cells, rather than the normal cells: glycolysis is greater in the cancer cell; which, when massive in established or advanced cancer, reduces the availability of glucose - lower glycolysis - in healthy tissues. This explains why the appearance of type 2 diabetes in terminal cancer is common. It has been known for more than a decade that oxidative stress plays a fundamental role in the development of degenerative diseases and cancer: the greater the resistance to insulin, the greater lipid peroxidation (due to the greater oxidative stress).

The diet is decisive for the appearance, but above all, the aggravation of an insulin resistance, but not obesity by itself she is responsible for more than 50% of overall mortality in subjects with cancer, in the western world [25]. The incidence of CA is very high in the presence of a diet high in caloric energy, rich in fats and / or refined carbohydrates [65, 66]. Over nutrition is closely related to carcinogenesis for more than 80 years [25]. Today it is shown that excessive fat consumption increases the expression of many genes that stimulate angiogenesis and the proliferation of cancer cells [34]. Thus, the excess energy ingested is decisive for the increase in atherosclerosis and tumorigenesis [65-67]. In particular, the excess of inflammatory fats, which leads to a rapid release of FFA free fatty acids, potent insulingenic by their direct action generating insulin resistance, is decisive for the permanence of excessive amounts of insulin.

The excess of omega-6 polyunsaturated fats is closely linked to the development of Cancer, by generating or aggravating hyperinsulinemia, especially when faced with high carbohydrate intake [67]. This acquires much greater oncogenic relevance when there is low intake of Fiber, Zinc and / or Omega 3, the micronutrients whose high intake can confer protection against malignancy. Particularly, the high chronic caloric intake in women that causes a deep synergism in the promotion and stimulation of cancer, due to excess insulin and estrogen, can be inhibited with Relative speed due to a high consumption of fiber and soy protein [68].

It has been pointed out that the increase in liver carcinoma, also mediated by hyperactivity of the IGF system, would be strongly induced by the PUFA Omega 6 [37]. Thus, any over-expression of the components of the hormonal system directed by Insulin is associated with liver carcinogenesis; in both animals and humans: PUFA Omega-6 polyunsaturated fats accelerate the development of precancerous lesions and tumors in animals. Triglyceride, glucose and insulin levels are associated with a higher risk of CA, in particular, colon cancer: diets high in simple sugars increase the risk of ovarian and stomach CA, especially high consumption of saccharose- A report of more than 60,000 women (between 38 and 76 years old) shows that a high consumption of dairy products - particularly milk - is associated with an increased risk of severe ovarian cancer, due to a sustained and marked hyperinsulinemia; Older girls (for their age) increase their risk for ovarian (mucinous) cancer due to hyperactivity of the insulin axis [72-74]. And, as will be seen later, in the Physician's Health Study, chronic insulin excess caused by the consumption of more than 600 mg. of calcium in dairy products, the risk of prostate cancer increased by 32% [75].

Calorical Restriction as Prevention and Treatment of Cancer

It is evident then that Insulin Resistance - whose clinical expression is hyperinsulinemia, is linked not only to an increased risk of hypertension, arteriosclerosis and cardio-cerebrovascular

diseases, but to increased risk of breast cancer, rectum-colon, pancreas, prostate, stomach, ovary, kidney and endometrium; even, according to a recent report to the extent of an osteosarcoma [76]. This in very close association with the size / or the BMI (body mass index) of the subject, a clear risk factor of nutritional cause. Caloric restriction inhibits tumor growth by favoring and inducing greater apoptosis on cell proliferation [25, 36]. This occurs in spontaneous, induced or transplanted tumors (Figure 2 and Figure 4). A recent experimental study demonstrates a reduction in prostate tumor growth, concomitant with a decrease in plasma ILGF-1 and reduced expression of Vascular Endothelial Growth Factor with energy restriction in tumor transplantable models. In contrast, supplementation of ILGF-1 eliminates the protective effect of caloric restriction on tumor progression. But most importantly: the greater the secretion (basal and stimulated insulin) - the higher its secretion rate in 24 hours -more intense will be tissue irrigation due to greater hair recruitment.

It is interesting that the arrest of tumor development occurs even when this caloric restriction is not necessarily accompanied by a lower fat intake; in other words, there was also a decrease in the tumor in animals (with calorie restriction) that consumed a higher percentage of fat, in relation to the control group [77]. This would imply that high fat consumption "per se" would not be as important as a direct cancer-promoting agent would, as excessive caloric intake would be. A concept that we should not forget, proven histologically in humans. Excess signaling of insulin-related factors IGFs - determined primarily by high calorie intake - it is the cause of colonic cancerous transformation [42]. On the contrary: energy use through exercise reduces the growth of cancerous tumors: a history of physical exercises reduces the risk of CA in man. (See later). Thus, the restriction of energy (due to lower calorie intake, and / or greater expenditure via exercise) decreases insulin levels, reducing the expression of oncogenes.

In addition, energy restriction produces a more efficient and effective repair of damaged DNA. How? by increasing the activity of several antioxidant enzyme systems [78]. We now know that the molecular structure of DNA, in addition to its genetic component - the same for all cells - has an epigenetic component, which is exogenously programmed by the nutritional / hormonal environment and lifestyle (exogenous methylation of a gene, which determines its silence or its degree of activity). Physio pathologically, progressively, Insulin regulates and activates the ILGF-1 receptor, which, as we said, has a direct oncogenic potential, since it can structurally become an aberrant receptor [42, 24]. There is ample evidence today that excess caloric energy in Omega-6 fats increases the development of cancers in humans, especially those of aggressive phenotype (Prostate and Melanoma Cancer) (Figure 3 and Figure 4) [79-81]. Excess insulin produced by excess calories in the diet - and aggravated by sedentary lifestyle - in addition to its direct influence, increases the risk of developing female (Breast) Epithelial Cancer by increasing ovarian androgen secretion. Female android obesity is a particular risk indicator for developing an epithelial cell atypia due to the hormonal increase of insulin, leptin and the resulting greater androgen secretion and bioavailability. Chronic hyper-insulinemia powerfully inhibits physiological apoptosis; which is decisive in the appearance of cancer. Calorie restriction retards aging and chronic degenerative diseases, particularly the decrease in animal protein; and it is the fastest way to decrease the degree of insulin resistance - a powerful phenomenon that predicts chronic diseases of aging: there is a powerful statistical correlation between the increase in IR and the increase in Cancer [82-85].

In addition to this interrelation between chronic insulin excess and malignant cell transformation, recent in vitro experiments: normal melanocytes, chronically exposed to insulin and supplemented with glucose (3 weeks) undergo oncogenic transformations (increased glycolysis and redistribution of methyl groups) [85]. The greater the exposure of the cell to hidden hyperglycemic (post-prandial) environments, the greater its risk of malignant transformation in the presence of elevated insulinemia. The severity of any chronic disease is mediated by the degree of insulin resistance (56): the more severe the concomitant insulin resistance, the worse the prognosis of the cancer; and diet is crucial to slow or accelerate the neoplasm. Although not every patient with IR has Cancer, every subject with Cancer does have Insulin-Resistance (Chronic Hyperinsulinemia) established. Conversely: the greater the degree of Insulinosensitivity there is a lower risk of acquiring Cancer [82, 83].

Inflammation and Cancer

Prostate cancer is being considered an aspect of Insulin Resistance syndrome: this is a chronic state of low-grade inflammation. It has been shown almost 20 years ago that exogenous insulin injections promote colonic carcinoma. On the contrary, low concentrations of insulin in the blood protect against colon-rectum cancer, by exerting its physiological anti-inflammatory effect [1, 10].

Physical activity is a powerful anti-inflammatory mechanism by progressively improving insulin sensitivity, reducing its excess; and therefore it constitutes a powerful primary preventive of Cancer; In addition, aerobic exercise produces a sustained reduction in the activity of the IGF axis, and enhances the anti-oncogenic suppressor protein p53 [67, 71, 86]. A recent study suggests that NSAIDs can prevent colon cancer by suppressing the expression of Hepatocite Growth Factor, a proven inflammatory peptide. And, today it is known that Chronic inflammation predisposes to Cancer [87]. Why? Because it immediately and cumulatively originates resistance to the biological effects of Insulin, a local Insulin-Resistance and then generalized. The transcription factor Nf-KB, -a transcendental molecular mediator in the inflammatory process and implicated in carcinogenesis is upregulated in chronic hyperinsulinemia. The chronic infusion of IGF-1 enhances the activation of the nuclear factor NF-kB, as well as the increased expression of adhesion molecules, events induced by TNF-alpha (tumor necrosis factor) [67, 40].

Acute Hyperglycemia as Inflammatory Factor and Permitting Agent of Cancer

Experimental studies suggest that both glucose and hyperinsulinemia increase the inflammatory response: There is a direct effect of glucose, insulin and leptin on the pro-inflammatory production of cytokines. But here insulin would act in a field of resistance to its effects. That is to say: chronically elevated endogenous insulin is inflammatory (contrary to its acute effect, see below).

The greatest glucose oscillations are a potential inflammatory endothelial factor: In non-diabetics, hyperglycemia increases the ICAM endothelial adhesion molecules, monocyto-endothelial adhesion, and the expression of the enzyme Cyclooxygenase 2, increasing Thromboxane A2 and decreasing Prostacyclin; and in diabetics, P-selectin increases [88]. Conversely, higher concentrations

of endogenous insulin and glucose will cause higher degrees of protein glycation, higher formation of advanced glyco-oxidation end products (AGEs), which in turn will increase lipid peroxidation, generating, finally, toxic products: the Aldehydes: highly deleterious to the genome and atherogenic.

Evidence-Based Medicine: Excess Insulin (Excess Energy) as a promoter of Carcinogenesis

Insulin and IGF-1 are directly involved in the degree of proliferation of prostate and breast tumor epithelial cells in humans [43-49, 89]. Thus, recent evidence confirms the role of ILGF-1 as a determining factor in the appearance of some aggressive forms of Cancer, by enhancing inflammation and reducing programmed cell death - apoptosis - of the neoplastic cell [90]. Eg By demonstrating vitamin C an anti-tumor effect on the growth of Gliomas, it has been shown in humans that the reduction in the expression of oncogenic receptors for IGF-1 powerfully reduces the growth and degree of invasiveness of human glioblastomas [90].

Insulin is capable of silencing the expression of certain protective genes against cancer transformation; and thus promote tumor growth: its excess increases DNA synthesis tumor, reduces the apoptosis of the neoplastic cell and enhances the neoplastic proliferative action of estrogens; this, in the presence of android overweight (which increases the conversion of androgens to estrogens) (rather than global obesity) triggers latent carcinogenesis: higher obesity is closely associated with mortality in most cancers [91-93].

1. Insulin ascends the expression of cancer genes in breast cancer cell lines (c-Myc and Cyclin-D1) [63].
2. The excessive action of Insulin, when it is in excess (hyperinsulinemia) or when there is resistance its effects (insulin resistance) is directly and powerfully, due to its anabolism and potent (and cumulative) cell survival effect (anti-apoptosis), the carcinogenic hormone par excellence [94].
3. There is current consensus in Europe (European Society for Medical Oncology) that refined carbohydrates are involved in the etiology of colon / rectum cancer, precisely through the Insulin-IGF axis: S. Frances chi et al. They confirm the hypothesis that Insulin Resistance generates colo-rectal cancer (insulin / colon cancer hypothesis) [95].
4. On the contrary: it is currently shown that diets with low glycemic load (by causing lower prolonged spikes of insulin) powerfully protect against cancer, especially breast and colon - straight [71].
5. Epidemiological and clinical evidence relate the highest risk for colon-rectum Ca, pancreas, breast, endometrium and prostate (in that order) with high caloric intake (International Agency for Research on Cancer, Lyon-France). The maximum growth achieved during the pre-adult period and the excess insulin during adulthood create an excessive risk of contracting cancer in the West [96].
6. Chronic insulin excess accounts for the excessive increase in many cancers, such as cancer of the colon, rectum, pancreas, prostate and breast, especially among those who are inactive or overweight. In particular, recent studies have observed an ostensible rise in the incidence of colon and rectal cancer among individuals with higher post-prandial hyper-insulinemia.
7. In humans, exposure of normal cells to permanent elevated insulin environments profoundly alters their DNA: thus, chronic insulin exposure plus glucose supplements in human melanocytes induce oncogenic changes, increase tumor proteins (oncoproteins) and cause alterations chromosomal [97].
8. The IMMEDIATE glucose increase that occurs in any acute condition (organic / traumatic / psychological) is due to Insulin Resistance generated (and increased) by Inflammation, not by "stress per se", and should be IMMEDIATE (eg oral dietary potassium) [98].

Chronic hyperinsulinemia is the promoter event of Colon Cancer, pancreas, endometrium, and, particularly, breast cancer initially due to an excess of caloric energy [77, 95]. And in this excess of energy, - chronic hyperinsulinemia - simple carbohydrates would be the most dangerous: an acute increase in glucose –from stress or post-prandial- increases the production of inflammatory cytokines in non-diabetic subjects and the activity of the factor of Nf-KB inflammatory transcription, clear carcinogenic factor [72, 83]. The recent isolation of functioning insulin receptors in ovarian epithelial cancer cells clearly demonstrates the involvement of the Insulin receptor, and particularly the receptor for IGF-2 in Cancer growth [73].

Scientific evidence continues to demonstrate (more than 170 observational studies) that exercise prevents Cancer: it clearly reduces the risk of breast, colon-rectum, prostate and ovarian cancer; It also improves advanced prostate cancer by reducing excessive activation of the IGFs-Insulin axis, which decreases tumor proliferation [99, 100]. At lower acute excursions of glycemia, less macrophage-induced inflammation and lower production of inflammatory adipocytokinases (IL-1, IL-6, TNF-x), and vice versa [38, 101]. In addition, in accordance with the above, malignant tumors acquire greater severity, incidence, prevalence and recurrence in subjects with higher adiposity, even in the absence of overweight, due to the greater inflammatory activity of their adipose tissue, and in causal relationship, the greater hormonal content of Leptin - Leptin Resistance [88].

Permanent aerobic exercise, the lowest cost treatment for Insulin Resistance has been shown to reduce more aggressive epithelial cancers, such as ovarian cancer and prostate cancer [88]. In this way, it is proved, with epidemiological evidence that excess insulin - or its chronic resistance - has a close causal and / or promoter relationship) with Carcinogenesis [76, 96, 102]. Concomitantly, and acting powerfully as an environmental agent of tumor potentiation; In the presence of acute increases in glycemia, the mitogenic potential of excess insulin is increased [103].

Nutritional Modification and Hormonal Therapy of Cancer: A Magnificent Weapon Today At Our Reach

The genetic therapy of cancer has fundamental endocrinological aspects, but which remain unknown to the tubular physician: the most important physiologically and physio pathologically, as we have indicated before, is that glucose is a powerful regulator of the mitogenic and carcinogenic capacity of insulin [103].

Being the Insulin Resistance Syndrome. Even in children, the greatest health problem in the present times, especially in those countries in epidiological transition, the predisposition to chronic diseases, particularly cancer and Alzheimer's disease due to IR, is today widely recognized [104]. Today, the most “simple” way for science, by which we can regulate the expression of a gene is to make it available for a repetitive physiological signaling such as acute glucose increase: it is, initially and finally, the environment

(and the cellular microenvironment) that regulates the expression and action of genes [104, 105]. In this regard, today it is known that there is a clear nutrition-hormone-gene interaction with a direct modulating action of nutrients on gene expression in the submucosa and intestinal mucosa, an endocrine unit; but above all, a hormonal action of insulin and leptin, suppressor (if they are in normal quantity) or activator (if they are, chronically in tissue / plasma excess) of certain carcinogenic genes. (Proto-oncogene RAS); on the contrary, adequate permanent levels of insulin (and leptin) activate powerful anti-cancer genes - the antineoplastic effect of aerobic exercise - (see above) [105, 106].

To consider only one hormone: Ghrelin, produced primarily by the stomach, and regulated by food and nutrition patterns, powerfully controls the proliferation of neoplastic cells in an acute manner [107]. And, in view of the insulin resistance epidemic in children who have lost their satiety, the secretion and proper function of ghrelin, would be very compromised. Very interesting, the direct regulation of this hormone by insulin; which would explain the complex relationship between insulin resistance and prostate cancer; since Ghrelin stimulates in vitro the proliferation of prostate cancer. (Seim, Lubik, Lehman and Chopin; Ghrelin Research Group, Institute of Health; Queensland, University of Technology, Brisbane, Australia: Journal of the European Endocrinology Society, 2012, Online ISSN: 1479-6813). Nutritional parameters, through a powerful regulation of peptide-hormonal growth factors are decisive for the presence or absence of Cancer in man; determining its prognosis [71, 108-110]. The degree of insulin resistance is a predictor of the severity of aging diseases, improving insulin sensitivity - nutritionally and pharmacologically - the prognosis of cancer will improve: Glitazones (by increasing the activity of nuclear receptors gamma peroximal proliferation), and probably Biguanides (Metformin) could play a crucial role in reducing established Cancer (see end) [85].

The alarming increase in breast cancer continues to rise due to the consumption of sweets among women under 45 [41, 111]. It is crucial to achieve an adequate energy-protein contribution for the patient with Cancer, but without intensely stimulating tumor growth [107]. Given the evidence that the neoplastic cell is stimulated by excess calories, especially simple sugars and inflammatory lipids (Figure 7), it is urgent to rethink today not only the prevention but the integral treatment of Cancer, both with nutrients-drugs, Omega-3 grease; flavonoids and derivatives ... .- as with caloric restriction (suppression of simple sugars and excessive animal protein ...), measures all aimed at reducing chronic hyperinsulinemia, authentic permissive-generating disorder of cancer [108, 112]. This is really worrisome to our obese children, who have increased (fasting) insulin levels more than 12 times; explaining this, the alarming increase in childhood cancer [108].

Increasing evidence confirms that the cellular processes that stop tumor growth due to energy restriction - malignant and premalignant lesions - are mediated through the regulation of IGF1 and glucocorticoids [113-116]. According to the Korean follow up Study, the highest risk of death from most cancers is associated not only with diabetes, but with elevated serum glucose levels: this proves that, in short, All mechanisms that raise the risk of Cancer reflect the consequences of Hyperinsulinemia [116]. Not only is calorie-synthetic energy restriction (crucial to reduce chronic hyperinsulinemia) the most effective strategy to increase life expectancy in subjects with Cancer; and raise its quality, but the avoidance of an excess of macronutrients is the optimal measure to prevent cancer [117-121]. This high nutrient intake, added to a sedentary behavior (relative or not) will be expressed (said simply) as post-prandial hyperglycemia (hidden diabetes) [120]. As we have indicated before, diabetes and cancer are two extremely interrelated entities that enhance their mutual risk; to the extreme that, when both occur in a patient, the chances of radical cure are virtually non-existent.

With regard to excess growth due to high-energy intake, those girls who have rapid growth (catch-up), and reach their final height quickly have a very high risk of breast cancer: this by increasing their insulin and leptin levels, which will accelerate the onset of puberty (precocious puberty, a known factor that predisposes to breast malignancies) [121]. Not surprisingly, dairy products and excessive calcium are strongly associated with an increased risk of prostate cancer and, when combined in a diet high in fat calories, with an early and aggressive pancreatic cancer [122]. A sharp discrete increase Intracellular Calcium ion facilitates the onset and progression of Colo-rectal Cancer, as just verified. Substantial experimental and clinical evidence proves that the current intake of excessive energy increases the circulating levels of insulin and particularly those of IGF-1, which powerfully increase the risk of the most common cancers in the West: clinically and epidemiologically, this is reflected in that The maximum growth during adolescence, with the hyperinsulinemia generated, permanent throughout adulthood, long causes an excessive risk of acquiring cancer [82].

The faster the increase in glucose absorption, and its increase in plasma, the greater the stimulated insulin secretion. As well: There is a direct association between the speed in the sharp increase in plasma glucose -measured by the glycemic index of food and glycemic load- and the greater risk in the aggressiveness of cancer [59, 66, 76, 4]. This may explain, to a large extent, the epidemiological evidence ignored extreme frequency of colon cancer in "mild" or hidden diabetes mellitus [112]. Leptin is another hormone, dependent on adipose tissue, that suppresses apoptosis, and that particularly because of its inflammatory cytokine hormone condition, dependent on excessive adipose tissue, powerfully increases the growth of breast cancer, and particularly that of prostate; p. Ex. In prostate cancer cells, the mitogenic effect of leptin is performed through PI3K and MAPK signaling, mutually dependent on insulin [123]. The more fat accumulated in the abdomen and / or trunk, the greater the production of leptin; and greater the permanent adipose-dependent (and systemic) inflammation that is offered to the precancerous cell. Today we know that, central adiposity in women may be the greatest risk of ovarian cancer, by promoting, in addition to greater disposition of estrogen to the circulation [124].

EXCESS OF HORMONES AS GENE MODIFIERS: The example of Insulin and Leptin

Hormones can regulate genes: Although every cell contains the genetic information to synthesize any protein, it only uses a small set of genes, according to their differentiation. RNA production is perfectly controlled by hormones. Therefore, the phenotype of a chronic disease is determined by the nutrient-gene interaction, specifically through the generation of insulin resistance. There is a clear and positive association between Omega-6 fats - unequivocally recommended - and the increased risk of cancer, particularly breast

cancer, which is mainly due to the generation or maintenance of an excess of endogenous insulin, and the survival of the cancer cell in response to the powerful anti-apoptosis [125, 126]. The evidence is strong: Omega-6 fats are potentially the cause of breast cancer, the clearest example of chronic insulin excess (insulin resistance) in women [62, 126].

When the Insulin-IGFs axis is genetically suppressed, as in subjects of short stature, who have not been supercharged in their early childhood, there is a marked reduction in the risks of acquiring cancer; particularly in men [127]. In this regard, today it is widely demonstrated (but unfortunately, forgotten) that the powerful stimulation in the secretion of insulin (and GH growth hormone) caused by amino acid supplements arginine and ornithine, promotes the growth of the primary tumor and accelerates the development of its extension at a distance [85]. An epidemic in our days is the Insulin Resistance syndrome, which, today, occurs even from childhood - chronic hyperinsulinemia -, which leads to accelerated atherosclerosis, from a dyslipidemia with HT, to Chronic degenerative diseases [111]. Definitely, dietary energy restriction limits excess blood supply (neoformed) to various tumor pathologies; effect that directly inhibits the entire carcinogenic process, when all of them are mediated by the modulation and control of the insulin-IGFs axis and glucocorticoid metabolism, particularly mediated by stress [117, 78]. It has been shown for a long time that the restriction of ingested calories inhibits cell proliferation and induces apoptosis of pre-malignant and malignant cells, decreasing the incidence of neoplasms; thus, the induction of solid tumors and radiation-induced leukemias is dramatically reduced when the caloric restriction is greater than 30% [85, 115-118, 127, 128].

Finally, considerable and growing clinical and epidemiological evidence shows that the rapid growth since puberty is decisive for the onset of Cancer, which is generated by the excess energy ingested (accumulated), through the cellular effects of chronic excess insulin and of the molecular signaling of IGF-1 [129]. There will always be obese children; but, apart, and independently of the diet, they can progressively and ostensibly improve the quality of their insulin (insulin sensitivity) by reducing their future risk of cancer, with regular aerobic exercises, which reduce the degree of its inflammation [130, 131]. In addition, with frequent consumption of Omega-3 fats Marine is further reduced - and powerfully - carcinogenesis by significantly increasing insulin sensitivity [131]. So, today, it is more than evident that the excess of circulating insulin, particularly combined with tissue insulin resistance by a diet rich in inflammatory fats, is a promoter of neoplasia, and in the absence of obesity: adipose tissue stromal cells secrete IGF.1 and increase early invasion -local- (see end of text) [132-134]. This is proven, in pre-diabetic women and especially in diabetics, who, before any therapy that increases insulin levels (sulfonylureas or exogenous insulin) have a significant increase in cancer mortality, compared to those therapies that reduce hyperinsulinemia, such as metformin (Figure 10) [135]. Cumulative animal cell models, and currently in clinical development, indicate that reducing insulin resistance and hyperinsulinemia can reduce tumor development [135, 136].

In an ideal "rural" world, where there is no excessive caloric intake, obesity, sedentary lifestyle, and carcinogenic inflammatory dietary patterns - that is, where chronic insulin excess is not caused - development, morbidity and mortality will be significantly reduced by Cancer. Eg cow's milk contains growth factors such as IGF-1, which, as we noted, has long been shown to stimulate prostate and breast cancer, directly or through its high content of poly fatty acids. Unsaturated Omega-6 [137, 123, 125]. As a clear anabolic hormone, Insulin has proven "per se" to be a potent stimulator of DNA synthesis, of RNA in Glioma tumor cells; and, on the contrary, a sustained reduction due to a restriction of calories, especially of proteins, has been shown to reduce its degree of malignant transformation: its excessive and chronic cellular stimulation will lead to an increased risk of cancerous transformation And, in the case that there is no "smallest genetic history of insulin resistance, or of family cancer (or of both, overlapping), the evidence is overwhelming, today: chronic insulin excess favorably favors the progression and metastasis of the breast tumor and prostate in vitro and in vivo, and particularly in diabetics [20, 138-140]. Today it has been shown that Insulin Resistance - measured by the homeostatic method (HOMA-IR) - in a control case study, represents a powerful independent factor for lung cancer [141, 142]. It is essential to emphasize that pediatric cancer; and the gynecological (including cervical cancer) continues to increase due to the excessive activity of the Insulin-IGFs system (5, rev); and whose relentless oncogenic signaling is not duly counteracted in the countries of America

Final Considerations

Epigenetics determines the appearance of cancer

WE AVOID the excessive weight gain and in particular, a high calorie intake since puberty, to prevent the development of Cancer, and control its extension (when it already exists) biologically and hormonally with caloric restriction [143, 144]. The interrelation between diet and genes cannot continue to be unknown, despite its clear causality in relation to the western cancer epidemic [145]. And, by reducing chronic inflammation, with physical exercise or a "simple" Aspirin, the future risk of Cancer can be reduced; and by improving the tissue action of insulin. In particular, in our Afro-descendant population, avoiding abdominal obesity, the excessive frequency of cancer would be avoided, and especially, its high degree of aggressiveness [146, 147]. (For every 10 kg of abdominal fat, the risk of prostate cancer is increased by 1.5, at Leptin and Insulin rise considerably [147]. Excessive insulin is, in short, the most powerful, potent and common carcinogenic hormonal factor [148]. Glucose intolerance - an immediate state that precedes diabetes - is also increasing vertiginously - independently predicts Cancer mortality. Thus, high consumption of beverages and simple sugars (including sucrose or common sugar) powerfully increases cellular inflammation [149]. The higher the refinement of sugars, the greater its potential to generate cancer; and the greater the "bulk of the subject in his youth" (insulin and muscular resistance and fat), the greater his risk of acquiring cancer: in them, the restriction of excess energy with food, in time, and in a regulated manner, you can effectively reduce cancer [150, 151]. On the contrary: the higher the amount of fasting plasma insulin, the worse the prognosis and the distance extension of early cancer [152].

The "epidemic" of cancer mortality in diabetic subjects that therapeutically increase their insulin levels could be reduced today if they reduce their high fat consumption inflammatory animals; and, as has been proven again, caloric restriction not only reverses the size of the tumor, but prevents the development of metastases [153, 154]. The lower the insulin resistance (and the less chronic

hyperinsulinemia), the lower the promotion and development of cancer in humans; which seems to be regulated, molecularly - and fascinatingly - by the beta cells of the pancreas [155-157]. Finally, if we want, with the current scientific truth in mind, to reduce the prevalence of cancer, by opportunely preventing its extension, we must reduce the environmental factors - hormonal and dietary - (epigenetic factors) that control the genetic footprint ("genomic imprinting") and its activity [158, 159]. Epigenetics describes the wide range of modifications undergone by DNA (and its Histone complex) that influence and potentially determine the expression of oncogenes (or the silence of cancer suppressor genes) without altering its encoded sequence; and this reaches its maximum degree in the western diet and environmental exposure, through hormonal disruption, Krashin, Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies, 2019 [160-162].

Insulin as an independent generator of Neoplasia

Chronically elevated insulin causes deep chromosome and DNA alterations in humans; being the ignored cause of Melanomas and other cancers in man: The powerful INDEPENDENT risk conferred by Insulin-resistance (hyperinsulinemia) for cancer has been confirmed again, today: a real and regulated caloric restriction is a powerful anti-cancer measure, by dosing gene expression; and vice versa: the higher refined sugars the cancer patient consumes, the greater their progression [163-167]. In Type II Diabetes, where, clinically and epidemiologically, the presentation of cancer has the highest incidence and aggressiveness, insulin therapy should be carefully monitored; and above all complemented with a comprehensive INTEGRAL treatment, to weigh the undeniable benefits of its use with its obvious mitogenic, proliferative effects and inhibitors of programmed cell death [168-170]. Even in a "terminal" cancer with an aerobic exercise program, the disease is significantly improved, preventing or reversing the intense degradation of tissues (cachexia). We must emphasize, particularly in our environment, that ovarian cancer - one of the most aggressive, hidden and rapidly lethal, especially among women with hidden thyroid disorders - continues to rise; However, its aggressiveness and incidence are reduced by daily exercise, as chronic ovarian inflammation and systemic power are diminished.

Finally, we must emphasize that increasing numbers of oncogenes require the presence of excessive chronic signaling of the Insulin axis - IGFs to cause the cumulative mutations that determine the genesis of the cancer cell; in such a way, that Insulin excess and its signaling are the events that confer resistance to ALL anti-cancer therapies [171, 172]. A fatty diet in the presence of a caloric excess increases the proliferation of breast cancer genes in VIVO, inclusive, without weight gain [173-175]. And, as has been proven once again, apart from diabetes, maintaining high glucose levels - even in non-diabetic ranges - raises the risk of cancer, especially in women [176, 177]. Thus, the greater the insulin in plasma and tissues and the consequent inflammation derived from adipose tissue (adipocytokines), the greater the risk of cancer: to reduce its extent, severity and recurrence, it is biologically necessary to reduce chronic inflammation Silent and maintained by the current "killer" lifestyle. Today, it is proven to reduce cachexia due to advanced cancer, by significantly reversing the multiple mechanisms of inflammatory cascades by improving insulin action and sensitivity; Thus, to prevent the progression of cancer with cytotoxic chemotherapy that induces numerous cytokines that further damage the neuroendocrine / steroidal-sexual system (increasing the baseline level of insulin), it is necessary to consider the endocrine principles of cancer gene therapy (Figure 9) [178].

Reducing the speed of malignant tumor growth depends on reducing the existing Chronic Inflammation that promotes and maintains it, regardless of fat accumulation and weight gain (especially in women, where breast cancer it spreads rapidly due to the excess of caloric energy ingested and without weight gain due to the very rapid increase in insulin resistance due to diet products); this is achieved through an optimal and accepted caloric restriction - especially refined carbohydrates, which powerfully increase tumor growth, particularly in humans - thus obtaining greater elimination of pre-neoplastic cells and a reduction in the expression of oncogenes: even in the progression of myeloid leukemia, adequate calorie restriction prolongs life, significantly improving its quality. Thus, a "benign" biopsy of a tumor will not quickly transform into a cancerous tumor of poor prognosis in humans [179-185].

This tight review of the denied evidence is intended to stop, in particular in Peru, the epidemic of gastric cancer among the poorest people due to the daily or excessive consumption of refined cereals and treats, high food glycemic load that disproportionately stimulates insulin secretion; and hidden diabetes (post-prandial hyperglycemia) worsen the prognosis of cancer, increasing its extent and severity [46, 186-191]. As a preventive measure, a categorical final message: the greater the energy ingested during childhood and puberty, the greater the likelihood of developing cancer (proven in a cohort study of more than 50 years -Boyd Orr Cohort Study- in England and Scotland) [168, 192, 193]. Even in several animal and human models of brain tumors of very different origin (cellular-biochemical-environmental) caloric restriction is demonstrating a significant reduction in nutrition (anti-angiogenic effect) and in tumor survival (pro-apoptotic effect) [194].

In a conclusive way, the energy restriction, demonstrated for more than a century, substantially retards tumor formation, being able to prevent the initiation of the carcinogenic process with the almost elimination of simple sugars, a fact demonstrated preclinically and that begins to be effective in humans; and on the contrary: the more energy ingested with food, since childhood, the greater the risk of acquiring cancer; and the higher the consumption of "smart" micronutrients that reduce the genetic damage caused, the lower the rate of cancer progression [195-198].

We give the alarm, because, even lung cancer in Peru rebounds surprisingly (unpublished communication from INEN-Lima, 2014): this is due, especially to the increase (parallel to insulin) mentioned in Leptin, which would induce an immune escape from cancer cells [199]. At the same time, liver cancer in the absence of viral hepatitis is rapidly increasing due to excess commercially promoted "protective" oils (the famous Omega-6); and childhood leukemia has exploded in its prevalence in Peru due to the daily lack of fruits, vegetables in the maternal diet, together with the excess of fetal insulin (macrosomia) [200]. People with a high risk of cancer, if they really want to prevent it, should, in conjunction with a non-sedentary life, avoid eating "normally" in excess: calorie restriction (without malnutrition) continues to prove to reduce the damage and mutations of the DNA and increase its repair capacity [201].

Before finishing, we must mention a magnificent experimental study that confirms that PUFA Omega-6 fats stimulate the growth of pancreatic cancer (while marine Omega-3s reduce it), which is mainly explained by the substantial changes in perpetuation (Omega-6) or decrease (Omega-3) in excessive insulin levels [202]. Clinical Oncology must be today, MULTI-DISCIPLINARY, and have a broad view on the old closed and isolated oncology [203, 204]. In the Institutes of Neoplastic Diseases there should be no free consumption of "junk food", as she continues to demonstrate even in hematopoietic cancers, powerfully accelerate their development, progression and invasiveness, such as acute leukemia, in dramatic increase in Latin America. The greater growth and proliferation of a cell enhances its mutation capacity, raising its carcinogenic risk, which occurs in its extreme degree in the face of permanent caloric excess and of "energy" micronutrients such as iron, as We will see in our next publication. In addition, excessive or free iron stimulates the proliferation of adipose tissue, complexly contributing to the resistance of cancer cells to any treatment [205-208]. Its restriction in a low-calorie diet is proving to reduce pre-neoplastic and inflammatory lesions [209, 210] (Figure 8).

Grape extract: its extract has demonstrated a high effectiveness in inhibiting cancerous intestinal and prostate lesions, particularly by reducing the carcinogenic action of the Insulin-IGF-1 axis and with it, its inflammatory genes (COX- 2, US). And, at the same time, the consumption of vegetable oils with Omega-6 fats (arachidonic acid) should not be further promoted by in vivo and in vitro evidence that they powerfully stimulate the growth of epithelial cancer, especially breast carcinoma [211-213]. Breast cancer is the greatest example that even in very early stages, cancer in situ does NOT STOP with the best surgery, if before or concomitantly the resistance or excessive activity of the Insulin-IGFs axis is not reduced, the which inactivates (phosphorylates) the main protein that defends us from cancer (p53) [214-216]. It is, finally, the uncontrolled stimulating metabolic environment of cell proliferation and the "greater uptake of sugar" by the cell, all that causes Cancer; and the resounding failure in its eradication when these metabolic disturbances are not combated [216, 217]. And, as long as the excessive and rapid weight gain among youth, more will increase the risk and progression of aggressive cancer, such as stomach cancer, in particular increase by the severe reduction of adiponectin, the only hormone that can reduce the risk of malignancy [5, 186, 218]. This is more urgent in the African-American population, where the aggressiveness of epithelial and hematopoietic cancer increases, due to the greater excess of insulin –adiposity-, which explains the increase in childhood leukemia, which begins inside the uterus [219].

The molecular mechanisms of hormones and nutrients alter gene expression: and as long as the excessive mitogenic signaling of Insulin is maintained, cancers of intense aggressiveness such as leukemia, myeloid and lymphoid will continue to increase, in addition to breast, prostate and pancreas, and gastric, salt-dependent, especially in Peru and Mexico [140, 180, 98, 220, 110, 187, 188, 189, 191, 194]. Backed by cumulative and strong evidence, hyper-insulinemia is the primary causative factor of cancer, and aggravated by the chronic (hidden) increase in glucose and insulin [221, 217]. A Yes, the higher insulin we have, the greater the growth of any tumor; and this will happen with greater speed and anarchy in cancer [221, 222]. Categorically, and, avoiding being simplistic, today it is shown that a greater increase in mitosis or cell division is the final or primary cause of cancer in humans: this is how Chronic Exogenous Insulin powerfully increases cancer risk in subjects with diabetes (other hidden evidence): it is metabolic reprogramming in response to excessive stimulation of cell growth, a central event in the pathogenesis of all cancer [223-225].

Even in advanced cancer disease, aerobic exercise is proving to improve severe cachexia and reduce the growth of the malignant tumor; and high aggressive cancers, particularly lymphomas, pancreatic cancer and stomach cancer, all of them can be inhibited with an early calorie restriction; including lung cancer, since Stem-Cells (progenitor cells) survive; and maintain the main cancer progression program (43arburg43e mesenchymal transition EMT) (Meséquima-Epithelial Transition) with excessive signaling of the Insulin system and refined obesogenic "nutrition" [226-235]. The higher insulin-dependent growth factors in the fetus, the greater number of Stem Cells and the greater the risk of future cancer [233, 236]. Thus, all protective mechanisms against neoplastic transformation and tumor development, included in Apoptosis are eliminated by the survival hormone of genetically damaged cells: Insulin, even among brain tumor malignant cells [237, 238]. Metabolic Addiction of Cancerous Disease Cancer, a dynamic metabolic process with modifiable genetic bases (epi-genetics) will not reverse if we do not modify the inflammatory tissue environment and the oxidative microenvironment of the tumor cell with a substantial improvement of the Insulin hormonal system, of which it continues to confirm its regulatory function of cancer genes [239-243]. Thus, Insulin Resistance is a predictor of greater weight for cancer than the individual's fat itself [244].

It is up to us to avoid inactivity and excess macronutrients - particularly dairy hypernutrition - and thus eliminate the expression of our cancer genes, and especially the hormonal tumor microenvironment and inflammatory metabolic, which is essential and decisive for tumor progression [245-251] (Figure 11). If we are going to use the conventional chemotherapy and radiotherapy treatment, it is therapeutically mandatory to reduce the Insulin Axis. IGF-1 to minimize damage to normal cells and maximize total eradication of tumor cells [252]. Otherwise, the cancerous disease will aggravate (a severe increase in gliomas in children is the best example when the Insulin axis is reinstated) [253]. It is a proven molecular fact the metabolic dependence of cancer cells, and that the best treatment should be directly focused on eradicating their addiction to excess growth signals and environmental over-nutrition. (After acceptance of this review, an extensive prospective study in the USA - National Health and Nutrition Examination Survey 1999–2010 - shows that, even and especially in subjects with normal and non-obese plasma glucose, excess insulin greater than 10 uU / Ml was associated with a significant increase in the risk of dying from cancer) due to severe tumor aggressiveness and the signaling that preserves Telomerase, the enzyme that maintains the division of the cancer cell indefinitely [253-254]. And it is that cancer has in its maintenance and probably in its etiology, a primary alteration in cellular metabolism: it is the excess of stressful energy, which stimulates the transformation and cellular malignancy [255, 256]. Thus, the death of cancer cells will only occur in an abrupt decrease in hormonal growth factors, which maintain the metabolic alterations of the tumor microenvironment [257, 258].

Blocking cellular insulin resistance, even in the presence of current carcinogenic nutrition (excessive iron and Omega-6), has a clear protective action against mitochondrial dysfunction and cancer [259].

Thus, even if we "eradicate" the addiction of cancer to oncogenes, it will never cure if the intense metabolic dependence that promotes and sustains it is not eliminated: "its metabolic addiction" and the hyperactivity of Insulin, a strong promoter of Tumor Malignancy, particularly cerebral and pulmonary, especially in the presence of chronic infections, generating greater inflammation [260-264]. So, let's not forget the accumulated evidence: current cancer treatments DO NOT CURE CANCER, by further increasing the Insulin Resistance general and tissue. Hormones such as Insulin have a decisive influence on the regulation of human physiology [265-268]. The greater insulin a tumor surrounds, the greater its acidification (300) - The defense against cancer will depend, initially and finally, on its sensitivity and action. The complex and dynamic cancer system will not stop if we do not reverse its acidified and altered metabolic microenvironment [269]. Excess insulin emerges as an independent, causal factor in the onset of cancer, and the altered endocrine pancreas could be the starting point for its appearance [270, 271]. Only when "Stem Cells" stem cells are destroyed that a complete recovery of the disease is possible, and this is achieved with drugs and nutrients that eliminate the ability to renew these stem cells, the root in the emergency of cancer; but never with drugs with renal toxicity and that increase insulin: Any cancer therapy that raises insulin levels will potentially increase the aggressiveness of the neoplastic tumor, such as Prostate Cancer [272]. Attacking the altered metabolism in the cancer cell - by reducing glucose, and the hormonal axis of insulin, initiating factors, promoters and that sustain tumorigenesis, together with caloric restriction and excess of iron, the most complementary and effective therapy to prevent and fight Cancer [273-278].

The dramatic increase in the incidence and Resistance of Cancer, especially Gastric and Thyroid Cancer, is concerned about the hidden increases in insulin and glucose and in people with abdominal / visceral adiposity and weight Low or normal: Insulin is the hormone with greater oncogenic and direct promoter power (PI3K / Akt signaling) of all cancerous diseases with a worse prognosis [279-282]. And if there is also a hidden hyperglycemia, the cancer cell will have greater resistance and intolerance to therapy, due to its greater phenotype of malignancy [283]. Previously and at diagnosis, cancer is always a complex cellular metabolic disease, both systemic and intra-tumor, so we must change radically his "disintegrated" current therapeutic approach [284, 285]. This is reaffirmed in the resurgence of cancer in particular in the larger woman, since the incidence of all types of cancer increases with the greater height of women and men: The greater the number of cells (and cell divisions) promoted by the Insulin axis, greater the accumulation of oncogenic mutations and greater the risk of cancer [286-288]. "More cells more Cancer" - First quantitative statistical study that demonstrates that the risk of cancer will increase with tissue size (Multistage model of carcinogenesis) [289]. We will demonstrate that only by minimizing all the inflammatory and pro-mutagenic hormones to a minimum, both the generation / promotion of cancer and that of many degenerative and mitochondrial (regulating the cellular degradation patterns (lysosomal) that digest their damaged proteins or organelles: Autophagy) [290-296].

A controlled activation of autophagy - such as caloric restriction - stimulates tumor suppression and suppresses carcinogenesis, and by a mechanism dependent on the axis of insulin, which (by preventing autophagy), is involved molecularly in the initiation of cancer by inhibiting, in addition to the P53 protein, the main cancer suppressor gene [297-301]. The lower the intake of proteins (without malnutrition: 0.9 gr / kg) and sugars, lower insulin, higher baseline autophagy, and lower cancer risk [302-305]. Regardless of the greater adiposity and inflammation, endogenous insulin is a powerful promoter of neoplasia, accelerating cancer rapidly, especially in the face of hidden diabetes [306, 307]. In vitro and in vivo, the suppression of simple sugars, even in the face of "terminal" cancer, is proving to significantly improve the disease (malignant pediatric cancers, neuroblastomas and gliomas; advanced gastric cancer, colon cancer), especially when accompanied by a high intake of anti-inflammatory fats, such as Omega-3 [308-312]. If you are sedentary or have a history of cancer, even if you are not overweight, do not use Insulin chronically, nor the recent insulins on the market, due to their greater mitogenic capacity they have greater direct carcinogenic power e indirect, stimulating fat hormones that accelerate and aggravate the bleak prognosis of cancer [313-319]. The worldwide cancer epidemic is due to the untreated or undiagnosed hyperinsulinemia (Insulin Resistance) epidemic [316, 320]. And its direct promoter role, and in conjunction with iron, on cell instability and all stages in cancer development, is recently demonstrated (it alters the epithelial adhesive protein e-cadherin and transforms it from suppressor to cancer promoter) [321-323]. It is the signaling of Insulin PI3K the most compromised in the origin of human cancer; which, by protecting telomeres and determining genomic stability and DNA damage, which predisposes the path to good aging or cancer [324]. Reduce the spread of more aggressive cancer, permanently reducing Insulin Resistance promoted and aggravated, particularly by protein overnutrition: It is proved today that the increase in fasting insulin is a robust Causal factor in the etiology of Cancer [325-333].

Addendum

Cancers in Hormone Tissues: those with a higher rate of increase and lethality (breast, prostate, ovary, endometrium)

After the first pre-published version of this review, it is shown that the increase in Insulin signaling increases the activity of the Salt-Inducible-Kinase protein –which blocks the cellular mechanisms that limit the abnormal growth of the cell- (in 2013 , the researchers Hirabayashi and Cogan demonstrate in the fruit fly that the cancer genes and the sugar in excess awaken this cancer protein, increased the cellular receptors of Insulin: Without a doubt, a chronic excess of Glucose and Insulin rapidly promotes tumor growth by significantly increasing its vascularization and nutrition, in particular. Categorically, the evidence is overwhelming: The higher the chronic elevation of Glucose, the greater the caloric energy ingested, the greater the overall mortality and the greater the explosion and precocity in the onset of Cancer [334-340]. (See Figures 1, 3, 11, 23, especially), and in particular among the population with the greatest size due to the greater tissue action of the GH-IGF-1 Axis insulin dependent.

"It is urgent to understand the regulation that the metabolic patterns exert on the Genes - and vice versa - and that underlie the Metabolic Plasticity of Cancer, which will determine their aggressiveness or detention" [341]. Today we begin to demonstrate that an effective anti-inflammatory therapy (from caloric restriction to low doses of Aspirin) not only reduces the incidence of several cancers, but also can eliminate them at the root, by reducing the formation of Stem Cells post-stem cells. Chemotherapy (eliminating its resistance

and its current high toxic dosage) [342, 343]. Genomic instability that initiates cancer can be REVERTED TODAY, including in cancer survivors by reducing the Inflammatory Axis of Insulin through Aerobic Exercise; In addition, it has been demonstrated in cancer survivors, the substantial improvement of the disease with a diet very low in Carbohydrates Nakamura H et al. Knowledge Translation of Low Carbohydrate Diet Intervention in Cancer Survivorship: From Basic Science to Clinical Practice and Policy Making Research Center, BC Cancer - School of Population and Public Health, Faculty of Medicine, University of British Columbia, 317-2194 Health Sciences Mall, Vancouver , BC Canada V6T 1Z3 https://www.researchgate.net/publication/267406831_Knowledge_Translation_of_Low_Carbohydrate_Diet_Intervention_in_Cancer_Survivorship_From_Basic_Science_to_Clinical_Practice_and_Policy_Making

The reduction in the generation of excessive Insulin can be achieved even from the intrauterine environment, preventing fetal macrosomia, highly promoter of early neonatal malignancy, by directly and severely altering the Physiological Autophagy that eradicates root cells in time of Cancer –Stem Cells [344-348]. If we do not reduce the hyperactivity of the insulin-dependent hormonal axis, cancer, and less metastatic cancer will never recede [349]. "You don't grow very fast, but you risks of acquiring cancer will multiply exponentially, and the risk to make it more aggressive, too, especially if you ingest the fats promoted as "healthy" rapid promoters of invasion and metastasis, especially in the Central and South American population with greater visceral fat accumulation and with hepatic insulin resistance at birth (in particular gastric, breast and breast cancer) of lung, which rapidly metastasize due to the high visceral adiposity [350-367]. Insulin is the master hormone that establishes and regulates the epigenetics of cancer [368-370]. Every advanced cancerous tumor, even, is reduced if the action of your immune system is optimized, with the anti-inflammatory stimulation of Exercise aerobic, which can reduce excess insulin, estrogen s and Androgens, and the current maelstrom in the onset and aggressiveness of cancer and hidden diabetes. (To date, the only known anticancer hormone, Adiponectin can be stimulated with caloric restriction [371-379].

In vivo, intranasal Insulin promotes proliferation and lung cancer signaling, while acute hyperglycemia - in diabetic range - promotes early tumor extension (epithelial-mesenchymal transition), especially given the current western insufficiency of the Vitamin D, of potential anti-neoplastic activity but in the absence of carcinogenic signaling of excessive calcium), because of the current hypercaloric diet (or enzymatic inducing hyperproteic) strongly insulin-causing, and causing the extension of hormonal and non-hormonal cancer [380-385]. The intraoperative spread of cancer can be reduced with one treatment metabolic and previous anti-inflammatory, as recently shown with low-dose cardioprotective Aspirin: so, everything that improves insulin sensitivity - decreasing visceral adiposity - will reduce the progression of cancer and its resistance to the cytoxicity and inflammation of Chemotherapy and Radiotherapy [386-398] (Figures 3, 6, 15, 17, 18, 28, 30. 35, 2, 8, in particular). Metabolism directly and indirectly impacts gene expression in response to nutritional availability (modifying epigenetics) [399, 400].

Insulin is the Hormone master in the regulation of Immunity protective or permissive of Malignancy, particularly in our populations with exclusive abdominal obesity and fatty liver [401-404]. The longer the duration of hyperinsulinemia, the greater the risk of high malignancy and invasiveness of cancer, particularly in women [405-411]. Classical Oncologists should not turn their backs on Oncological Endocrinology [412]. The pivotal gene of cancer biology in its adaptation to inexorable promoter hypoxia of cancer is positively stimulated by the Insulin Axis and its hyperactive signaling: it is the inducible Hypoxia Factor (HIF- 1) [413-415]. "Without excess insulin, genetic mutations that lead to cancer are not possible" https://www.youtube.com/watch?v=S395qX6G6HM&t=14s

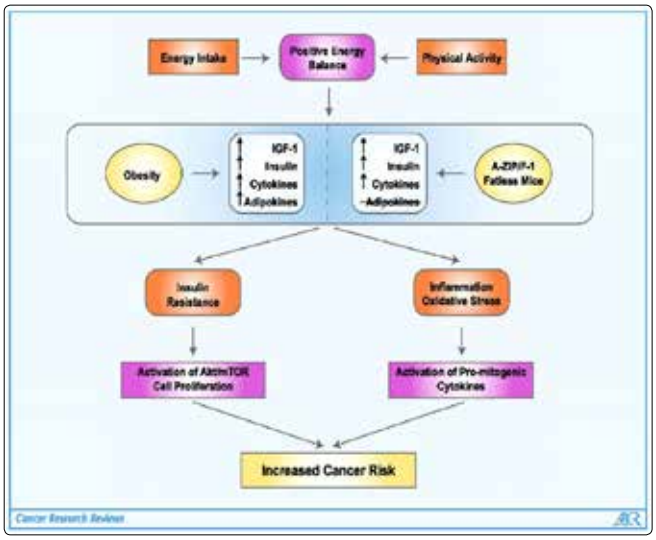


Figure 1: Scheme that shows how excessive energy intake (Energy Intake) generates Excess Insulin, Adiposity and Inflammation, even without obesity. The increase in insulin and resistance to its effects form a vicious circle perpetuated by the excess of inflammatory immune proteins, Citokinas, adipocitokinas - the latter coming from adipose tissue -, which, in the presence of Insulin Resistance (Insulin Resistance) Activate signals of cell growth, perpetuating inflammation (Oxidative Stress) and maintaining cancer (or increasing your risk). Taken and Modified from: Friedenreich [416].

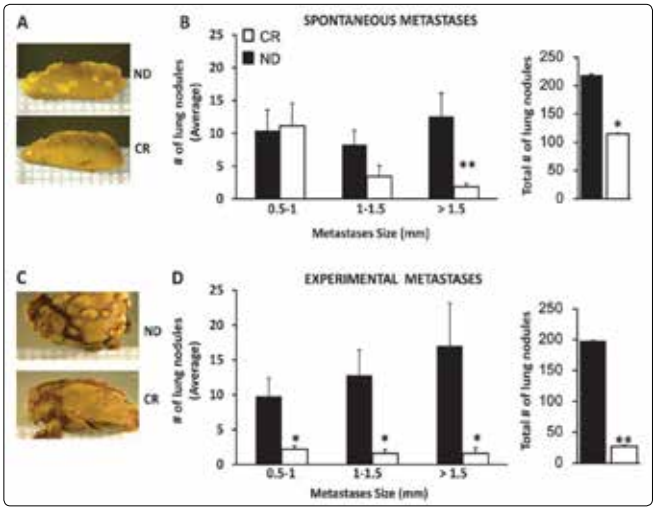


Figure 2: Caloric Restriction (CR) causes a decrease in the number of lung metastases (breast cancer), both spontaneous and induced; the regression of the metastases was greater in the lung tumors of greater size. With the CR, the reduction in the circulating and tissue levels of Insulin (and of the Insulin Axis - IGFs) is achieved.

Taken and modified from: De Lorenzo [159].

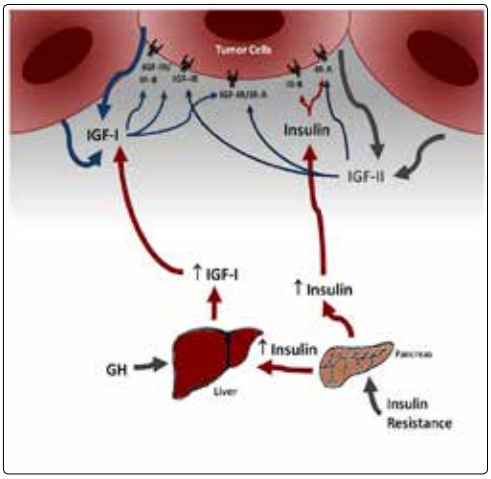


Figure 3: Stimulation on Insulin and Insulin Axis cancer cells - IGFs (endocrine, autocrine and paracrine signaling). Taken from. Gallagher [153].

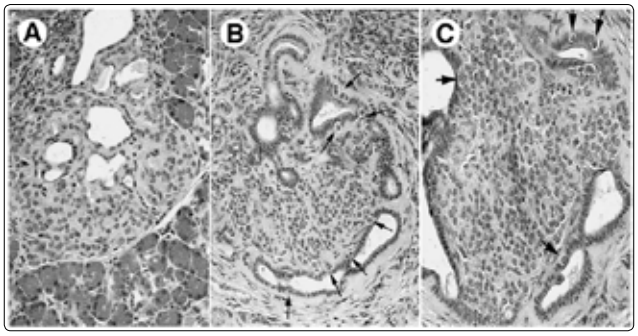


Figure 4: Excess Insulin (caloric excess) is permissive for pancreatic cancer development

Particularly because it greatly increases the inflammatory tumor microenvironment and the subsequent deregulation of cellular immunity, significantly facilitating the immune evasion of cancer cells and giving them greater invasiveness.

Final text taken from: Tumor microenvironment of pancreatic cancer: molecular and histopathological features dictate immune landscape

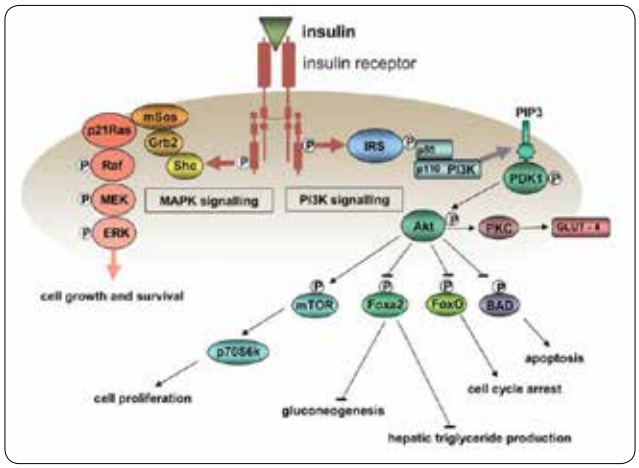


Figure 5: Schematic chart showing the main cancer signaling of excess insulin, over-activated by its receptor

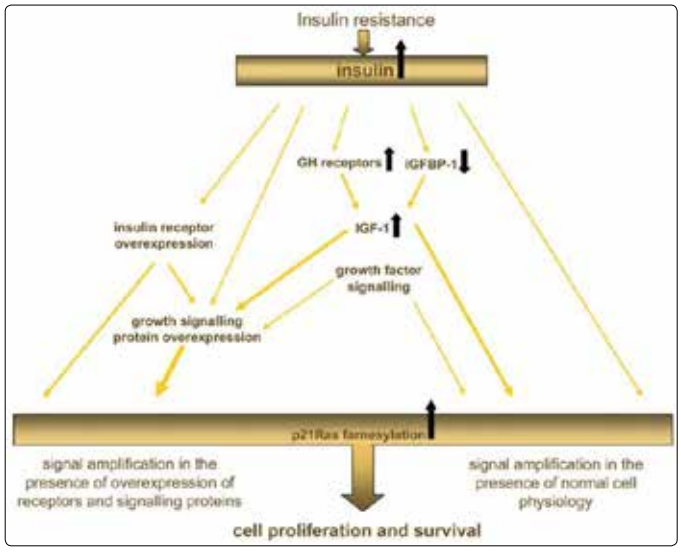


Figure 6: Interaction between insulin resistance (initial, genetic) (which leads to subsequent excess insulin) and excessive cell proliferation and "immortality"

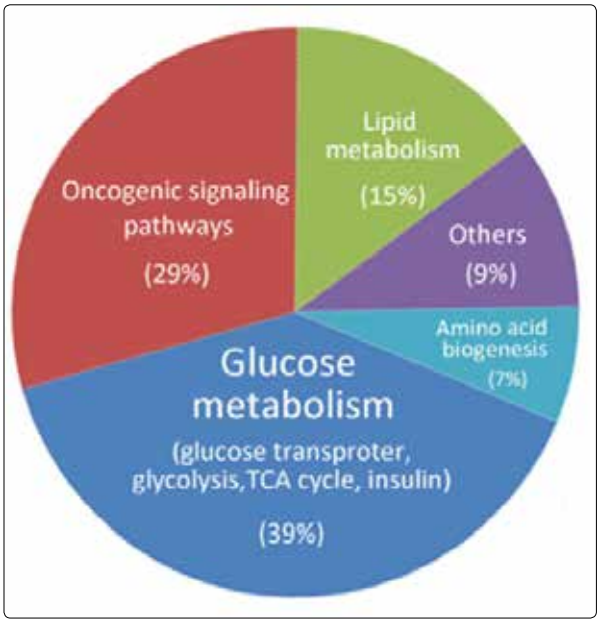


Figure 7: Approximate proportions of Nutrients that feed the growth of the neoplastic and cancerous cell, and together with the oncogenic hormonal signaling.

Taken and modified from: Chen B;

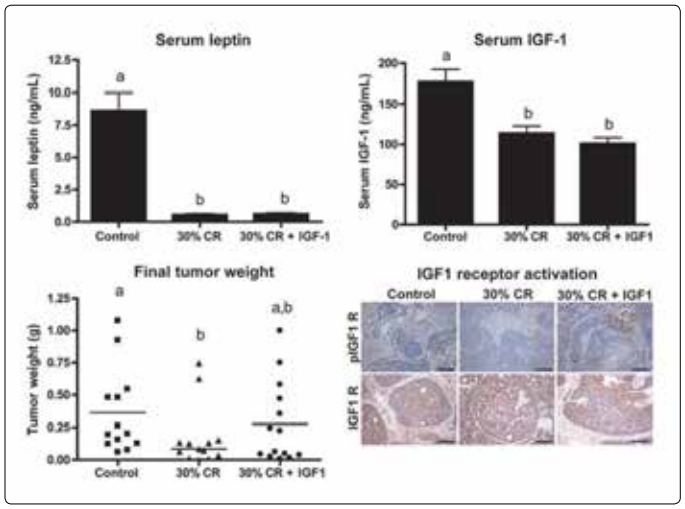


Figure 8: Effects of a 30% Caloric Restriction (CR) on breast cancer growth: its effects on the hormones Leptin and IGF-1 (above). Significant reduction of tumor weight with caloric restriction (30% CR); and breast tumor image showing reduction in the activation of the hormonal receptor for IGF-1 with CR, and its re-activation with the serum addition of the receptor for IGF-1 (below). Significance ($P < 0.05$).

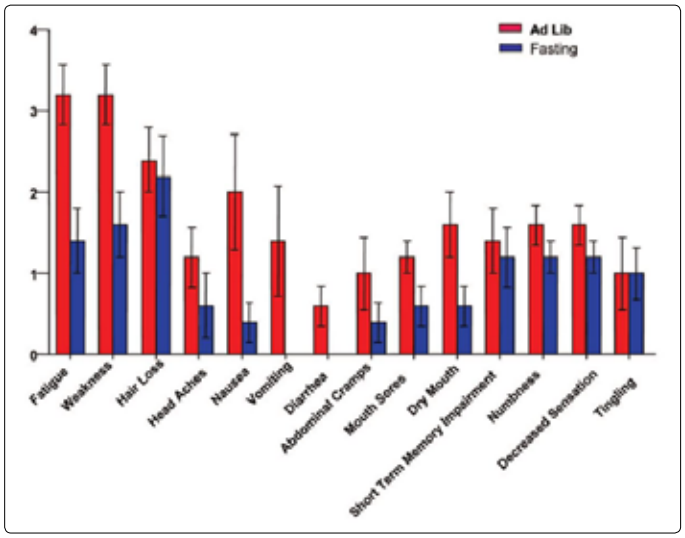


Figure 9: Average in severity of symptoms in patients with cancer chemotherapy with (blue) or without (red) fasting
Predominant symptoms of the cancer patient decrease in severity (with caloric restriction or intermittent fasting) due to a significant reduction in insulin levels, which in turn is due to a substantial decrease in the main human oncogene demonstrated: the recipient of IGF-1 [418]. (24 hours of fasting induce anti-inflammatory genes on neuroimmunoendocrine system- Lavin et al.

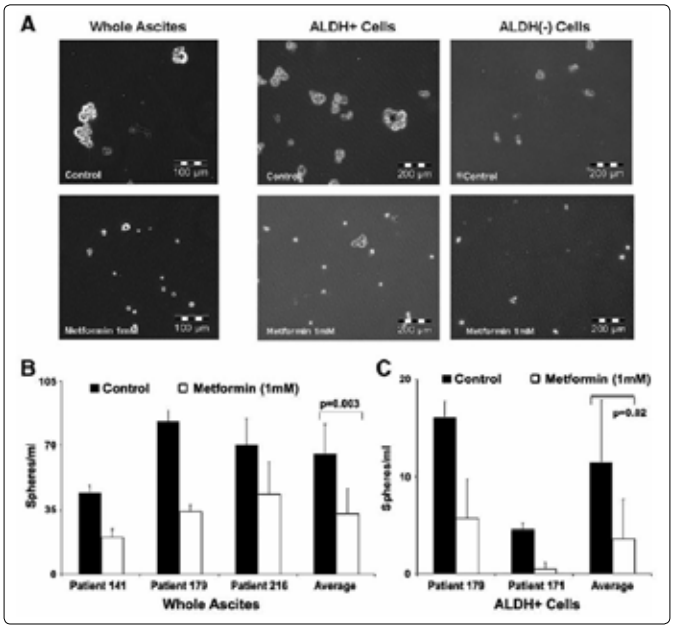


Figure 10: Marked Insulin Reduction Reduces Ovarian Cancer Cell Metabolism and Activity: Molecular Evidence
Inhibition of tumor spheres in patients with ovarian carcinoma (173) mainly due to significant reductions in Insulin
(explanation in the text)

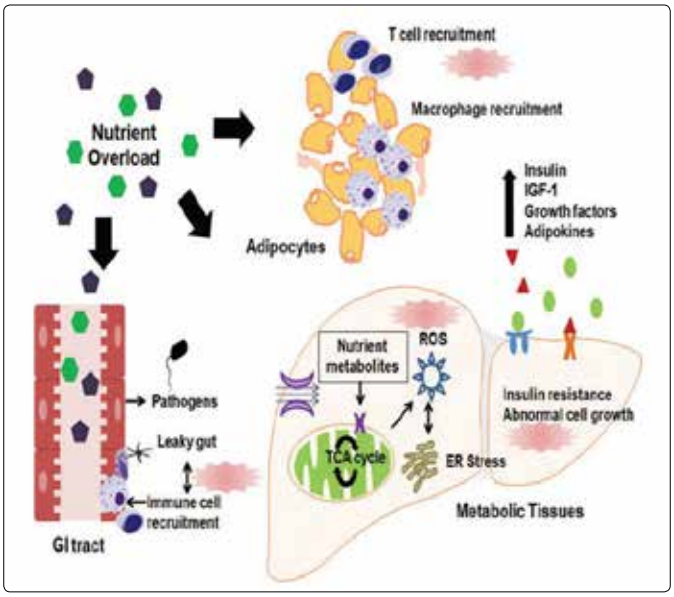


Figure 11: Scheme showing how Overnutrition (Excess Caloric Energy) promotes and perpetuates the vicious circle: Inflammation of Adipose Tissue - Insulin Resistance - Abnormal Cell Growth: directly (increasing intestinal endotoxins) and indirectly (causing greater secretion of growth factors, adipokines and immune cells, recruiting and altering them.

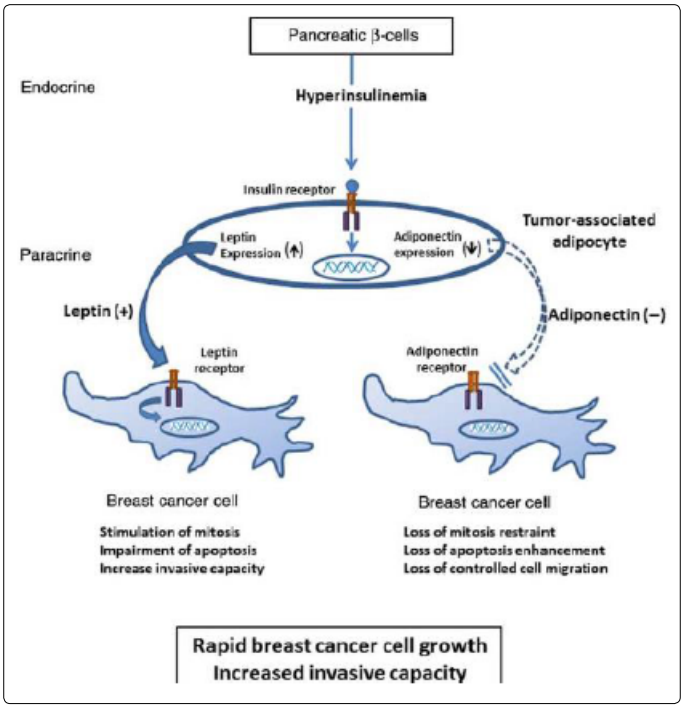


Figure 12: Paracrine stimulation in the growth and invasiveness of breast cancer by leptin, generated and perpetuated by excess insulin; It also shows the inhibition of cancer progression by Adiponectin, the only hormone that reduces insulin resistance.

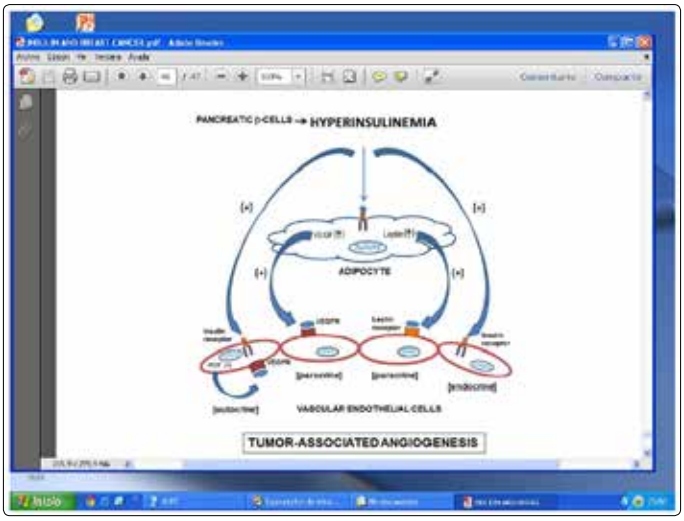


Figure 13: Scheme showing how Insulin directly stimulates cell proliferation of blood vessels that supply and nourish the tumor; and indirectly, through the hormone Leptin and vascular endothelial growth factor (VEGF) said angiogenesis; all this through endocrine (direct), and paracrine (indirect) routes through peritumoral fat (which secretes even more inflammatory and angiogenic leptin) [419]. Taken from David P. Rose and Linda Vona-Davis; August 2012. Personal Manuscript (prepublication): ERC-12-0203 (Personal Courtesy: U. Complutense de Madrid, September 2012)

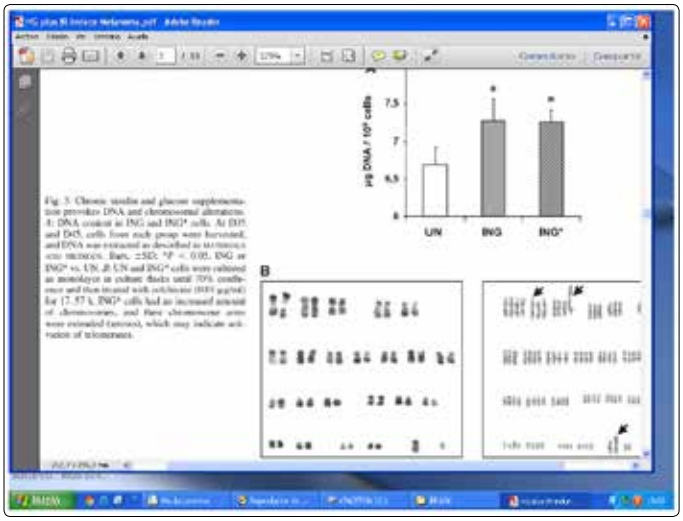


Figure 14: Chronic Insulin exposures plus glucose supplements cause chromosomal and DNA alterations in normal human cells (melanocytes). Detailed explanation in the Text.

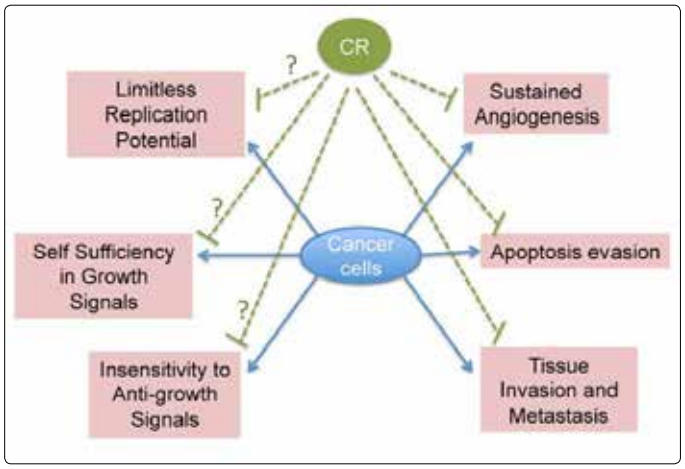


Figure 15: Scheme showing the main effects discovered by the caloric restriction on the development of the cancer cell:
1- Limitation of tumor replication
2- Limitation of angiogenesis
3- Control of Growth signals
4- Promotion of programmed cell death (Apoptosis)
5- Restoration of cancerous anti-growth signals
6- Control of local and distant tissue invasion (metastasis control)

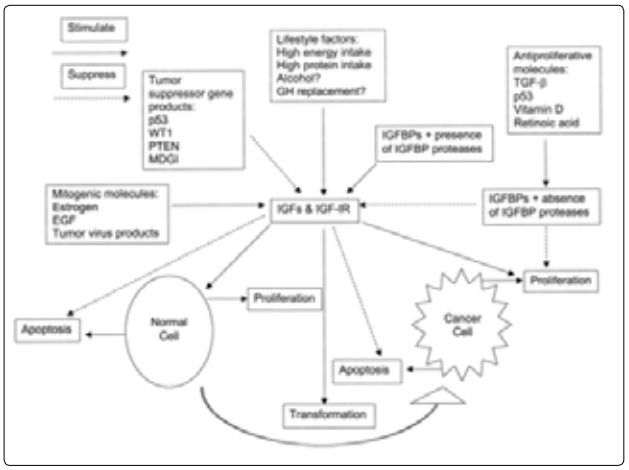


Figure 16: Effects of the Insulin-like growth factors and ILGF-1 receptor on normal and cancer cells; and as modified with mitogenic and antiproliferative molecules, life factors and p53 tumor suppressor genes (solid arrows indicate Stimulation; dotted arrows indicate suppression). EGF: epidermal growth factor; GH. Growth hormone, IGF: insulin-like growth factor; IGFBP: IGFs binding protein; TGF-b: Tumor growth factor b

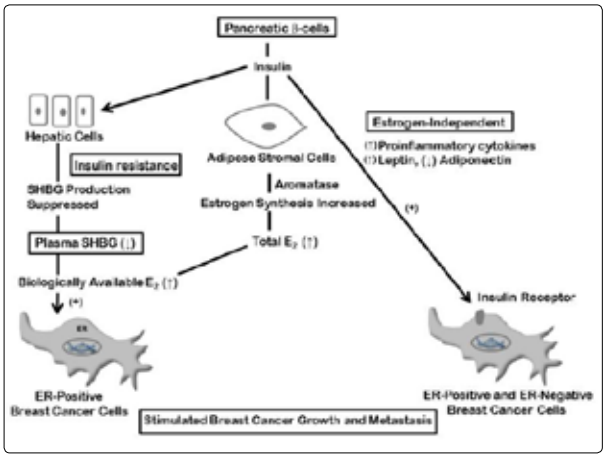


Figure 17: Stimulation of the proliferation of breast cancer cells, their growth, invasion and metastasis by Insulin.
The greater production and bioavailability of estrogens by adipose tissue is highlighted; Thus, it is the chronic excess of Insulin that de novo promotes breast cancer, including the most serious

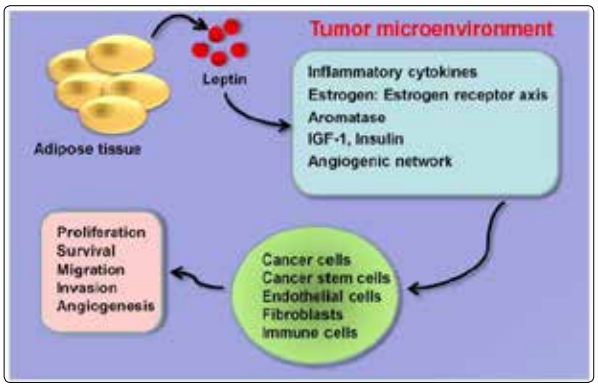


Figure 18: Concept map showing how the hormonal inflammatory Inflammatory Tumor Microenvironment is a determinant for the proliferation, survival, migration and metastasis of Cancerous Disease

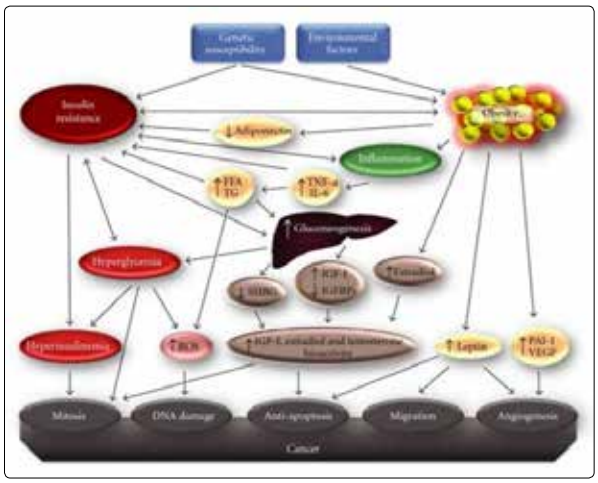


Figure 19: Multidimensional model in the development of cancer, emphasizing Hyperinsulinemia (insulin resistance) and Inflammation as the precursors and determinants of cancer disease.

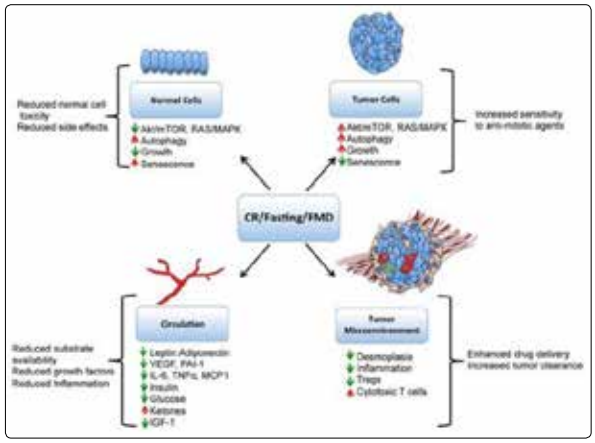


Figure 20: Mechanisms by which the Caloric Restriction, by minimizing the inflammatory microenvironment of the carcinogenic niche and the growth and antiapoptosis signals (reducing the axis of Insulin, mainly) profoundly reduces the side effects (cytotoxic) of current Chemotherapy and Radiotherapy (giving resistance to normal cells); and decreases the size and transformation of the tumor [420].

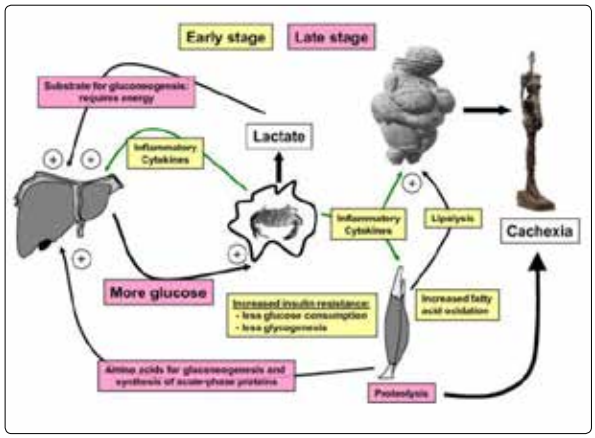


Figure 21: Development of the cachectic state in Cancer:
The severe increase in insulin resistance as the cancer disease progresses increases hepatic gluconeogenesis and tissue inflammatory

storm (proteolysis and lipolysis), all of which decreases and recedes with a profound restriction of carbohydrates or a ketogenic diet [421-424].

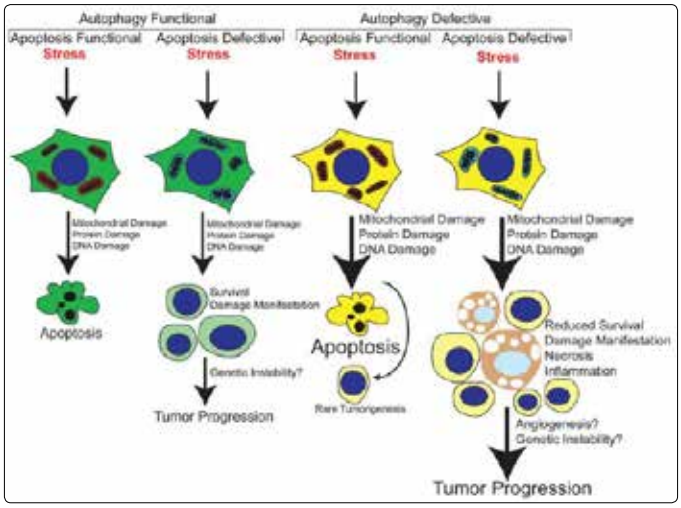


Figure 22: When all protective mechanisms (Autophagy) that guarantee optimal cellular function fail - continually renewing mitochondria and "old" or damaged proteins of their cytoplasm, and their Programmed Cell Death (Apoptosis) is also inhibited, it is inevitable the Progression of Cancer [425]. And this occurs first of all excess nutrients and carcinogenic hormones, such as Insulin Image taken (modified text) from: Jin, Autophagy.

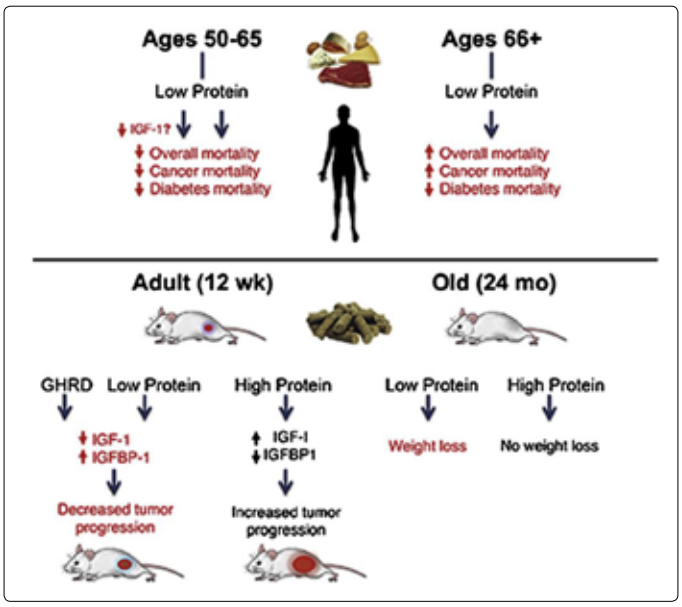


Figure 23: Experimental and clinical evidence is shown: Protein restriction (without malnutrition) reduces mortality from cancer and diabetes, particularly in young adult subjects, by reducing the action of the Insulin-IGF1 axis
–High levels of Insulin (IGF-1) increase direct relationship between mortality and animal protein intake-
Taken from: Levine

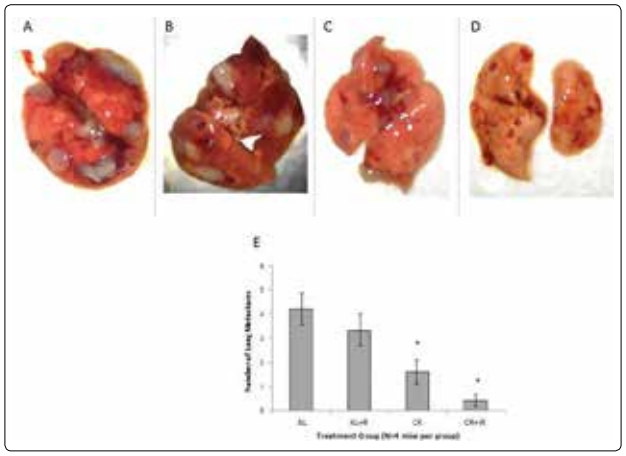


Figure 24: The external anatomical appearance of four lungs with metastatic lesions is shown:
A) Ad-libitum diet without two; B) Ad-libitum diet with radiotherapy; C) Caloric restriction, D) Caloric restriction plus Radiotherapy.
Note the progressive reduction of metastatic nodules, which is maximum in group D
In the IMAGE bar graph, the average of the visible number of metastases is observed, which progressively decreases, from the Ad-libitum cohort (first bar) to the group with caloric restriction and radiotherapy (last bar). Note that only the calorie restriction (CR) of the third bar reduces the size and number of metastases by more than 60% Figure taken from: Simone, Cell Cycle.

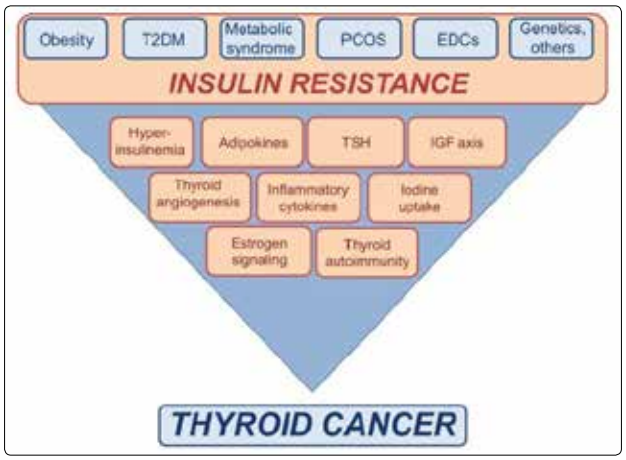


Figure 25: Scheme showing how the chronic Insulin Resistance epidemic (Hyperinsulinemia) is responsible for the current Cancer, and Thyroid epidemic in women, regardless of weight (eg Low in Severe Ovarian Polycystic, PCOS, or high in prediabetes, Metabolic Syndrome).
Taken from: Malaguarnera

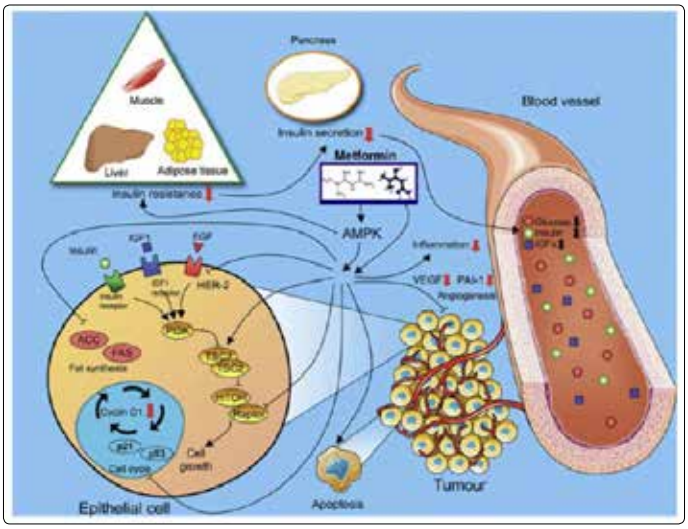


Figure 26: The molecular signals of Caloric Restriction or Metformin to reduce excessive secretion of Insulin by the pancreas are shown, Insulin resistance in liver, muscle and adipose tissue is decreased, which in turn decreases inflammation, prothrombosis and tumor angiogenesis. It stops the cycle and abnormal cell growth, restores physiological apoptosis and reduces the rate of cancer spread
(Caloric restriction or Metformin activates the global cellular energy sensor, AMPK adenosine monophosphate-activated protein kinase)
Taken from: Romero.

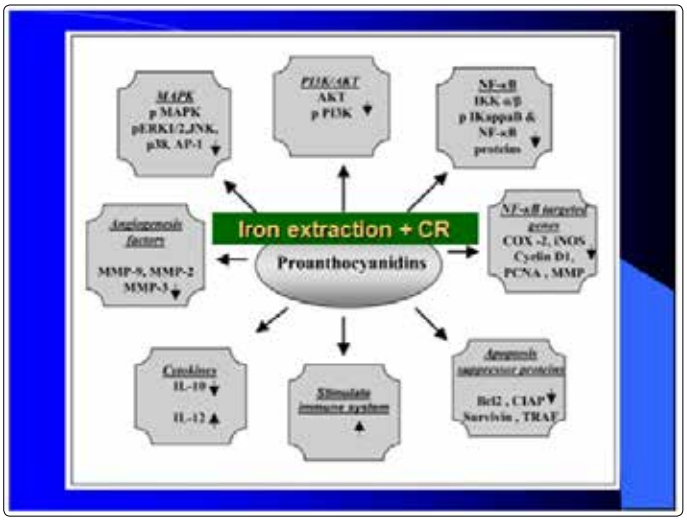


Figure 27: Potential Molecular Effects of Caloric Restriction and Iron Extraction in the preventive and curative treatment of Cancer
All of which reduces high chronic levels and corrects the signaling and cellular actions of Insulin
(Proven efficacy in a diet rich in Flavonoid Polyphenols (Cyanidines)
Graphic taken (modified text) from: Nandakumar

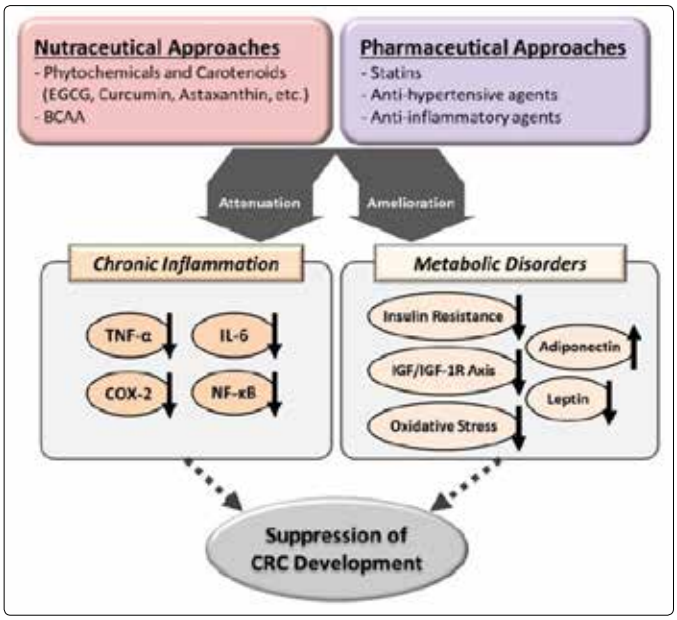


Figure 28: Scheme showing the suppression of Carcinogenesis (particularly Colo-rectal) by Nutritional and Pharmacological Medication, by reducing Chronic Inflammation and Insulin Resistance, which reduces the excessive activity of the Insulin-IGF Axis (Hyperinsulinemia), excess of Leptin (oncogenic) and increases the only anti-inflammatory and cancer suppressor hormone, Adiponectin
Taken from: Shirakami

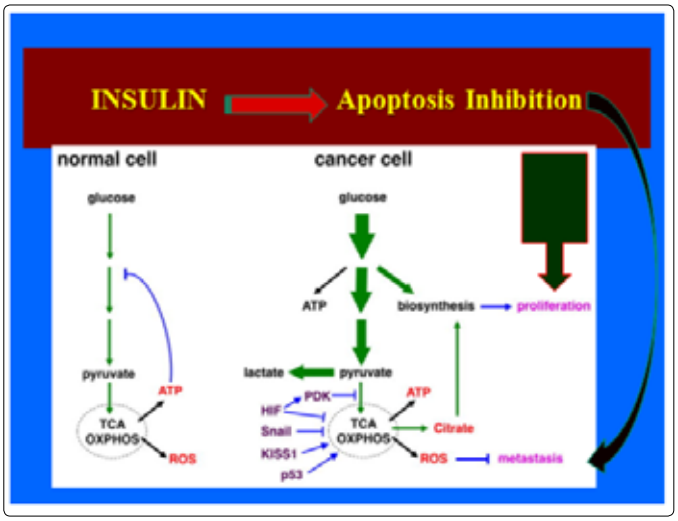


Figure 29: Summary scheme showing the molecular steps by which, the abundance of glucose and its greater uptake by the neoplastic cell increases tumor cell proliferation, which, in the presence of insulin, leads to a progression and metastasis by its powerful inhibitory action of the apoptosis programmed cell death. The increased glycolysis due to Insulin, and the reduced oxidative phosphorylation (OXPHOS) greatly facilitate metastasis. In the presence of excess insulin, iron and inflammation, the increased glucose uptake is used for cell proliferation, and not for efficient energy production, by generating excess lactate, generating greater cell acidification inhibition of cancer suppressor genes (dark purple). Image taken and modified
For further explanation, see the text: Lu [426].

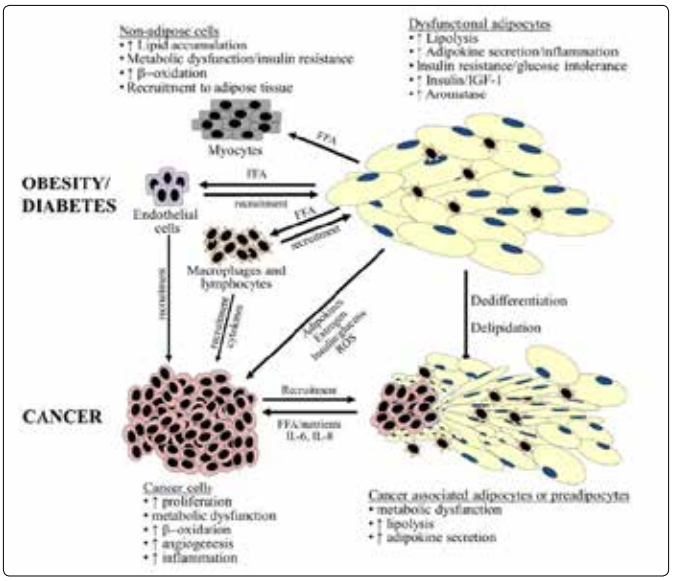


Figure 30: Diagram showing how the Accumulation of Adipose Tissue, through Muscular Resistance to Insulin (due to excess of caloric energy), overactive the Immuno-Inflammation, through the recruitment of macrophages, lymphocytes and proinflammatory cytokines, directly and through the Insulin, nourishing and altering the fibroblast-adipose peritumoral stroma; and especially cancer cells For further explanation, see the text: Nieman [427].

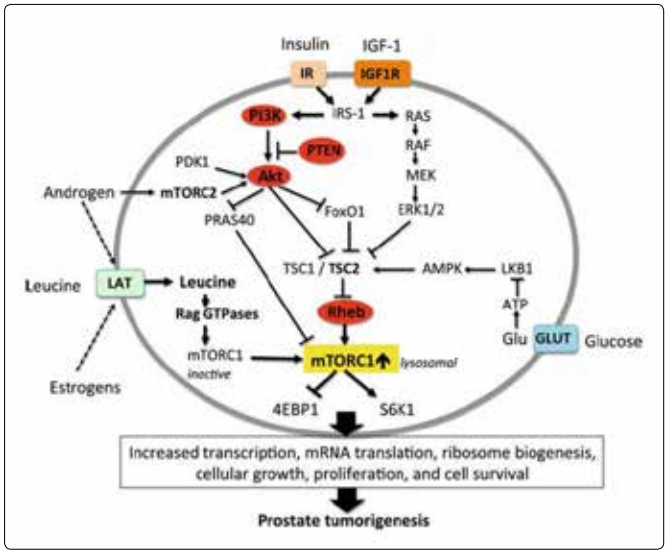
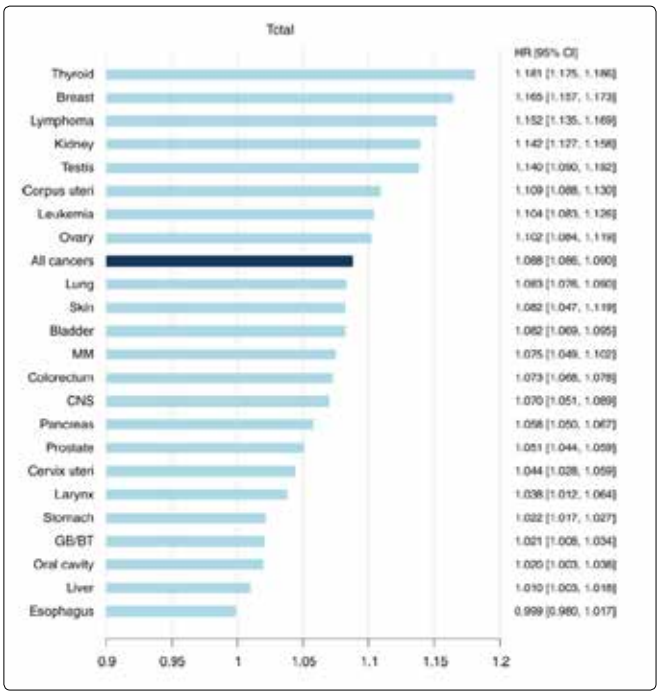


Figure 31: It shows how the Insulin System overactive mTORC cell survival signaling and its high oncogenic power:
Molecular evidence that Insulin hyperactivity not only promotes but Starts Cancer
Image and text taken from: Melnik [428].

Table



The correlation between size, all cancers and 23 specific types of cancer is statistically shown.
Hazard ratios and 95% confidence intervals per 5 cm increase in height for all cancers and 23 site-specific cancers.
For further explanation, see the text: Choi [429].

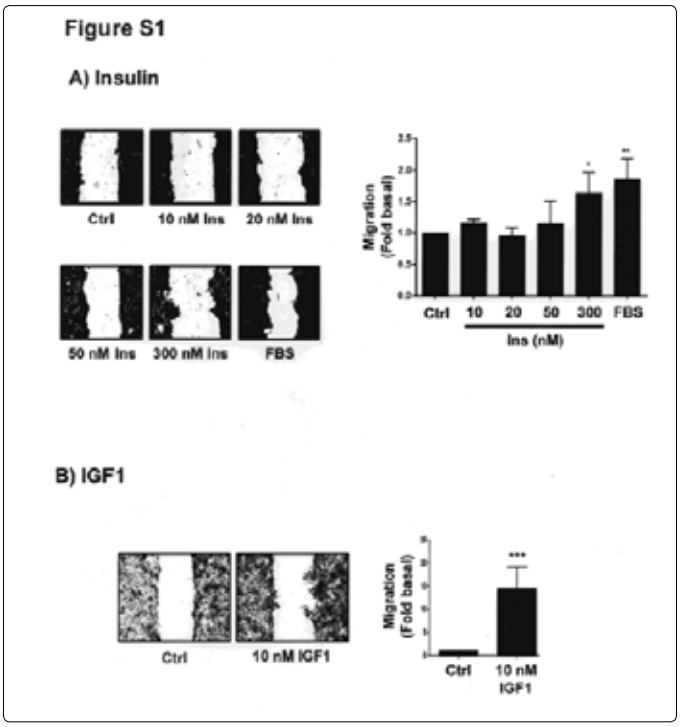


Figure 32: It is shown that Insulin (a) and IGF-1 (b) increases powerfully (considering the Axis in vivo Insulin-IGF-1) the Epithelial-Mesenchyme Transition (EMT) - initial process of carcinogenesis, where epithelial cells are transdifferentiate into mesenchymal cells - strongly stimulating the migration of cells and

the non-neoplastic stroma MCF10A (insulin reduces the expression of e-cadherin, which prevents the migratory process, and increases n-cadherin, Vimentin and tumor metalloproteases 2 and 9). This shows that, in vivo, non-cancerous cells can easily become cancerous due to the effect of excessive insulin [429, 430].

Image and text taken from: Rodriguez-Monterrosas

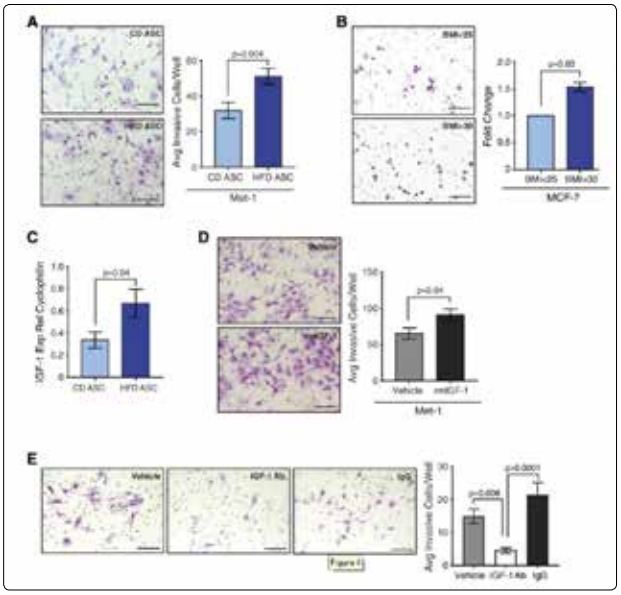


Figure 33: It shows how IGF-1 is secreted by adipose tissue stromal cells (ASC) in response to a hyper-fatty diet (HFD) induces mammary cancer cell invasion (local invasion). This stromal tissue, transplanted to totally normal thin mice, was inducer of tissue malignancy. (Detailed explanation for oncologists in the text) Here it is shown, how the intake of inflammatory fats promotes early breast cancer invasion, and in the absence of weight gain
Figure taken from: Hillers

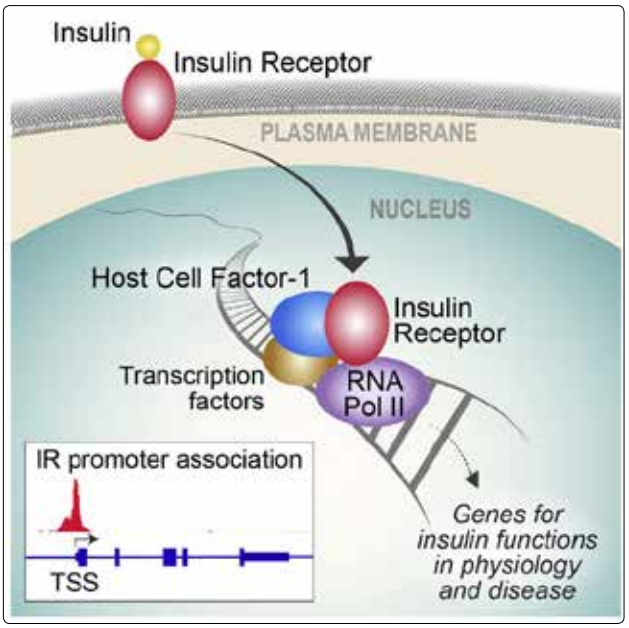


Figure 34: Insulin, through its Insulinoreceptor regulates in the nucleus of cells, the expression of insulin-dependent genes, in health and disease, physiological and pathophysiological especially those of lipid metabolism and protein synthesis; and from prediabetes, neurodegeneration, to cancer Figure taken, with modified text, from: Hancock

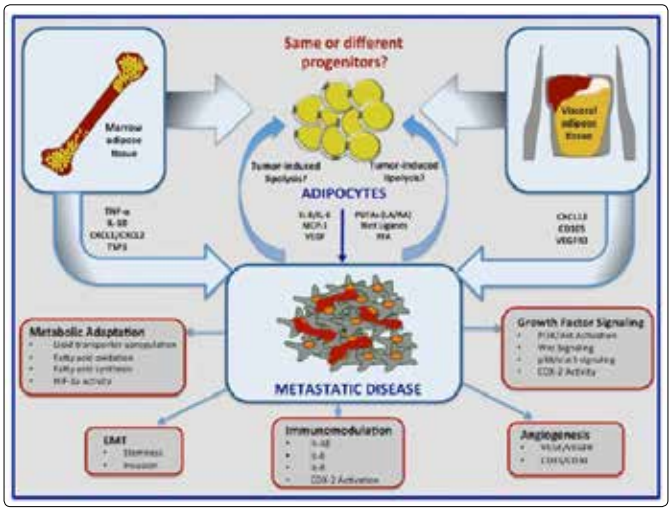


Figure 35: The complex metastatic power of Visceral Adiposity (and bone brown adipose tissue) is shown:
adipocytes promote a great proliferation of cancer cells, making them invasive, through a torment of growth factors, of immunoinflammatory cytokines and chemokines, all of which viciously alter the immunological modulation, causing the onset of the metastatic cascade (epithelial-mesenchymal transition) EMT); being the anabolic hormonal pivot (chaired by the Insulin-GH-IGFs axis) permissive and promoter. Figure extracted and modified text from: Chkourko Gusky [431]. If we do not fight the inflammatory tissue and vascular microenvironment, antitumor immunity will not be improved and cancer will not be eradicated.

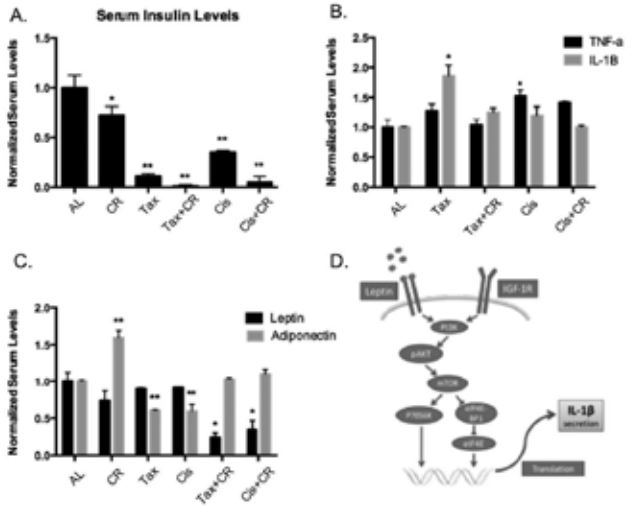


Figure 36: Chemotherapy-induced inflammation is neutralized by the added Heat Restriction (CR)
A) Serum Insulin levels are reduced by 25% by CR alone compared to control group (AL); Chemotherapy combined with CR significantly reduces insulin, compared to its isolated therapy (Tax and Cis bars)
B) The inflammatory cytokines IL-1B and TNFx that are significantly increased with the use of chemotherapy alone (compared to the

control group AL) are reduced with the addition of CR
C) While the anti-inflammatory hormone and anti-cancer potential Adiponectin reaches its maximum increase with isolated CR (and decreases to the maximum with Chemotherapy alone), the combination of both raises its levels; on the contrary, Leptin - inflammatory and oncogenic - decreases more with CR compared to QT alone, reaching its maximum reduction with too. Combined
D) It is plotted how the receptor for IGF-1 (IGF-1R) (in addition to Insulin) together with Leptin increases to tumor size
Complete figure with modified text, in: Simone [432].

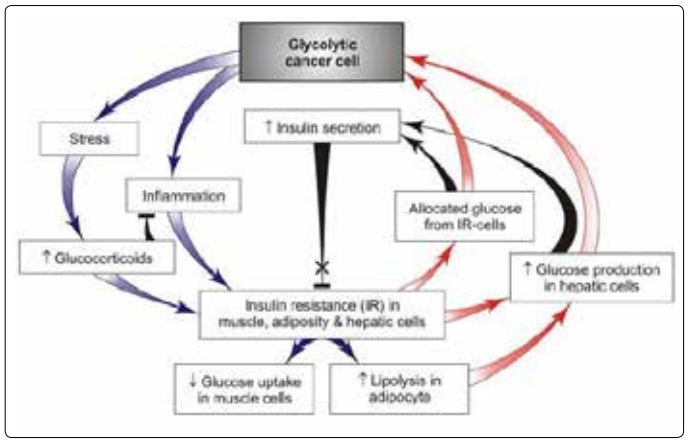


Figure 37: Simple Feedback Model showing the Metabolic Hormone Interaction of the Patient with the Tumor - Vicious Circle - where the increase in insulin secretion is the central pivot for cancer growth [433]. Further explanation in the text, taken from: Schwartsburd, Front Oncol [434].

After acceptance of the first edition of this research, at the Medical College of Peru, a revealing discovery comes to my hands: 4 hours of insulin (infused at physiological levels) increase in vivo the expression of oncogenic genes in the muscular system of the man, which irrefutably proves the oncogenic action of insulin: and that, molecularly is strongly supported by the recent confirmation that the increase in glycolysis perpetuates the proliferation and survival of cells cancerous, by increasing its inflammatory response: then, the avidity of the malignant cell by glucose (Warburg effect) is pathophysiologic ally increased by insulin, even in the presence of a conserved sensitivity [434-447]. The more glucose metabolism increases, the greater the invasive capacity of cancer, its aggressiveness, and its resistance to the best treatment [448-459]. The higher the oncogenic (mTOR 1) or proliferative (Akt) signaling of Insulin, the greater the risk of cancer onset, progression and aggressiveness. Macrophage cells that defend us from the onset of cancer can spread and aggravate it, according to our nutritional excess. The regulation of gene expression is the major component of the action of Insulin. In addition to the molecularly known, its receptor directly regulates gene expression - by translocating to the nucleus - Thus, Insulin regulates the Physiology in Health and Disease [440]. "Insulin regulate gene expression in a tissue- and cell-specific manner" The regulation in Gene Expression as an effect of Insulin, is in a specific Tissue and Cellular way [460-463]. Insulin reduction by ketogenic diet potentially reverses in vivo preneoplastic tumor formations [464-470].

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