Review Article

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Iron in the Promotion and Initiation of Cancer How Free Iron Accelerates Predisposing Insulin Resistance

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Abstract

Iron is physiologically essential to life, but biochemically it is harmful because of its evident -but unappreciated- oxidative and inflammatory tissue power when it accumulates, is dosed in excess, or is free; and that because, after entering the body, unlike any other metal, its elimination is almost non-existent in man; thus, metal is a powerful promoter of chronic degenerative diseases, from diabetes, neurodegeneration to cancer, through extensive coronary and cardio-cerebrovascular disease; modifying its clinical expressivity and accelerating its severity.

Iron is a powerful oxidizing and inflammatory agent, and its accumulation causes and promotes the proliferation of cancer cells in particular, both in animals and in humans. Free and accumulated iron triggers a powerful uncontrolled Cell Proliferation, permanently feeding the survival of the neoplastic cell.

After more than 50 years of experimental and preclinical studies, it is clearly demonstrating the carcinogenicity of iron; and this is also proven in humans, from breast cancer and endometrium, in women, to cancer of the colon-rectum, prostate, and pancreas in men.

In Western men and women, the reductions in iron deposits have an important anti-tumor and preventive effect for the development of cancer or diabetes, two entities biologically interrelated by the states of Resistance to Insulin, an inflammatory state that favors the development of malignant neoplasms, and can accelerate its aggressiveness.

It is the chronic excess of insulin or its Tissue Resistance, the biological event and the clinical syndrome that increases the cancerous power of excess iron, both silent epidemics in modern man. Moderate increases in body iron levels increase the risk of acquiring cancer, and raise the level of their mortality. And its deficiency or chelation in vivo decreases the Tumor growth (Wang F, Elliott RL, Head JF: Inhibitory effect of deferoxamine mesylate and low iron diet on the 13762NF rat mammary adenocarcinoma Anticancer Res. 1999 Jan-Feb; 19 (1A): 445-50). If excess iron mediates and increases the risk of cancer associated with Insulin resistance, any subject with this syndrome can minimize any associated health risks (and their increased risk of cancer), avoiding iron-rich diets and donating blood with regularity; Iron is the metal that causes "exponential" and punctual mutations and fusion of genes through chromosomal translocations, constituting the greatest risk factor for human carcinogenesis.

Iron is physiologically essential for life but biochemically dangerous. Chronic accumulation of iron causes pantropic organ damage and excess body iron play an important role in carcinogenesis, coronary artery disease, neurodegenerative disease, stroke and inflammatory disorders. Iron is very slowly excreted from humans once it is absorbed into the body.

The significance of iron excess has been markedly underestimated, despite the fact that iron overloading disorders are as common place in the US white population.

Iron-overload and catalytic iron promotes activation of oxidative responsive transcription factors and pro-inflammatory cytokines that increase cancer extension and aggravate them. There is accumulative evidence for iron as a carcinogenic metal in epidemiological, clinical, animal, and cell culture studies. The role of iron in various cancers, such as colorectal and liver cancer was demonstrated. Recent advancements on the molecular mechanisms of iron carcinogenesis evolved the Insulin-resistance generation and promotion, fisiopatologic condition that is not only permissive, but may be generated cancer and promoting it. Unlike other nutritional metals, iron is highly conserved: toxicity due to excess iron can occur either acutely after a single dose or chronically due to excessive accumulation in the body from diet. In vivo studies have demonstrated that an iron deficiency induced by either feeding a low iron diet injecting the iron chelator deferoxamine mesylate decreases tumor growth (Wang F, Elliott RL, Head JF: Inhibitory effect of deferoxamine mesylate and low iron diet on the 13762NF rat mammary adenocarcinoma Anticancer Res. 1999 Jan-Feb;19(1A):445-50). Iron supplementation has at times proven ineffective and even detrimental to health.

Thus, iron excess may mediate the increased cancer risk associated with insulin resistance and heme-rich diets, and subjects who are insulin resistant can minimize any health risk associated with iron overload by avoiding heme-rich flesh foods and donating blood regularly. The energy that sustains cancer cells derived preferentially from glycolysis depends on the gene p53 deficiency-iron induced. This nutrient is postulated to contribute to the initiation of cancer in vivo, but iron overload initiates and sustain cancer development if chronic infection or insulin resistance conditions are present. Cancer cells require considerably more iron than normal cells. Since iron catalytic can induce driver point mutation and create fusion genes through chromosomal translocations, iron overload is one of the most important risk factors in human carcinogenesis. Because free iron may play a catalytic role in "spontaneous" mutagenesis, moderately elevated iron stores increased overall risk for cáncer.

Introduction

Iron is a carcinogen and cocarcinogen, and it increases the risk of cancer in animals; and its cancer-inducing power in animals and humans is rapidly cumulative; reversing the neoplastic histological changes in the presence of low physiological diets in iron: it is shown in animals that diets low in iron can slow the progression of cancer [1-7].

It is fully proven that exogenous iron plays a transcendental role in cell proliferation and tumorigenesis, and this is explained by the "inflammatory and mutagenic accumulation" that occurs and it is enormously potentiated through time - iron is the only metal that is practically not eliminated; except in menstruation -: only a low dose of oral iron increases the generation of free radicals and systemic inflammation in the faces of healthy subjects [1,8-16].

Free iron, which increases markedly in the presence of the superoxide radical, is "persé" cytotoxic, mutagenic and carcinogenic; being able to provoke an acceleration of the arterial thrombosis by directly altering the coagulation systems and the vascular reactivity, and platelet [1,17-19]. Iron directly activates the nuclear transcription factor NFkB, which initiates a cascade of inflammatory activation; and also stimulates the secretion of interleukin IL-1 in macrophages (stimulated by LPS); and its overload, on the contrary, inhibits the expression of inflammatory cytokines necessary for tumor suppression [20]. In fact, damage to the cellular DNA that occurs under pro-oxidant conditions is mediated by iron, which can initiate or increase pre-mutagenic and pre-malignant damage, and become powerfully carcinogenic to its tissue and dietary overload [1,5,8-10,21].

Why is Iron, today, Carcinogenic? The Forgotten Evidence

Iron is a vital metal for life, but it is potentially harmful, as it is a promoter of the hydroxyl radical, the most reactive of free radicals, which generates considerable oxidative stress and tissue inflammation; and not to be eliminated, except in the physiological menstruation, it accumulates slowly and progressively in the organism, provoking a vicious circle of inflammation and degeneration, before the current nutritional inflammatory aggression [1].

Specifically, accumulated body iron is directly and powerfully related to the original appearance or promotion of neoplasms, cancer, and the highest risk of mortality [1-10].

Physiologically, the adequate use of iron and defense for its accumulation is found in the transferrin protein, proven anti-inflammatory; and in cellular Ferritin, which initially constitutes a defense against latent iron damage [1,10].

The superoxide radical, which is physiologically increased in the current systemic (nutritional) inflammation situation, is a powerful factor that increases the release of iron from its binding molecules: lactoferrin, transferrin, ferritin or hemosiderin [1].

For more than 25 years, it has been completely proven that iron feeds the survival and growth of the cancer cell above that normal; by promoting the accelerated generation of reactive oxygen species, which play a crucial role in chronic pathology, from atherosclerosis to neurodegenerative diseases [1,3,7-10,22]. Therefore, pathological situations of abnormal iron accumulation, such as hemochromatosis, are accompanied by a high frequency of neoplasms [1].

In the first National Health and Nutrition Examination Survey (begun in 1971 and followed up between 1981 and 1984) it was found in more than 14 thousand patients that the iron body status (measured as transferrin saturation, its plasma transport protein) increased the cancer risk in males; and then, after extending its follow-up until 1988, it was evident that in both sexes (3,287 men and 5,269 women), the highest risk of cancer -and death- occurred with only moderate iron levels [22,23]. And this is because, a very thin surplus of unused iron is enough to be used more efficiently by neoplastic cells (or pathogenic microorganisms) [1,3].

Currently, iron by itself can initiate or be a decisive cofactor for the development of disease [24,25]. For example, even in the presence of normal iron stores, a simple exogenous intake of iron increases the risk of infection, and this, specifically, by increasing the Insulin Resistance, -the hormonal event predictor of Chronic Disease [24,26]. And because it is a powerful activator of the NFkB factor, whose signaling is increasingly recognized as decisive in the promotion of tumorigenesis: NFkB is a powerful factor that confers resistance for the programmed death of the tumor cell; that is, it is a potent Anti-apoptotic, conferring survival to the neoplastic cell and promoting its metastatic power [27]. If leukemic cells proliferate easily in an iron-rich environment, the neoplastic common epithelial cell that feeds almost exclusively on cellular iron [3-5,7,8,10,22,24,25,27,28].

Iron Reserves, Start, Progression and Mortality from Cancer: The Hidden Evidence

As we have pointed out before the physiological, experimental and epidemiological evidence,
fast-growing neoplastic cells are necessarily fed iron; the greater your tissue availability, the greater your growth (without differentiation); On the contrary, iron deprivation produces a pronounced effect on neoplastic cell proliferation [7].

However, it has been known for more than 50 years - Richmond, 1959- that exogenous iron loads produce rapidly, and de novo, sarcomas in vivo; After almost 20 years, in which there was an inexplicable silence on the matter, today it is convincingly demonstrated in vivo, that a "normal" diet of iron promotes breast cancer in humans

[1,29]. And this happens, since approx. Five and a half years, where in this part of the world (and Latin America) all that they offer us for a "better health" has absorbable iron supplements, promoting, unscrupulously, in conjunction with food (deeply inflammatory and carcinogenic oxidative stress promoter), which, "normally", the human being, today, damages its cellular nuclear DNA and is exposed to rapid cancer-promoting mutagenesis [1,8,10,20,21,24].

A single example, in the most aggressive cancer: in 113 children with acute myeloblastic leukemia, those who had higher reserves of iron-measures, such as Saturation of Transferrin, or serum Ferritin- had a profoundly lower Survival (in follow-up of 2 years) , with higher organomegaly index ($p < 0.001$) [28].

This explains, for a long time, why the index, for example, of breast cancer has increased dramatically in the Asian continent; but especially among Chinese immigrants in the USA, where the environmental aggressors promoting neoplasia have changed drastically: again, iron reserves increase the risk of preneoplastic transformation of the healthy mammary epithelium (fibrocystic changes); and the dietary intake of iron, but it alone, increase the risk of progression of these fibrocystic lesions to cancer [29].

This is corroborated in another cohort study among more than 9,000 women with benign fibrocystic disease of the breast, in which a moderate elevation of breast tissue iron predicted an increase in cancer [30].

Then, it is found in humans that elevated body iron deposits increase the risk of cancer and mortality; In addition, and this is a very important epidemiological determinant, iron deposits such as serum ferritin confer an increased risk in general morbidity and mortality; but with special relevance in cardiovascular pathology, by slowly but profoundly damaging the quality of one of the most pleomorphic and protective hormones of our organism: insulin: it is its deficient tissue action -Insulin Resistance- Hormonal event predictor of Chronic Diseases, from cardiovascular pathology to cancer [22-25,31-34].

Cancer Nutrition: When the iron becomes our Assassin

The postprandial increase in glucose is a crucial and causal determinant for the development of cardiovascular disease (35), since it is an expression of an Insulin-Resistance Hidden (34) that promotes disease (33) (even in non-diabetics) [33-35].

And all this metabolic alteration is due to the excess of oxidizing iron, one of the most powerful generators of free radicals in vivo, activator of the most powerful inflammatory factor NFkB and, therefore, inducer of an insulin-resistance in liver, adipose and vascular tissue [20,31,36,37].

It is demonstrated that the reduction of iron reserves by blood donation, even in healthy subjects - with normal levels of ferritin - prevents the onset of Diabetes Mellitus type 2 (DM 2); and ostensibly improves vascular function, improving hemodynamic parameters by reducing oxidative stress and systemic inflammation; decreasing cardiovascular and metabolic risk [31,32].

Humans with GE reflux and high iron intakes can develop adenocarcinoma of the esophagus by increasing chronic inflammation (and the production of reactive nitrogen species) by the esophageal epithelium, which reinforces the concept by which persistent oxidative damage causes, and it explains the biological changes that occurred in the cancer cell: "persistent oxidative stress and chronic inflammation as a cancer generator" [38,39]. It has long been shown that a local overload of iron is directly responsible for the promotion of carcinogenesis; and systemically, rapidly and cumulatively, exogenous iron is a powerful initiator of liver damage; being able to play a determining role for the generation of chronic fibrosis or acute liver toxicity [2-8,10,38,40].

Iron Extraction is Protective of Tissue Damage and Cancer

When Iron Retention Facilitates Tumor Development

Iron must be used, not retained and not accumulated in excess: iron retention prepares and facilitates tumor proliferation, both inside and outside the cell; and it is supported by the biological fact that in all dysplastic or dysplastic tissue there are greater transferrin receptors as a defense mechanism against the perennial aggression of the deposited and free surrounding iron [39-41].

There is cumulative evidence that the reduction of systemic iron by phlebotomy or by donation substantially reduces visceral malignancies and mortality in patients with peripheral arterial disease or hypertension (insulin resistance) [42,43].

A diet deficient in iron is effective in effectively reducing acute liver damage and chronic liver fibrosis in animal models and clinically, this has been demonstrated in humans with hepatitis C (see later) [40].

Again, the growth and nutrition of cancer cells is strongly promoted by the exogenous administration of iron; and is retarded by his dietary deprivation; specifically by activating iron directly the signaling of NFkB factor in macrophages, especially when it is intracellular; and it is the factor NFkB that controls and finally determines the genes of proliferation, angiogenesis and metastasis, as it constitutes a powerful anti-apoptotic factor, as does Insulin [20,24,25,33,41,44]. In addition, this transcription factor is the molecular key that links inflammation with carcinogenesis [41].

And if we remember now that it is insulin the anabolic hormone whose signaling disinhibits and activates this carcinogenic factor kappa-B; the oncogene circle is permanently activated.

Regarding the carcinogenicity of iron reserves, and like the insurmountable advantages of phlebotomy or blood donation, agents that capture iron, ferrous chelators have become (for more than a decade) an effective method in the reduction of cancer, and especially with advantage over other treatments with serious side effects, since the development of lipophilic chelators that capture intracellular iron can kill the cancer cell selectively, without damaging normal tissue [45-47].

Iron and Oxidative Stress as Initiators and Promoters of Cancer

It is established biologically, experimentally and epidemiologically that the overload of iron contributes decisively in the generation of cancer in humans, particularly, of the colon-rectum [24,25]. Intracellular iron promotes genomic instability, rearrangement at the chromosomal level and double mutation of both proto-oncogenes and tumor suppressor genes [41]. Moreover, at achievable physiological minimum concentrations (200-500micromoles), iron increases genetic damage 2 and 3 times over the control [48,49].

This is long patent in normal humans, where only 19 mg. of iron sulfate cause damage to the colon mucosa due to iron-dependent increase in the synthesis of ROS, potentially inflammatory and oncogenic free radicals; even worse, if ferrous sulfate is administered together with vitamin C, at doses as low as 14 mg / day, oxidative damage increases in leukocytes of healthy subjects [16,50]. This indicates that the mutagenic damage exerted with DNA oxidation occurs with the simple exogenous addition of absorbed and non-absorbed iron.

To greater cellular and tissue availability of iron, would there be a greater cellular proliferation? The answer is undoubtedly yes. The over-expression / induction of transferrin receptors with cell proliferation "uncontrolled" is clearly established, both leukemic and esophageal cells [38,51].

If, as shown in vivo, high body iron stores reduce the survival of the infant patient with acute leukemia, probably by increasing the speed and extent of the disease, its neutralization by chelation, cause the death of the cells neoplastic [28,52].

The first iron chelating agent (developed more than 3 decades ago), Deferoxamine has recently shown that, in a promising dose-response efficacy, it induces the programmed death -poptosis- of the leukemic cells, by reducing the intracellular pool of labile iron. , which exercised an anti-apoptotic survival power; and intracellular iron deprivation activates caspase-dependent apoptotic cascades) [52,53].

The deprivation of free cytosolic iron inhibits tumor growth by the mitochondrial expression of ferritin, as just demonstrated, reliably in vivo [54].

Biologically, only the cellular deprivation of iron will reduce tumor growth and proliferation, because it is long demonstrated in vitro and in vivo, in animals and humans that cancer is a pathology derived from iron toxicity [10,55].

It has been known for more than 15 years that iron chelating agents have antiproliferative properties, restoring the alteration in the cell cycle caused by free iron, which favors deeply, the proliferation of neoplastic cells; and, what is worse, its premalignant transformation from normal cells due to cumulative DNA damage [1,8,10,24,56,57].

This is biologically proven with the iron deprivation that causes the apoptosis of the cancer cell, and the consequent regression of the tumor by the iron deficient diet, verified in vivo [54,57].

Today it has been shown that intracellular iron, or its overload (when it exceeds the anti-inflammatory protective mechanisms in serum -transferrin- and tissue -ferritin- to indicate the most known), profoundly alters the cellular physiological cycle in normal liver cells [58,59]. For this reason, in particular, all "revolutionary" treatments for cancer have a high rate of failure, since the iron-rich tissue environment confers a high degree of tumor resistance [57].

Exactly, given their enormous avidity for iron, for their optimal nutrition, growth and proliferation, ferrous chelating agents are emerging more and more as an effective and effective therapy for the ideal treatment against cancer [60-63].

In a biologically determining way, iron protects the survival of tumor tissue, exerting a clear carcinogenic activity and promoting neoplastic growth; particularly by neutralizing the bactericidal and antitumor action of macrophages [10,60,64].

Today, in the extreme presence of tissue and environmental inflammation (diet, infections, genetic resistance to insulin or family diabetes); iron becomes a powerful cellular and tissue oxidant, catalyzing the most powerful reactive oxygen species, the hydroxyl radical, which is a powerful inducer of cancer animal and human [1,7,10,36,39,48].

Therefore, iron greatly enhances both the risk of initiating a neoplastic transformation, by originating and promoting a genetic modification and an active and permanent inflammation and proliferation that generates human cancer [39,41,65].

Current Iron as a Promoter and Aggravating Disease: It's Role in Chronic Inflammation

If after a parenteral infusion of iron, it is known that a marked clinical oxidative stress occurs, it is not surprising that, after a single intravenous iron injection, a systemic inflammatory reaction occurs acutely, aggravating experimental sepsis [66].

Interestingly, exogenous iron deposits rapidly in any tissue that is previously inflamed; and, in turn, chronic inflammation is an extraordinary breeding ground for the appearance of neoplasia, since it rapidly activates the Wnt oncogenic signaling necessary for the development of epithelial cancer [38,67,68].

Models of esophagooduodenal anastomoses that are exposed only once to iron, develop neoplasia and cancer; and this is proven again in humans, where a single dose of exogenous iron causes cancer [15,14,38]. And that is that iron is directly a cellular mitogen; in particular in conditions in which there is permanent exposure to environmental inflammatory aggressions: several epidemiological studies have shown that elevated chronic iron plays an important role in the genesis of lung cancer, both at the beginning and in its progression respectively [9,70-72].

It is very relevant the clinical verification that indicates that any parenteral administration of iron, powerfully cytotoxic, varies directly according to the release and tissue uptake of iron; and that it is potentially damaging to the kidneys because it causes an endothelial glomerular lesion, and progressively interstitial nephritis [73].

Very interesting: fulminant hepatitis can be prevented with iron restriction, as demonstrated in animal models of genetic copper accumulation (Wilson's disease); indicating a strong acute cytotoxic synergy between the two metals [74].

By the way, it is widely proven that in Hemochromatosis (abnormal tissue accumulation of iron) the incidence of carcinomas to the liver and breast is extremely high [10,24,25].

It has been strongly suggested that the lower dietary intake of iron, and in particular, the lower body iron status, reduces the risk of acquiring prostate, lung, colon (colon-rectum) and ovarian cancers [75].

If the excessive accumulation of copper and iron is a proven cause of liver cancer in animals and humans, respectively, the "simple" mild iron liver overload causes hepatic insulin resistance (by interfering with its proper anti-insulin signaling) [76,77]. Inflammatory and antigluconeogenic), in such a way that the iron load is causative of the Non-Alcoholic Fatty Liver (NASH); and its reducing therapy (dietetic or by phlebotomy) can reduce the high risk of hepatocellular carcinoma, and very especially in subjects with Insulin Resistance (IR) [78].

Definitely, lipid peroxidation and the accumulation of oxidative stress causes cancer in genetic Hemochromatosis [79].

The accumulation of the marker of oxidative damage to DNA, 8-hydroxy-2'-deoxyguanosine (8-OHdG), which occurs as a result of a continuous generation of ROS (chronic inflammation) has been reported in preneoplastic lesions and in cancerous tissues; In this regard, and in a fascinating way, it has been proved conclusively that short or long term iron reducing therapy respectively, it reduces this product of DNA oxidation in non-alcoholic steato-hepatitis NASH and in chronic hepatitis C [78-80).

Then, once again, it is strongly proven that the increase in body reserves of iron damages cell DNA; and that phlebotomy, in addition to reducing the increase in liver enzymes, reverses DNA damage- measured by 8oxodG-; consequently, Oral Iron restriction or Phlebotomy reduces the risk of liver cancer in subjects with NASH and in those with hepatitis C [78,80]. In addition, iron-reducing therapy will reduce chronic inflammation (inducing dysplasia) dependent on oxidative stress and lipid peroxidation caused by free iron.

Phlebotomy as Preventive of Cancer: The Hepatic Evidence

Just as oral iron depletion reduces the speed of aggressive progression of skin cancer, it has been proven in humans that phlebotomy (combined with a reduction in dietary iron intake) significantly reduces the risk of acquiring hepatocellular carcinoma in patients with hepatitis C, by reversing the oxidative damage of cellular DNA [7,80,81].

Knowing that an iron-rich environment - high transferrin saturation and ferritin levels- strongly favor the growth of leukemic cells, in more than 100 children with ALL - Acute Lymphoblastic Leukemia - a lower incidence of mortality (longer survival) was found. Those children with low transferrin saturation (<36) and lower ferritin levels ($p < 0.001$) [28].

This study is corroborated with other clinical works. The greater amount of serum and tissue iron is associated with a worse prognosis for numerous malignant neoplasms, appearing as a powerful risk factor for more aggressive cancers such as infantile Hodckin lymphoma, neuroblastoma and acute lymphocytic leukemia [1,82,83].

With all the biological, experimental, epidemiological and clinical evidence, to date, it should be known that the suppression of dietary iron (especially animal, Hem) reduces the risk of cancer in endometrium and breast and colon-rectum, particularly in subjects with excess insulin. And it is the iron overload, which increases the levels of this hormone (reducing its catabolism in the liver), and reduces its action; and insulin (directly and indirectly) increases the tissue uptake of the metal, appearing a feared vicious circle of oxidative stress-inflammation-proliferation-inflammation-oncogenesis [31,84-86].

Experimental lesions in the endometrium show, as in other metaplastic tissues, epithelial cell proliferation before iron loading; and this increases substantially in the presence of insulin [87].

It is proven that insulin resistance, indicated pathophysiologically by the reduction of Adiponectin, is a clear independent factor that increases the risk of breast cancer and endometrium, respectively [88,89]. And, exactly, it is free iron that reduces the production of adiponectin- the only adipocytokine that elevates the hepatic sensitivity of insulin, and that can, by various mechanisms, reduce the inflammatory risk of cancer [90,91].

As we previously saw, the depletion of iron by phlebotomy produces a significant improvement in insulin resistance, but independently between subjects with metabolic syndrome and fatty liver, because it significantly improves glucose uptake by improving liver signaling of insulin and improve its receptors [92,93]. Thus, it is verified -in vivo and in vitro that the depletion of iron improves the clearance of glucose, while its oral administration reduces it; By this mechanism, too, phlebotomy and blood donation can significantly reduce the occurrence of diabetes and cancer (see below). And, as has recently been proven, the dietary overload of iron induces Visceral Insulin Resistance [93].

Diabetes and Cancer: The Connection of Iron

High iron deposits such as Ferritin are now part of the Insulin Resistance Syndrome (Metabolic Syndrome: Dyslipidemia, Arterial Hypertension and Central Obesity); and this syndrome, a true epidemic of the century and a predictor of chronic disease, is strongly associated with the presentation of neoplasia [34,94].

The iron-insulin-glucose interrelationship is very exciting: if the free iron profoundly alters the glucidic metabolism, on the other hand, it interferes with the hepatic clearance of insulin, causing its increase and reducing its sensitivity (iron reduces glucose uptake by the fatty cell). And insulin also increases the synthesis and deposits of ferritin, by inducing the uptake of an iron cell-in parallel with glucose uptake [95]. Then, excessive iron becomes a potent hyper-insulinemia-inducing factor, and by this mechanism alone, it constitutes an indirect factor that favors the survival (anti-apoptosis) of cancer cells.

Today we know that high insulin levels, like insulin resistance, independently increase (from obesity and other risk factors) the development and progression of cancer: the hormone is a powerful growth factor in the tumor formation, by increasing the synthesis of DNA and inhibiting the apoptosis of the neoplastic and cancerous cell [96,97].

There is a strong, cumulative evidence that insulin is linked to the etiology and prognosis of cancer; especially in breast cancer [96-98]. But all this, with the hidden presence of tissue iron, which increases the cell inflammation cycle: Insulin Resistance-Hyperinsulinemia - >> Insulin resistance.

However, an interesting meta-analysis of epidemiological studies indicates that prospective and cross-sectional studies, especially for breast cancer, maintain the suspicion that hyperinsulinemia would

generate neoplasia and cancer. According to a secondary factor; and we bet that this evident biological and experimental preclinical factor is iron [99].

Coincidentally, premenopausal breast cancer occurs with great frequency in nonobese women - that is, not apparent hyperinsulinemic [98]. And it is now known that insulin, physiologically, when it has good sensitivity and is not chronically elevated, can even be protective of cancer by activating the IGFB-3 protein (IGF-1 factor binding agent), and have a global apoptotic effect [96]. Accumulated iron, potential carcinogenic, is essential for cancer to appear.

It is widely known that diabetes or glucose intolerance are predictors of poor prognosis in cancer, in addition to strongly increasing their risk, (both by insulin resistance and by glucose toxicity); and this occurs, despite reductions in insulinemia; thus, the toxic metabolic link, we affirm categorically, is iron; In agreement with this, it is evident that hepatocellular cancer is the one with immense cumulative power of iron, the malignant neoplasm that has a worse prognosis in subjects with diabetes and glucose intolerance [100,101].

Iron in Pathogenesis of Type 2 Diabetes: A Path to Neoplasia?

Accumulative epidemiological, experimental and clinical evidence, proves that it is the animal Hierre (Hem) and the supplementary added iron, which increases ferritin reserves, chronic oxidative stress, and confers directly and indirectly an increased risk of suffering from Type 2 diabetes mellitus in healthy populations [102].

The lower muscle glucose uptake due to the high iron reserves, explain by themselves, their causal effect in the generation of hyperglycemia with hyperinsulinemia; and extensive oxidative-inflammatory tissue damage is a potential cause of diabetes and chronic disease, due to provoking (and aggravating) Insulin resistance, the predictive hormonal constellation, disease promoter [33,34,101,103-105].

As we have pointed out, the coexistence of diabetes and cancer is very high: for diabetes to appear initially, there would be a preferential deposition of iron in the pancreatic cells with apoptosis of the beta cells and the excessive deposition of pancreatic collagen; the insufficiency in the insulin secretion, relative, would be added to the systemic and hepatic insulin resistance, triggering the DM2 [106].

Glucose Intolerance in Cancer: Is Diabetes Hiding the Way to Neoplasia?

Naturally, not all cases of adult diabetes follow the same evolution, nor do they present the same pancreatic reserve: we affirm that the greater the residual capacity to continue (or increase), chronically, the excessive levels of insulin, the greater the overdose will be cellular exposure to mutagenesis and oncogenesis.

In other words, the more "light" the hyperglycemia of fasting in a diabetic subject (due to greater insulinemias, as long as the tissue resistance does not increase ostensibly), the greater the probability of a future cancer; Diabetes, on the other hand, could be protective against aggressive cancer if insulin levels (diabetic autonomic neuropathy) are reduced significantly, and ferritin stores are elevated: chronic anemia in a diabetic subject (considerable diabetic nephropathy) would protect the patient from aggressive cancer (eg, pancreatic or breast cancer) Reduced levels of insulin or ferritin have been shown to reduce the risk of cancer; however, if the subject continues to "accumulate" iron, even the current levels of the metal, considered "normal", progressively damage the function of the pancreatic islets, given its extreme susceptibility to oxidative damage (as than the brain) [90,97,106].

But, if the patient has a high tissue (and pancreatic) antioxidant reserve, comparatively, the chronic excess of free and accumulated iron; and the hyperstimulation of the Insulin Axis-IGFs, would generate (first) neoplasia; in particular by maintaining a strong anti-apoptotic signaling, which is determinant for adverse prognosis in cancer, and resistance to therapy [98].

The accumulative evidence is overwhelming: in humans, iron, insulin resistance and excess insulin levels are biologically interrelated, translating an elevation of iron reserves, which predispose diabetes and cancer [31,95,101].

There is a high risk of diabetes; but particularly cancer in men and women with moderately high iron levels; as verified in a cohort of more than 10 thousand subjects, participants in the first National Health and Nutrition Examination Survey [23,103].

In subjects with DM2 - with high levels of ferritin - it has been shown that phlebotomies that reduced the deposit iron, approximately 50% (from 460 to 222 ng / ml)
Osteologically, glycemia and insulinosensibility improved [107].

Then, in addition to the experimental studies carried out on animals, clinically it is evidenced in men and women, a clear protection of iron losses against the risk of suffering from diabetes and cancer [42,107].

Gestational Diabetes, which seems to be caused by excess body iron accumulated in the third trimester, confers a higher risk of future cancer, as we will see later.

Insulin and Iron in the Initiation and Promotion of Cancer: The Example of Breast Cancer

Insulin can potentiate the carcinogenic effects of iron, and this seems to be more forceful in women, particularly due to leptin and estrogen, promoters of tumor growth: in vitro, insulin increases the cellular uptake of iron by increasing the redistribution of tissue transferrin receptors, potentially increasing the nutritional susceptibility of the cancer cell to its iron-dependent growth [1,91,108].

If insulin by itself increases the cellular uptake of iron (in parallel with the uptake of glucose), progressively, high levels of free iron (and transferrin) significantly alter the transport of glucose to adipocytes, promoting their resistance- similar to iron-dependent muscular resistance [109].

Circulating levels of insulin, and tissue signaling (Insulin-IGF-1) are particularly increased in early stages of breast cancer, even in the absence of obesity; it is known that central obesity confers an increased risk of cancer (especially in colon, rectum, endometrium), increasing mortality, respectively; and in all of them the chronic excess of insulin is very relevant as a causal factor [91,110-113].

And this greater cellular exposure to insulin (and iron) occurs from before birth: excess size and weight of girls is a powerful risk factor for breast cancer, which can originate in the uterus [114].

It is demonstrated that Glucose Intolerance associated with Gestational Diabetes and Gestational Diabetes in the third trimester are caused by the excess of maternal body iron; and as shown in an extensive prospective study carried out in Israel, the incidence of primary cancer in women is markedly increased [115,116].

If we have seen that the woman could originate her future breast cancer, in utero, given her greater exposure to several factors of cell proliferation, especially insulin and estrogen, it should not surprise the latest studies that indicate that the prognosis of early breast cancer (especially in premenopausal women) is closely related to high levels of plasma insulin: the greater the fasting insulins, the worse the cancer prognosis [117,118].

Both within breast tumors in humans and in tumor cell lines, a significant increase in receptors for insulin and IGF-1 has been demonstrated; Along with the accumulated evidence, today there is no doubt that insulin is the causal link between excessive caloric intake, free sex steroids and breast cancer [118-120]. In addition, it is the Insulin Resistance, particularly, that physiopathogenic event that accelerates the presentation of the tumor and its aggressiveness. And here the free (or catalytic) iron has a determining role [121].

The higher the intake and accumulation of iron, particularly as transferrin, the greater the resistance to insulin muscle and fat; and the lower will be the bioavailability of Adiponectin [88,90,122]. And the lower the efficacy and protective action of this hormone, the greater the progression of the tumor will be favored [91].

Adiponectin: The Hormone that Opposes Cancer: When Free Iron Eliminates the Last Hope

It is reported that adiponectin inhibits angiogenesis and neovascularization that promotes rapid progression and tumor expansion [91].

Adiponectin, the only "protective" hormone, exclusively dependent on adipose tissue (adipokine), which has exclusive insulin-sensitizing and deeply anti-inflammatory effects, is very reduced in Insulin Resistance syndromes (hypoadiponectinemia of the metabolic syndrome). But, in addition to hyperinsulinemia, free iron depresses serum adiponectin levels by negatively regulating its expression and activity [90].

These findings agree in an exciting way with the reports that indicate another potential powerful effect of iron as a carcinogenic agent: in unselected Western populations, a transferrin saturation greater than 60% confers a greater risk of acquiring cancer [122].

And this, particularly due to other direct factors that damage DNA, is that excess cellular iron reduces the oxidative-inflammatory, antiproliferative and antineoplastic protection of adiponectin [88-90].

It has also been affirmed, with sufficient biological, epidemiological, experimental and clinical basis, that, in normal subjects - that is, today, with a simple, moderate chronic iron accumulation like transferrin -, the only intake of approx. 19mg of oral iron is significantly associated with an increased risk of cancer [121].

We have investigated how the expression of genes related to altered iron metabolism are linked to the prognosis of breast cancer [123]. Of the 61 genes involved in iron regulation, almost 50% are statistically and significantly related to survival in metastatic breast cancer [123]. And they are profoundly altered by the excessive body accumulation of iron, and naturally, with their current, direct and indirectly high intakes [1,10,27,122,123].

As we pointed out initially, clinically and epidemiologically it has been demonstrated that the increase in body iron reserves is strongly associated with a worse prognosis of more aggressive cancers in humans, such as Neuroblastoma, Hodgkin's Lymphoma or Lymphocytic Leukemia and acute lymphoblastic, particularly in children [1].

This poor prognosis associated with the increase of tissue iron, which, as we mentioned earlier, is associated with numerous acute and chronic pathologies, is explained by the generation and maintenance of adiponectinemia; and in turn, these reduced levels circulating adiponectin are associated with an increased risk for cancer, mammary and endometrial invasiveness; and a considerable delay in the diagnosis. Special mention regarding the inverse and independent relationship of adiponectin with the highest risk of colon cancer [88,124].

Then, the more iron a patient with cancer ingests, the more advanced the neoplastic process will be at the moment of its detection; and the greater the aggressiveness of the disease [88].

In addition to the anti-proliferative, vasoprotective, anti-inflammatory and insulin-sensitizing actions of Adiponectin, the hormone has been shown to have direct inhibitory effects on tumor growth by increasing apoptosis and reducing the proliferation rate of cancer [91,125,126].

Yokota et al. have shown that Adiponectin suppresses the growth of myelocytic tumor cells and induces apoptosis of leukemic myelomonocytic cell lines [126].

The signaling of adiponectin directly modulates the behavior of the tumor cell; and if excess insulin increases the risk of cancer, abdominal obesity or the metabolic syndrome in each of its components does so much more intensely due -particularly- to the circulating adiponectin reduction; originated, promoted and maintained over time by excess free iron [96-99,111,125,127]. High iron concentrations in adipose tissue negatively regulate serum adiponectin levels and confer increased risk for diabetes; on the contrary, reducing the excess of iron (by chelation or restriction in the diet) prevents the experimental toxicity and the destruction of the beta cells of the pancreas, and to a large extent, this responds to the non-interference in the physiological actions of adiponectin [90].

The anti-angiogenic activity exerted by adiponectin is due to its vascular endothelial apoptosis inducing effect, and its inhibition in the migration and proliferation of cells: the hormone can inhibit the tumor growth of transplanted fibrosarcomas in mice [125,128]. Recall that, on the contrary, a single parenteral infusion of iron causes the development of sarcomatous tumors [13,14].

It is noteworthy that, the inverse correlation between circulating adiponectin and the increased risk of breast cancer, is independent of the body mass index-overweight or obesity [91,125].

In this regard, it has been shown, and again independently of body weight, that Adiponectin has an inverse correlation with Leptin, the pro-inflammatory adipocytokine par excellence, both in females without neoplasia, and, particularly in women with endometrial carcinoma [124,129].

It has been reported that leptin, clearly correlated with the percentage of body fat, controls the proliferation of mammary epithelial cells, malignant and normal, but it is a clear growth factor in breast cancer in an inflammatory tissue environment, where pre-adipocytes also synthesize them (in response to inflammatory cytokines such as TNF-x and IL-1b [91,125,130].

Increased weight in rodents increases the spontaneous and induced formation of breast tumors; and that, in addition to increasing insulin, the abundant local production of leptin can induce breast carcinogenesis; and it is potentiated intracellularly by tissue iron [131,132].

Always aggravated by excess iron, the leptin system plays a key role in the pathogenesis and progression of cancer, particularly breast and endometrial - premenopausal for breast, and postmenopausal for endometrium, respectively [131,133,134].

Leptin, which particularly modulates excess appetite and angiogenesis-for its powerful stimulation of VEGF (134) is also involved in the promotion of ovarian cancer and prostate cancer [135,136].

Thus, indirectly, to greater tissue iron, greater mitogenic effects of insulin, and particularly of leptin, establishing an inexhaustible inflammatory-oncogenesis broth. Hyperinsulinemia or IR syndrome (elevated ferritin, low adiponectin, see above) induces human cancer through signaling and leptin-dependent mechanisms [137,138].

Why does Iron prevent the death of the Cancer Cell?

When Your Reduction Can Prevent the Emergence of New Oncogenes

Insulin together with leptin are powerful hormones that stimulate the development and survival of tumor cells, but especially their resistance to treatment; even in the presence of estrogen-negative breast cancer cell lines [131,138].

Basically, excessive iron confers a powerful protection to tumor (and bacterial) cells because it reduces the macrophage activity and the microbicidal and antitumor release of inducible macrophage-dependent nitric oxide [64].

Naturally, a marked deficiency of iron is equally counterproductive; but minimal amounts of iron are enough to exert its superoxide-dependent primary antitumor protective effect. But, if naturally, free radicals can protect against tumor cells, their excess rapidly causes the opposite effect: it promotes nutrition and tumor growth, initially by suppressing the activity of tumoricidal cell-mediated immunity [1].

The appearance of tumor resistance that increases every day is closely related to the biological evidence that iron is absolutely essential for the nutrition of cancer cells; and that, conversely, iron chelation has been shown to increase and activate the P53 tumor suppressor protein, which is determinant for the molecular preventive development of cancer; and the most relevant thing to maintain the suppression of new oncogenes - and the antineoplastic molecular prevention (in time). is that iron depletion stabilizes the P53 by inducing the accumulation of HIF factor (hypoxia-inducible factor, determinant for the control of oxygen homeostasis, and angiogenesis) [139].

Iron regulates the expression of several protooncogenes (n-myc, c-myc) involved in the genesis of neuroblastoma, the most aggressive childhood cancer; and, again, it is the high levels of ferritin present in advanced disease, which predict its poor prognosis, by continuously stimulating survival, and the cell cycle of neoplastic cells [139,140].

When the tumor cells are full of iron (and with a normal oxygen tension), there will be no interruption of the cell cycle in the cancer cell, nor its apoptosis. The restriction or chelation of the metal, effectively interrupts the progression of this cycle, exerting anti-proliferative and apoptotic effects that manage to destroy the cancer cell; and most importantly, selectively, fully respecting normal cells; since the avidity for cancer iron -translated in its high receptors for transferrin- are very high in the neoplastic cell, compared with that normal [38,45-47,139].

With the enormous weight of biological, experimental, epidemiological and clinical evidence, it has been proposed, particularly in postmenopausal women, the preventive and recuperative treatment of breast cancer, with iron chelation therapy [141].

The combination of genes that propitiate and maintain a low intracellular iron content is associated with a better prognosis in advanced breast cancer (estrogen positive ER + monotherapy with tamoxifen) [123].

Now, let's look at a proven biological fact: When free iron in adipose tissue inhibits the only hormone with anti-tumor properties, adiponectin. Preserved levels of adiponectin, (or better elevated, in the presence of adequate sensitivity to insulin) have anti-carcinogenic activity by promoting tumor apoptosis, dependent on caspases enzymes; and reduce the angiogenesis of neoplastic tissue [91,142].

In an interesting prospective cohort study that included more than 51 men - The Health Professionals Hollow Up Study - a strong negative correlation between adiponectin and the risk of colon cancer was evidenced independently of the measures of adiposity and sedentary lifestyle [143]. Ferritin and other ferric parameters were not measured. However, we affirm categorically that this strong adiponectinemia found in cancer is due, in the first instance, to the excess of ferritin and adipose tissue iron (and then to the Insulin Resistance generated) [88,89,124].

We must remember that, even with the appearance of new aggressive oncogenes, if there are high levels of adiponectin by reduced tissue levels of iron (and probably Leptin), the physiological mechanisms that suppress cancer, such as the anti-tumor protein P53, will not be inactivated, being able to eradicate The greater the cell proliferation, the higher the mutation frequency; and the more we feed the preneoplastic cell with iron, the higher the biological rate of mutations [1,10,139]. If, at present, Adiponectin is the only hormone that has been proven to directly modulate the expression of several

regulatory genes of apoptosis and decrease the growth of myelocytic tumor cells, the lower the effectiveness of the hormone, and more reduced levels -independent of the presence of obesity-, the greater the tissue and cellular resistance to insulin, clear promoter, first, and predictor, after cancer [98,144].

In the genetic disruption of Adiponectin causes proliferation of the arterial intima and experimental Insulin Resistance; in the same way as iron: iron depletion by chelation prevents the formation of neointima (coronary stenosis) in models of animal vascular injury, which proves that cell proliferation is iron dependent [145,146].

Cancer and Atherosclerosis: Crucial Iron Intermediation

When inactivation of cancer protective genes (caretaker genes), and / or continued cell proliferation, are produced by free iron, a high rate of mutagenesis and progressive carcinogenesis appears: Hydroxyl radicals, originated by excess intracellular iron (in its reaction with hydrogen peroxide: Fenton reaction) cause chromosomal damage promoting tumorigenesis [10,24,25,48].

Iron is the most accumulable metal; in such a way that even small exogenous quantities predispose the human being for an early onset of cancer [6].

The biological events that relate Atherosclerosis and Atherothrombosis to Iron are intrinsically different, compared to the interrelation between Cancer and Iron; but they will help us understand the onset of uncontrolled proliferation "caused by oxidative inflammation dependent on free iron.

It is widely proven that high saturation of transferrin (the protein that binds extracellular iron) powerfully increases the risk of acquiring cancer in humans; Likewise, the highest iron deposits (transferrin saturation / Ferritin) are strongly associated with asymptomatic atherosclerosis and its inflammatory parameters (fibrinogen, IL-8) [22,23,147].

Active iron deposits progressively and intensely in the places of greatest inflammation, its deposit being directly proportional to body content [6].

There is direct evidence that free iron initiates atherogenesis when it is deposited in the arterial wall: thickening of the arterial intima and vascular muscular cell proliferation is inhibited by iron depletion; and the dietary restriction of the metal or phlebotomy reduces the size of the atheroma lesion by minimizing its content and intralesional inflammation [148-150].

Current parenteral iron therapy in anemic subjects with advanced renal failure has been shown to produce arterial vascular damage and increase carotid atherosclerosis. Physiologically, iron must be mobilized and not accumulated [151].

Moderate iron loads markedly accelerate the formation of thrombi after an arterial injury: iron overload can promote thrombosis directly, by affecting the coagulation system; By profoundly altering vasoreactivity by elevating vascular inflammation, exogenous iron can increase the incidence of cardiovascular events, particularly ischemic events [17,152].

Biological evidences show that elevated arterial iron promotes platelet instability by powerfully elevating vascular endothelial oxidative stress [17,148,152].

The proliferation and in particular the vascular cell migration is dependent on iron; and reverses with its depletion; if the induction of ferritin genes occurs early during the formation of experimental aortic atheroma, and if the expression of this ferritin persists until advanced lesions in humans, the close cause-effect relationship of iron is not surprising [146,148]. excessive arterial, atherosclerosis and ischemic cardiovascular pathology, considering the massive generation of toxic, iron-dependent ROS, which capture the NO basal regulator of cell proliferation [153].

The Iron is undoubtedly a powerful cellular mitogen; and this, as noted above, is confirmed in numerous experimental and clinical studies that chelation has potential anti-proliferative effects, both in Neoplastic tumors as in the experimental reduction of atheroma, It has been reported that, in subjects with coronary syndrome, increased levels of circulating ferritin could be predictive of premature coronary obstructive pathology, in men, and independently of the presence of diabetes (where the highest iron deposits are found) [58,148,154].

Experimental iron overloads are able to increase cardiac fibrosis induced by Angiotensin-II, and to increase de novo formation of the arterial intima; while iron chelation attenuates perivascular fibrosis and thickening of the aortic arterial media, according to Ishizaka et al [148,155].

It is clinically and epidemiologically demonstrated the reduction of cardiac infarction with blood donation; the reduction of iron deposits by frequent extractions of blood or by the tissue sequestration of iron substantially improve vascular endothelial function, and high oxidative stress, significantly reducing cardiovascular risk [32,156,157].

Given that iron deposits are harmful to their progressive increase caused by the current hypercaloric diet, it is convenient to keep normal iron deposits in low range to avoid the accelerated progress of atherosclerosis and atherothrombosis [6,148].

The dietary increase of Iron Initiates Human Cancer, by maintaining an increasing inflammation and irreversible DNA damage

The increase in cellular iron is highly harmful, carcinogenic and de novo genotoxic; even in small increments [1,10,158-160]. Only the increase in free iron twice in reticulo-endothelial cells or macrophages profoundly alters cellular signaling, activating factor NFkB, profoundly protective of cancer cells and promoter of tumorigenesis; in addition, elevated iron strongly alters the function of the normal cell by "capturing" and neutralizing nitric oxide and its antiproliferative actions [27,158,159].

Ferric iron has been shown to be significantly genotoxic (to profoundly alter DNA) even in primary human colonic cells, without any transformation; that is, it has been shown to be the initiator of colorectal cancer [160].

Like free hemoglobin in the circulation, iron is powerfully oxidizing and virulent when stimulating bacterial growth, particularly in conditions of acute stress [69]. And in the same way, in the presence

of any dysplastic or pre-cancerous tissue, the faster cell growth, the greater and more intense its obligatory iron demand; in such a way that its deprivation exerts a pronounced effect in the decrease of tumor proliferation and pre-tumor [7,160].

In humans, specifically, lower body iron stores, the lower the incidence of cancer [75]. And, in addition to all the above, today it is known that iron is potentially a direct cancer-initiating agent, particularly liver, causing cancer in the absence of cirrhosis: chronically generated and iron-dependent reactive oxygen species cause peroxidation lipid; whose products (such as malondialdehyde) profoundly damage protein synthesis, causing promutagenic DNA damage (due to deoxyguanosine residues) [161].

Heme iron, contained in red meat, in addition to its high cancer-causing power in the colon, is increasingly showing an impact on the high malignant transformation in the lung: independently of other confounding factors (obesity, cigarette, saturated fat, lower intake of vegetables and fruits, etc.), red meat excessively increases the risk of lung cancer in women and men, respectively. Clearly, the high temperatures increase the mutagenic content and profoundly elevate the release and lipo-peroxidative potential of iron [162,163].

A biologically proven and clinically forgotten determining event: only free iron, is essential, both for the initiation and permanence of lipid peroxidation reactions, sustaining reactions and permanent-eternal-exacerbation of cell damage. And let's not forget that free iron increases strongly in the presence of the insulin resistance syndrome, a chronic inflammation of "low grade", and as such, the best and most lasting breeding ground for proliferation immortal of cancer [33,94,132].

The co-carcinogenic effect of iron has been shown in excess, for many decades, however, it has not been given the crucial and determining role in its progression (as today, in its etiology): For example, the metal added in the diet potentiates the incidence of mammary and renal, estrogen-induced tumors; and this, in particular, is due to the fact that exogenous estrogens increase the accumulation of iron, in vivo, greatly facilitating its cellular uptake [164].

In an interesting case-control study of more than 7,000 women in China, it was observed that elevated animal iron increases the incidence of pre- and post-menopausal breast cancer, but especially in the presence of saturated and monounsaturated fats; this neoplastic effect of iron was also observed in relation to endometrial cancer in this group of Asian women [85,86].

It is confirmed again, today, that the overload of serum and dietary iron is the clearest and most decisive risk factor for the increased risk of breast cancer, participating in carcinogenesis, particularly in post-menopausal women [132,165].

Inflammation is a critical component and determinant of tumor progression; and although, today it is clear that the intense cell proliferation -hormono-dependent: insulin, leptin, estrogens, androgens, GH- by itself, is not a cause of cancer, we now know that, a sustained cell proliferation in an inflammatory tissue environment (such as visceral adipose tissue) with an activated stroma rich in growth factors, and with agents that promote direct damage to DNA, (such as iron), certainly promote initiation and / or enhance the risk to acquire a neoplasia [67,71,72].

In humans, the increase of the 8-hydroxy-deoxyguanosine derivative has been found in several inflammatory preneoplastic lesions, from uterine, gastric dysplasia; to cancerous tissues of colon, lung, breast and stomach [80].

Because the liver contains about 30% of body iron, it is one of the most susceptible to iron-induced mutagenesis [80]. As we saw earlier, an abrupt iron accumulation in the liver of Long-Evans rats develops hepatocarcinoma [74].

It has recently been confirmed that the controlled loss of iron is anti-carcinogenic: FeAST is the first randomized study, in which the iron-reduced group-which reduced its ferritin from 122.5 to 79.9 ng / ml-presented a significant reduction of new tumors at 4.5 years later (compared to the control group); In addition, among patients who presented new cancers, those who had iron reductions had a significant reduction in overall mortality. It is confirmed, then, that reductions in body iron reserves have a potential and powerful anti-tumor effect [101].

We will emphasize here that, in addition to the inflammatory reduction of the oxidative stress generator or enhancer of neoplasia, the reduction of free and accumulated iron ostensibly improves the anti-neoplasia immunity: free iron reduces profoundly immune surveillance against malignant cellular transformation, especially by inducing a marked alteration in the efficacy of T-lymphocytes (increasing CD8 suppressors and reducing CD4 helper) [132].

With a low iron nutrition, the prognosis of cancer will be improved, as the therapeutic approach to an iron-dependent tumor reduction will be significantly improved [7].

Free Iron: Our Slow and Progressive Killer, Today

When We Alter Increasingly the Natural Metabolism of Iron

The current Metabolism of Iron is profoundly altered, and we collaborate daily with it, for example, by deeply increasing the reactive oxygen and nitrogen species with our current inflammatory diet that alters our protective genes and awakens those that promote neoplasia, in particularly among the population with Insulin Resistance, the predictive syndrome of disease; as we pointed out before, Insulin Resistance is a generator of Chronic Disease in the human being [33,34,166].

For this reason, free iron, which under ideal conditions -plasma with neutral PH- should be exclusively bound to transferrin (and not more than 30%), is internalized in the tissues, damaging the nucleic acids and membrane lipids of the cell [167].

Thus, a coordinated orchestrated system of protein peptides is started immediately when iron is released both intracellularly (Ferritin) and extracellularly: transferrin and lactoferrin (plasma sequestration); haptoglobin and hemopexin (they bind the iron of hemoglobin, and iron Hem); in such a way that free iron levels do not cause cellular oxidation, inflammation and disease [69].

The saturation of all these physiological "binding" mechanisms of catalytic iron (free or redox) leads to an accelerated tissue degeneration, also present in hereditary iron overloads, such as Hemacromatosis, in which the incidence of cancer (hepatic, esophageal, melanoma, myeloid leukemia) is very high [167].

The recently discovered Hormone, Hepcidin, produced in the liver, is the quintessential regulator of iron metabolism, and is what determines what percentage of free iron will be retained in macrophages, hepatocytes and enterocytes: its secretion, strongly stimulated by inflammation or iron overload, inhibits the inflow of iron to the plasma, retaining it in the macrophage cells [167-170].

Would there be a lower secretion of hepcidin in patients with cancer?

Low levels of the hormone increase the duodenal absorption of iron and cause greater release of the metal, from the reticulo-endothelial system, into the circulation [167,168]. And this would happen in subjects predisposed to cancer, unlike of those who suffer first coronary disease and severe atherosclerosis, who would have higher concentrations of iron in macrophages: excessive chronic levels of hepcidin would be a marker of risk of heart disease [170].

This is corroborated with hereditary hemochromatosis, where the major neoplastic pathology due to iron overload is NOT accompanied by coronary artery disease; probably because the expression of hepcidin (in the liver) is inappropriately low [167].

Iron: The Metal that accumulates progressively and generates disease

Free iron produces a disturbance in the metabolism of zinc, of proven activity and anticarcinogenic signaling; and in particular in women, alcohol contributes significantly to the greater release of catalytic oxidizing iron from the ferritin deposits [132].

No metal accumulates to such a degree and as fast as iron; and metal is a clear substrate for the enzymes directly involved in cell proliferation, in addition to its direct effect as a promoter and initiator of cancer (see above); in particular in women with endometriosis, and in men with viral hepatitis, where persistent chronic inflammation in continuous increase, is the best breeding ground for the "eternal" survival of the tumor cell: iron overload creates an environment hyper-inflammatory that powerfully stimulates angiogenesis and overgrowth, migration and invasion of tumor cells, and this independently of sex steroids; and, as we pointed out above, the metal induces the activation of several antiapoptotic signals -including that of insulin, and that of the transcription nuclear factor NFkB [171,172].

The hepatomegaly found in the genetic overload of iron, such as Hemochromatosis, reverts with phlebotomies; and although the exogenous iron overload in rodents does not induce the immediate expression of proliferative genes in insulin-sensitive livers, it does clearly modulate the expression of TNF-x by Kuffer cells: the proliferation of hepatocytes (rodents) is a consequence of the elevated iron diet, and is due to the overstimulation of the cell cycle induced by the increase in the levels of Cyclin D1 [20,44,58,59].

Therefore, iron is a direct mitogen, in the same way as lead nitrate is in hepatocytes; In addition, hepatic (and probably dietary iron) overload stimulates increased secretion of TNF-x and consequent tissue inflammation (hepatic insulin resistance) [58].
In an extremely interesting report, the increase in hepatic cholesterol secretion due to elevated iron has recently been shown in mice [173].

Biological evidences prove that ferric iron plays a crucial role in the initiation of cancer in non-transformed cells, or in the early promotion of neoplasia in intestinal adenomatous cells; this demonstrates, again, the genotoxic role of iron [10,174].

Recently, also in prostate cancer, there has been a high saturation of transferrin (greater than 30%), but above all, higher deposits of ferritin [175]. A case-control cohort (CARET Study) has shown that diets high in iron significantly increased the risk of clinically aggressive prostate cancer; and iron caused greater aggressiveness of cancer in men with low dietary antioxidant inputs (fruits and vegetables) [176].

Diabetes and Cancer: The Murderous Intermediation of Iron

Every patient with adult diabetes is at increased risk of cancer; and the inverse seems to be confirmed in the case of pancreatic tumor. Thus, in general, there are more and more hidden hyperglycemias in subjects with initial or evolving cancer [177].

There is a complex, direct and underestimated association between diabetes and the increased risk of cancer initiation, progression and mortality; and this reciprocal interrelation may be narrower considering that type 2 diabetes is a commonly undetected disease due to compensatory hyperinsulinemia, which turns it into a hidden diabetes, with "normal" glycemia [177,178]. and this we are sure is very relevant in the case of prostate carcinoma, which is the only one whose global risk does not seem to increase with the presence of overt diabetes.

Recall that hyper-insulinemia significantly favors the development of malignant neoplasms because it is a clear and complex growth factor and with multiple mitogenic effects; both at the receptor and post-receptor levels [177].

Recently, the EPIC-Norfolk prospective study has clinically demonstrated the prediction of diabetes (of recent onset) with elevated serum ferritin levels; thus, as we said before, but now in healthy women, the greater the body deposits of ferritin, the greater the risk of suffering from the disease [179,180]. And excessive body ferritin is the link between diabetes, obesity (especially android-abdominal) and cancer.

It should be emphasized that iron by itself is capable of initiating disease in humans, such as lung cancer, and primary osteoporosis - iron increases osteoclastic activity and bone resorption [71,181-183].

Several epidemiological studies have reported a positive association between high ferric body deposits and the increased risk of type 2 diabetes and other insulin resistance states, from the metabolic syndrome and polycystic ovarian disease to gestational diabetes; all of them with a higher incidence of cancer; and it is that a greater oral intake of heme iron increases the risk of DM2 in healthy populations due to drastically elevating hyperinsulinemia and tissue resistance to insulin (particularly at the adipose, hepatic and muscular levels) [102,180]. By elevating insulin, but, most importantly, directly, free iron (not linked to transferrin) amplifies the action of genes carcinogenic (beta-catenin) and promotes the deletion of genes (1) protectors and inhibitors of malignant neoplasia such as protein P-53 [139].

Categorically, hyperinsulinemia associated with diabetes not only promotes but potentially causes carcinoma, particularly in breast, colon, liver and endometrium through its powerful cell survival

signaling PI3K / Akt; which when inhibited has been shown to regress the breast cancer; however, despite the growing evidence on the promotion and progression of cancer from diabetes -and independently, when chronic hyperinsulinemia compensates for insulin resistance, greater the risk of cancer, and in the absence of diabetes; thus, by reducing tumor antiapoptotic signaling of insulin (PI3K / Akt), tumor growth is reduced, but hidden hyperglycemia is evident [184-188]. This is due to the fact that, while iron deposits remain high (and inflammatory catalytic free iron), glucose intolerance will not disappear, nor will the neoplasm be eradicated, given that the high permanence of ROS will maintain the oncogene phenotype of cancer cells [189].

Hypercaloric Nutrition, Hyperglycemia and Cancer: The Malignant Help of Iron

Caloric restriction without malnutrition has been shown to reduce the incidence of cancer, in animals and in humans (pre-menopausal women reduce risk of post-menopausal breast carcinoma); there is growing evidence that reduced levels of IGF-1 (and insulin) mediate many of the antiproliferative, proapoptotic and anticancer effects of caloric restriction; and that the restoration of IGF-1 levels reverses the anti-tumor effects of calorie restriction [190].

Apart from its regulatory actions of the cell cycle, IGF-1 strongly increases the cellular accumulation of iron by increasing the transferrin receptors, a protein that by itself stimulates the replication of DNA in the neoplastic cell [191,192]. And IGF-1 in isolation, although it has a powerful oncogenic power, is not capable of promoting the growth of cancer: the presence of transferrin is necessary for the proliferation of human myeloblastic leukemia cells [193]. In addition, free iron is a potent survival factor for myeloid cells; and its malignant transformation [194].

The accumulation of adipose tissue induced by a hypercaloric diet with or without visible obesity, produces high proportions of reactive oxygen species (ROS), inflammatory cytokines, angiotensinogen and the chemotactic protein MCP-1, powerfully reducing genome stability; and this, we think is due to the higher content and tissue uptake of iron dependent on the adipose resistance to insulin [91,125,195].

Glucose intolerance is an independent factor that increases cancer mortality in the general population, according to an extensive study conducted in USA (Second National Health and Nutrition Examination Survey and the Second National Health and Nutrition Examination Survey Mortality Study); in such a way that chronic hyperinsulinemia would confer a higher predictive risk of cancer mortality than diabetes "per se", due, precisely, to the fact that higher insulin levels would be more powerful for the induction of cancer, than hidden hyperglycemia (post-prandial) (as in prostate cancer, not associated with overt diabetes) [196,197].

However, the opposite occurs in relation to the pancreas: given that the high exogenous contribution of heme iron confers a higher risk for diabetes (especially for women), it is indirectly explained that post-prandial hyperglycemia increases the risk of risk for pancreatic cancer; mainly in males; Pancreatic carcinoma could mean the final stage of an iron-dependent "bordeline" diabetes [198,199].

Hyperglycemia is common among cancer subjects; both the high intakes of sugars and refined carbohydrates and high glycemia are strongly associated with an increased risk of cancer; being able to determine its mortality: there is clinical evidence that indicates that a high carbohydrate diet is associated with a poor survival (post-diagnosis) of early breast cancer [200,201].

Hyperglycemia is a prominent feature of overnutrition, as is excess body iron; and epidemiological evidence supports that high glycaemia - even in the non-diabetic range - is an independent risk factor for developing cancer [201].

Today it is known that acute glycemic excursions increase the activation of the anti-apoptotic nuclear factor NFkB in mononuclear cells of healthy thin adults; just as iron does in macrophages; and in that way, by activating the main factor associated with the initiation and promotion of cancer, whose signaling is strongly anti-apoptotic as well as activating numerous inflammatory cascades chronic and promutagenic [10,20,27,202,203]. It is necessary to emphasize, here, that, even in normal thin young subjects, the normal-elevated physiological increases of post-prandial glucose are inflammatory [202].

It is necessary and urgent, today, an early detection and a therapeutic correction of chronic excess of insulin, especially in women, which will substantially help the reduction of cancer morbidity and mortality, and particularly, mammary [184,195,204]. The crucial role of iron in the generation of hyperinsulinemia; and directly in the generation of human cancer of hormonal etiology, it must be today, urgently prevented by reducing the carcinogenic accumulation of metal [22,164].

The anti-diabetic par excellence, Metformin, by reducing chronic hyperinsulinemia, improving insulin resistance at the liver, adipose and muscle levels, is demonstrating a powerful anticarcinogenic effect [205,206,207]. This anticarcinogenic action could be due, initially, to the reduction in iron absorption, which has been suggested based, would significantly improve insulin resistance in women with ovarian polycystosis: this syndrome, even subclinical (with the presence of ovulations) presents high incidences of breast cancer; confirming that the chronic excess of insulin powerfully increased by iron, would be the underlying cause of breast cancer [120,208].

Reduction of Body Iron: The Most Effective Therapy to Reduce Disease

Iron depletory therapy can reduce fibrosis and liver cancer, symptomatic and decompensated atherosclerosis hemodynamically, and gouty arthritis; and all this, especially because insulin sensitivity is improved: even in non-pathological conditions, reducing accumulated body iron reduces insulin resistance, which, as we pointed out before, is a clear-but undervalued-predictor of disease [31,34,209-211].

Recently, the first case of complete remission of a severe case of acute chemo-resistant monocytic leukemia has been reported, with Deferasirox, a powerful iron chelator, similar to the improvement that iron depletion promotes in many patients cases of childhood leukemia (see above); thus, the new pharmacological agents that capture free iron constitute powerful antiproliferative agents in cancer, even advanced [212,213].

Corroborating the mutagenic and neoplastic effects of iron, the most evident and powerful known exogenous carcinogen, Asbestos, is

proportional to the iron concentration contained [214].

The measurement of body iron deposits, measured as serum Ferritin is a risk factor for stroke (Stroke) according to a large cohort study with more than 11 thousand postmenopausal patients, by increasing by several mechanisms the thrombogenesis and the vascular inflammation [215].

In addition, more evidence is accumulating that iron plays a crucial role in the promotion of neurodegenerative diseases, particularly in Parkinson's disease: intranígricas iron injections selectively damage dopaminergic neurons; while metal restriction strongly protects against induced parkinsonism [216,217].

Hemoglobin is a potent neurotoxin that contributes significantly to neuronal death following trauma or intracranial hemorrhage; and its neurotoxicity is substantially mitigated with iron chelation by apotransferrin [218,219]. And, the greater the amount of Ferritin, the greater the risk of suffering a stroke in post-menopausal women [215].

Elevated Free and Accumulated Iron: A Risk for the Promotion and Extension of Disease

The recently discovered Ndrg-1 metastasis suppressor gene is negatively regulated by iron; the greater the iron ingested and accumulated, theoretically, the greater the metastatic power of cancer [220].

Changes in iron regulation characterize the cellular state of malignancy: Free iron induces, mediates and increases oxidative stress [10,123,221].

Exogenous iron is capable of modifying the four bases of renal chromatin only 24 hours after its administration, demonstrating its damage to DNA in vivo; and while it is true that it can intervene at the same time in its repair, it is insufficient to prevent genotoxic aggression; however, beta-carotene, for example, is capable of completely preventing the intense liperoxidative damage to the iron-induced prostate tissue [221,222].

Interestingly, DNA damage caused by Retinol is inhibited by iron neutralizers (Scavengers), which indicates that retinol-induced DNA injury is associated with a regulation of iron turnover; thus, accumulated iron is responsible for the high incidence of lung cancer associated with retinoid supplementation [223].

Subjects with cancer who consume more calories, regardless of their adiposity, will have a worse prognosis, by perpetuating a chronic excess of insulin (and other inflammatory hormones, such as leptin, sex steroids, etc.) [184,185,187]. and thus increase vascularization (angiogenesis) and the capacity of tumor metastasis, by increasing and activating VEGF (vasculo-endothelial-growth-factor) by insulin [224].

In this way, reactive ROS oxygen species -increased by iron- amplify the growth of cancer (insulin-dependent), and its distant dissemination (dependent on VEGF).

Oral iron overload, in addition to not improving malnutrition, on the contrary increases resistance to tuberculosis, as it has been for decades in Africa, since it increases aggressiveness and bacterial replication [225]. Dietary iron is clearly associated with a high incidence of disease, in addition to promoting its aggravation, by increasing any pre-existing inflammation: cellular iron behaves as a pro-inflammatory agent, and its high tissue levels contribute decisively in the pathogenesis of disease [69,226]. There is huge and cumulative evidence that excessive dietary iron is an initiator and promoter of disease [226].

A high saturation of Transferrin increases the risk of general mortality; and this has proven in the 12-year cohort study (The second National Health and Nutrition Examination Survey 1976-1980 -NHANES II- and the NHANES II Mortality Study 1992): High iron intake in subjects with high transferrin saturation significantly increases the overall risk of dying [227].

On the other hand, in any pathophysiological state where there is a decrease in serum transferrin, such as hyperglycemia or gestational diabetes, iron charges are gastrolesive, and, what is more serious, potentially teratogenic Recall that pregnancy is a state of physiological insulin resistance that is frankly pathological in women with previous android obesity [228-230].

Nonenzymatic glycation -induced by hyperglycemia- significantly increases oxidative stress in the presence of iron; thus, reducing the contribution of the metal in gestational diabetes prevents fetal malformations [95,228]. Clearly, numerous clinical studies show that the symptoms of gestational diabetes, hidden diabetes or pre-eclampsia, should not receive iron supplements in the first half of pregnancy: multiple evidence indicates that iron elevated during the gestational organogenesis human is potentially teratogenic [229,231].

Free iron is toxic to cellular systems, and must be neutralized and captured immediately by ferritin (intra and extracellular) so that it does not cause, increase or perpetuate the cascades of inflammation, a critical event for tumor formation and progression [67,232]. Moreover, in the presence of the current diet, clearly acidogenic, free iron is released much more quickly: all iron-dependent lipid peroxidation processes are enhanced when the extracellular pH is acidified, when greater amounts of iron are released from protective sites, such as ferritin [232-234].

In addition, if the dietary loads of iron were not, so inflammatory, eg. A decade ago, now they are more and more: in the presence of saturated fat, its mutagenic damage is enhanced, as the passage of iron to the mitochondria increases and its consequent chromosomal injury [235]. And, the greater amount of free iron in the mitochondria induces alteration of its energy homeostasis; and the commitment of mitochondrial energy, generates genomic instability, and the potential appearance of cancer [236].

In other words, the integrity of the nuclear genome and its mutability depends primarily on mitochondrial function, and it depends on intracellular iron levels [236,237]. It is noteworthy that, nuclear genetic mutations, by themselves do not cause cancer; and that the mitochondria and their metabolic environment play a dynamic role in the regulation of carcinogenesis (epigenetic metabolic regulation) [236].

In accordance with the above, the reduction of permanent

inflammation (induced by viruses, radiation or iron) to prevent the development of cancer is decisive [67,203,236]. A 24-year study conducted in the USA among white population shows that the highest dietary intake of iron is directly correlated with ten types of cancer (bladder, breast, colon, esophagus, stomach, rectum, and Hodgkin's lymphoma). Very interesting, these same neoplasms were associated with a low zinc nutritional index; and the tissue availability of zinc is reduced by the high dietary iron intake; thus, excessive iron, also indirectly, increases the risk of cancer by reducing the repairing effects of zinc, antioxidants and antineoplastics [238,239].

Excess iron causes deletion of the guardian gene of the CDKN2A / 2B genome, (generator of the ARF tumor suppression gene), as it has recently shown Toyokuni; Iron compounds by themselves generate malignant mesothelioma, by affecting this gene [240].

Currently, phlebotomy together with a low iron diet is the second therapeutic line for the prevention of hepatocellular carcinoma in Japan [81]. The lower the body iron deposit, the lower the incidence of cancer in humans; thus, in 2008, it has been shown that reductions in body iron by phlebotomy reduce the risk of visceral cancer by 35% and decrease mortality by 60% in subjects not pathologically overloaded with iron [42,75]. Free iron increases the invasiveness and distant metastasis of invasive cancer by increasing the expression of metalloproteinase MMP-9 [241].

Besides increasing slowly and progressively any subclinical inflammatory pathology, excessive iron is considered today as a powerful initiator of liver and cardiac damage: iron is crucial in the pathophysiology of liver fibrosis as well as in liver injury acute and on the contrary: a diet deficient in iron effectively reduces liver damage, in models of acute injury, and chronic [40]. In fact, it should not surprise us that high tissue iron causes apoptosis and cardiac fibrosis, since it does so, and much more easily, in liver cells [242].

In agreement with all the evidence already mentioned, it has recently been shown that an acute increase in free iron causes structural remodeling of the pulmonary endothelium, as a result of causing a proinflammatory cellular phenomenon [243].

Even in the presence of an exogenous non-high intake, ideally, iron should be used, distributed, eliminated and not accumulated in excess, so that it is not harmful and promoter of disease: the problem, added to the almost zero physiological elimination, is that the metal is not properly distributed in the presence of a systemic or hepatic inflammation, being accumulated in macrophages and tissues; This is evident in chronic anemia, where the oral exogenous iron supply does not solve the inflammatory or infectious problem that originates it [1,69].

A chronic anemia can be protective in the presence of accumulated iron excess due to an infection and / or previous chronic inflammation. Thus, before any degree of hepatic steatosis (or much worse, aggression to the hepatocyte) there will be no good redistribution of iron, by altering the secretion of the iron regulatory hormone Hepcidin, which will increase and sequester the Ferroportin-iron complex, preventing it from entering the circulation [69,240].

Elevated exogenous iron loads, in a dose-dependent manner, cause programmed cell death of cardiac, hepatic and pancreatic cells [244]. It's more: Even at "normal" levels, iron has deleterious effects on the function of pancreatic beta cells; and at high doses in its structure; pancreatic function is reversible with dietary restriction [90,244]. Extensive and growing epidemiological, experimental and, to this day, clinical studies, prove a very close relationship between carcinogenesis and exogenous iron overload: it is still reported that regular semi-annual phlebotomies reduce the risk of cancer even in normal populations; and the extraction of accumulated iron is much more urgent is those subjects with hemochromatosis genetics, chronic viral hepatitis, ovarian endometriosis, and asbestosis -pathologies that induce greater iron overload- and that lead, respectively, to hepatocellular, ovarian or human mesothelioma carcinoma [240].

A person may have anemia and at the same time an excessive accumulation of iron in the tissues: this is extremely frequent in the presence of chronic inflammation; this is evident, for example. in diabetic women, who, despite having more anemia than their male counterparts, accumulate more iron in their retinas [245]. In this regard, the toxicity of elevated iron on the retina is fully demonstrated, especially in the diabetic population [245,246].

We must emphasize that chronic anemia due to advanced cancer is not solved by providing oral iron, because the cause of it, as in any chronic anemia, is due to the overproduction of Hepcidin, the hormone that, pathologically, reduces duodenal absorption, and promotes tissue and liver retention of iron [1]. If we do not treat the cause first, we run the risk of aggravating the prognosis of the pathology: eg. it is demonstrated that, in a dose-dependent manner, the greater the transfusion of globular packages, the greater the risk of post-operative infections: the greater bioavailability of iron increases viral and bacterial replication, increasing its virulence and aggressiveness; and that, the excess of iron -or its greater deposits as ferritin- increases the susceptibility to infections because iron is the fundamental nutrient for the growth of germs, in addition to cancer cells; In this regard, new clinical and epidemiological evidences point out that dietary iron participates in the pathogenesis of cancer of the esophagus, stomach and lung [247-249,250-253). In a prospective study that included 7 years and more than 400 thousand subjects of both sexes, it was evidenced that the minerals ingested in the diet are a risk factor for lung cancer; and there is growing evidence that dysregulation of iron metabolism, and especially its free fraction, is the primary cause of neurodegenerative pathology [253-255].

Furthermore, as we pointed out earlier, each cell needs iron to proliferate and grow, and with much greater avidity, this occurs with the neoplastic cell: thus, an iron-rich environment facilitates and promotes tumor growth, and the amount of DNA synthesized increases. in the presence of metal; as occurs with the hepatitis B virus, which activates its replication and increases its capacity to infect with the increase of tissue ferritin [77]. Then, the greater exogenous iron disposition is able to strongly enhance the infectivity and the viral replication.

Severe deficiency, but particularly iron overload is clearly thrombogenic, inflammatory and cytotoxic, promoting retinal cell degeneration, of the lens, and neurons [150,152,153,155,254-258]. And, in the presence of important insulin resistance, such as the Hypertension of Pregnancy, exogenous iron supplements are deeply deleterious, since Pre-Eclampsia is a potential pre-diabetic state; profoundly exacerbating endothelial dysfunction, by increasing tissue resistance (vascular, hepatic and adipose) to insulin [230,259].

Clinically, in the population without genetic risk markers, the excess of free iron tissue will favor first (and early) the appearance of Diabetes Mellitus, contributing, clinically and histologically, to its complications [90,102,103,106,115,260]. Then, it will take us more easily to cancer. If, as has been demonstrated in an interesting pilot study, only 4 months of a high ("normal high") iron diet are enough for the infantile development of Diabetes 1; the time will be increasingly "short" for the appearance of degenerative diseases, and cancer [260].

The pathology of iron accumulation, currently growing due to the uncontrolled contributions of free iron in the diet, is very insidious: to this day, iron constitutes a "quiescent time bomb" [93,174,226,240].

Today, the basic sciences reveal us that the diseases of aging overlap -cardiopathies, diabetes, degenerative diseases (oculo-neurodegenerative) and cancer-; and that in all of them, tissue iron deposit, and insulin resistance is very evident; therefore, dietary iron, increasingly dangerous in the context of the current "nutrition" is powerfully carcinogenic, aggravating its morbi-mortality; and, in addition, and a potential contributor in neurodegeneration [34,90,216,234-236,254,255,257,261].

Messages to not forget

1. Iron overload in our diet generates tissue and cellular resistance to Insulin [93].
2. Reducing iron deposits by donating blood, increases sensitivity to insulin, prevents the early onset of Chronic-Degenerative Diseases, and in particular Diabetes Mellitus, even among people with normal levels of serum Ferritin [31, 34,107,209,210].
3. It has been repeatedly demonstrated, for more than 25 years, that the malignant cellular transformation induced by oxidative stress is strongly mediated by intracellular iron [21].
4. Increasing evidence shows that drugs that capture iron (chelators) "kill" the cancer cells, without causing damage to healthy tissue; which makes them, potentially, the most effective anti-tumor agents [46].
5. Chronic anemias do not benefit from the exogenous iron intake, while the INFLAMMATORY / Infectious cause that originates it is not solved, given that it is an anemia caused by poor distribution of iron (which does not pass into the blood due to being retained in the liver cells and throughout the reticulo-endothelial system).
6. Phlebotomy, epidemiologically, reduces the risk of acquiring cancer in the general population: Cancer: a Ferrotoxic Pathology [1,54].
7. The excess of iron reserves is a predictor of Occult Diabetes Mellitus, of Early Coronary Disease, independently and early, and of poor prognosis and mortality in subjects with cancer, particularly of the pancreas [262,263].
8. Epidemiological, experimental and clinical evidence proves it convincingly: processed animal iron causes human cancer [264,265].
9. The treatment of Chronic Inflammatory Anemia has changed Radically; and it is NOT with Iron Supplements, but with Vitamin C, Zinc, which facilitate their mobilization, and adequate re-distribution; but, above all, looking for the Causal Disease, in its very advanced stages, from a Parasitosis, a chronic infection, to a Cancer [266].
10. Regardless of Central Obesity, the accumulation of Visceral Fat directly increases the risk of intestinal cancer and its presence; and that, with a causal and irrefutable evidence [267].
11. A growing cumulative evidence shows: the restriction of calories (without malnutrition) promotes the apoptosis of the cancer cell; and its invasiveness (reducing its angiogenesis) (Fig. 2); Likewise, the depletion of body iron through the donation of blood strongly reduces cardiovascular disease, especially the risk of cardiac infarction and, probably, cerebral [156,190,268,269]. (A high iron intake increases the risk of ischemic stroke to the brain [270]. There is evidence that iron in neonates accelerates brain aging by causing neuronal death and iron not only free but accumulated powerfully activates the main intracellular and carcinogenic inflammatory gene: the NfkB [20,27,271,272].
12. The greatest risk for the acquisition of cancer is not the genetic one: it is the metabolic-hormonal profile; and its nutritional overload of iron and other metals: accumulated iron directly induces tissue injury, and alters, specifically the chromosomal activity of oncogenes [1,189,273-275].
13. The fine regulation of iron metabolism and its accumulation is determinant for the extension and prognosis of epithelial cancer [274,276].
14. Frequent extraction of iron by phlebotomy- blood donation - can decrease the risk of malignant tumors in the general population; and, it reduces the risk of cancer in "ordinary" humans with insulin resistance [1,277].
15. Pathophysiologically, free iron is harmful, and confers, particularly greater neuronal toxicity, and heart-cardiovascular when it accumulates more in tissues: and this is much more significant Zinc nutritional deficiency, a common event in our pregnant population [210,255,257,269,278,279].
16. The progression of a disease, from a cancer, to a serious infection (eg cerebral malaria) can be substantially alleviated thanks to the chelation of iron: the capture of the metal, its extraction (phlebotomy / donation), or a diet deficient in iron has been shown in animals and humans to inhibit tumor proliferation [1,45,46,56,57,60,277,280,281]. (as well as therapy-induced cardio-toxicity), and diabetes mellitus [107,277,280].
17. How can an optimal energy / protein contribution for each patient be achieved, but without intensely stimulating the advancement of cancer?: with an adequate restriction of protein calories and inflammatory fats, controlling the excessive secretion of INSULIN and its resistance induced by iron; the nutrient par excellence that immortalizes cancer cells [31,107,282,283].
18. Free iron increases the instability of the genome and the chromosomal rearrangement; promoting the mutation of proto-oncogenes and the inactivation of cancer suppressor genes [41,284]. Its overload alters the DNA and is causal of specific, strongly oncogenic mutations [189,284].
19. Epidemiological data in humans reveal the current evidence, to 2014: the greater exposure of exogenous iron or its overload is correlated with the increase in the genesis of cancer: thus, the metal supplementation, if absolutely necessary in periods critical, should be limited ONLY to the periods of extensive treatment; It can be a long-term counter-productive: iron metabolism must be extremely controlled so that the cancer does not spread at a distance [285].
20. We cannot continue "feeding cancer", except when it is incipient; worse if it is advanced: it is scientifically possible today to stop its advance by reducing the abdominal (visceral) accumulation of fat with the reduction of exogenous iron and the excess of Insulin, the generator of de novo cancer [286,287].

21. The storage of iron as ferritin in serum is initially protective and antioxidant; but, in the presence of cancer, when it is excessive it confers greater aggressiveness to the tumor: High Ferritin is responsible for the progression of the cancer, and especially its resistance to treatment [28,288]. It is up to us, to begin to abort the greater epidemic development of cancer, with an Integral Oncology Medicine TODAY.
22. El Hierro is an extremely reactive and oxidizing metal, and its physiological overload increases potentially an increased risk of cancer by directly causing genome instability, so it is essential to modify the current recommendations in its preventive intake, which can become in harmful [289]. The treatment of cancer -not more important than its prevention- should focus on locating DNA damage in the genome caused by high oxidative stress dependent on iron and copper, metals whose "normal" levels become toxic and promoters of disease [31,95,290,291].
23. At the end of this review, it is verified in Spain, after 59 epidemiological studies in 18 years, that for every mg. Additional animal iron increases the risk of human cancer [292]. The higher the iron intake, the higher the insulin resistance and the higher the risk of cancer, and this seems to be more relevant in women, as is the regression of breast cancer after an intermittent restriction of calories and iron [293,294].
24. At the end of this review, highlighting the clear and complex interaction between glucose and iron, it is shown that glucose loads reduce the concentration of iron in serum ONLY (Aigner, 2013); (causing confusion about their levels); and this by increasing tissue sequestration by an elevation of hepcidin, the iron-regulating hormone [95,295].
25. Iron loads promote profound deleterious changes in proteins (Cyclins) that control the cell cycle, potentially generating cellular malignancy. And within all the metals in contact with man, the iron is the one that most permanently modifies the genetic material, its contribution being unbalanced (due to the lack of natural zinc, eg) the initial cause of carcinogenesis and aging [58,59,189,296,297].
26. Liver cancer (Hepatocellular carcinoma), the third leading cause of cancer death, especially among developing countries, can be clinically reduced by phlebotomy, since iron overload is a significant factor in its development: and deprivation of the metal is proving to suppress the growth of cancer (Ba, 2011): free iron can be cytotoxic and genotoxic, in the central nervous system [101,285,298,299].
27. The experimental evidence that began 30 years ago is categorical, although unfortunately dismissed by the "great researchers": the cellular deprivation of iron strongly reduces the proliferation of tumor cells (280, 301); which initiated the most effective anti-cancer treatment: iron depletion and chelation; which, in addition, prevents the usual cardio-toxicity of chemotherapy, as well as super-infections almost always fatal [45,47,53,56,60-63,280].
28. And, closing the evident and hidden toxicity of exogenous iron, it is the excess of tissue accumulation of the metal that probably causes neurodegeneration and is compromised in the etiology of the degenerative diseases of the nervous system [24,255,278,302,303]. The increase in the poor countries of America of cancer and / or of neurodegenerative diseases would be the consequence of a greater bioavailability of these metals [303].
29. As well as estrogens, which, while reducing lipid peroxidation caused by the metal (304), induce DNA damage, exogenous iron increases the incidence and exacerbates the severity of the induced cancer [1-10,305].
30. There should not be an Iron / Zinc imbalance in favor of nutritional iron; given its complementary and antagonistic physiological actions, especially in the face of carcinogenesis: any deficiency, including Zinc magina, will increase tissue iron accumulation and its cytotoxic, inflammatory and carcinogenic potential: its chronic accumulation definitely causes an organic damage (pantropic) subclinical and unappreciated by the current medical community [306,307].
31. The genetic inheritance (Genotype) DOES NOT determine the appearance of Cancer: it is the conjunction of Metabolism and Environment (Nutritional and Physical) that finally determines the PHENOTYPE that will indicate the appearance and aggressiveness of cancer: This is the forgotten basis of the interaction Nutrients-Genes. When the production of glucose exceeds its use (insulin resistance), the biological system is allowed for the appearance of cancer [308].
32. If, as we have appreciated, the excess of iron perpetuates the immortality of the cancer cell (powerfully inhibiting its programmed cell death directly or through the resistance (excess) of Insulin, in the specialized normal cells, the excess of iron (like calcium) induces its degeneration and death (like neuronal degeneration) [257,261,278,309].
33. At the end of this work, it is verified, in a very well achieved meta-analysis (449 articles and 11 prospective studies) (until 2012) that the high consumption of Iron Hem and / or the increase in body iron reserves are significantly associated with an increased risk of Diabetes II; which confirms, once again, the Diabetes-Cancer interrelation (and vice versa) [310].
34. The greater the "sequestration" of iron in the cell, the greater the severity of a cancer: the smaller the amount of iron exported from the intracellular (the hormone hepcidin inhibits its cellular efflux when degrading to ferroportin), the greater it will be the aggressiveness of cancer in women (as it has been confirmed in incredible genetic studies for breast cancer) [311].
35. In diabetes and hematopoietic cancer in particular (leukemia) (and in any neoplasm and cancer in general) should not be given free iron or isolated because it increases microbial growth and profoundly damages phagocytosis (altering neutrophil lactoferrin, responsible for capturing iron and reduce its bioavailability for bacteria) [312,313].
36. An excess of iron, especially in the face of any biological stress, affects the physiology and leads to the injury of the cell [314,315]. Given the direct evidence that its regulated deprivation induces apoptosis in animal lymphoma, it constitutes an innocuous and effective rational strategy for the treatment of human cancer (Kovar, 1997); and especially when it has been demonstrated that the greater dietary intake of iron is greater the risk of invasiveness of human cancer [1,316,317]. And, like unbound iron, free (or excessive) hemoglobin is strongly oxidizing and toxic cellular and tissue, so that its reduction by a contribution restricted in iron decreases the size of the tumor, especially if it is malignant [318-320].
37. After the publication of this review article, it is verified once again now in a very large Asian cohort of more than 300 thousand adults 81997-2008), and in populations without a family history of cancer, that elevated serum iron is today a common disorder and a risk marker for cancer [321,322]. Moreover, even among the population with cancer, blood donation significantly reduces their mortality, which has been solidly proven in 20 years of

epidemiological studies ("healthy donor effect"): better health with blood donation will be achieved even among patients with cancer [323].

38. Solid and growing epidemiological, experimental and clinical evidences prove to date that: only a discrete increase in exogenous iron contributions increases the growth of any tumor, significantly increasing the risk of cancer occurrence, and especially its mortality [23,324,325].
39. Without fear of making mistakes, we can affirm that, in both men and women, the chronic excess of iron is still of greater mutagenic and oncogenic power than cigarette smoke, being powerfully synergistic in the acceleration of cancerous disease: iron is, evidently, the largest regulator and promoter of the cell cycle [244,322,326].
40. Reductions in blood iron levels prevent morbidity and mortality from cancer, since the higher the concentration of free iron, the higher the incidence of cancer in humans [165,317,327,328].
41. Iron facilitates the evasion of the tumor to its eradication by the immune system: that is: the reactive metal protects the cancer cell from its immunological destruction [329]. Therefore, no cancer can be effectively eradicated if high levels of tissue iron persist.
42. Iron supplementation is currently ineffective, and is potentially harmful to health; being deeply in the presence of obesity or sedentary lifestyle [330]. Recall that the permanent recycling of 95% of body iron (iron from animal source Heme) is the most powerful energy source for the development of the cancer cell and for any neoplastic disease, constituting its greatest risk for its prevalence, severity and mortality [331].
43. It is conclusively confirmed that the greater the accumulation of body iron or circulating free iron, the greater the risk of acquiring diabetes, and of dying from cancerous disease; and the greater the exogenous contribution of vitamin C (its natural chelator), the greater the protection against genotoxic and mutagenic damage of free iron [1,159,165,283,317,332-334].
44. A patient with cancerous or hematological disease will have a worse prognosis when greater accumulated iron is present; and transfusions can be extremely deleterious, causing potentially fatal complications: the largest malignant transformation induced by iron, epidemiologically proven is reduced with the reduction of metal [1,335].
45. Particularly, the dietary excess of iron and arsenic in a context of deficiency of anticancer micronutrients (Omega-3, Zinc, Selenium) is one of the most powerful factors in the promotion and spread of cancer pathology due to causing genome instability, irreversible promoter of malignancy [336]. Fetally, the contributions of iron (and its metabolism) are the final determinants in the synthesis and repair of DNA; and to this day, crucial not only in the promotion but in the beginning of cancer [1,41,240,284,336-339]. (An increased risk for acute myeloid leukemia in Down syndrome has also been reported in relation to iron and multivitamin supplementation, Blair, 2008) [340]. This demonstrates once again that excessive iron is crucial for the birth of cancer [1,36]. And this is strongly demonstrated in hepatocellular cancer, where dairy products enriched with iron potentially increase tumor size; on the contrary, its restriction reduces the advance of the cancerous process, by decreasing the proliferation of malignant cells [341-344].
46. Specifically, the contribution of iron suppresses the programmed death of the tumor cell and its restriction limits the growth of the tumor mass (American Society of Hematology, 1990) and the extension of the cancerous process [1,47,344,345]. Let's not forget this overwhelming evidence; even so, iron must not accumulate and on the contrary, it must be "exported" out of the cell, otherwise, it will cause malignancy (1,278,280,346-348].
47. Justly, ferritin measured both in serum and tissue, is the most effective predictor for the diagnosis and prognosis of cancer; because tissue ferritin directly stimulates tumorigenesis: The integrity of the genome is established and determined by our diet [287,288,349,350,352]. And if the man donates blood it will reduce his increased risk of cancer, as demonstrated by recent and rigorous epidemiological studies in humans and animals, while reducing oxidative damage to your DNA, even in optimal health [10,353-356].
48. Chemotherapy and radiotherapy, which have been shown not to eradicate cancer, are and will be ineffective as long as the cells that initiate cancer / Stem Cell are maintained, which will survive while maintaining high levels of cellular iron; thus, it has been confirmed in humans that iron promotes greater aggressiveness of cancer by inducing Stem Cells, that is, the root of cancer, and its accumulation strongly induces greater mortality [1,10,335,357].
49. Dieteically isolated, and molecularly free (catalytic) iron is a potential generator or inducer of spontaneous mutagenesis, whether it is an initiator or promoter of cancer (358, rev): and the lower its exogenous acute contribution, the lower the inflammation in the microtemporal environment, clearly promoting cancer, where iron not only contributes to the progression, but also to the initiation of cancer, especially hematopoietic agents -such as leukemias and myelomas- [1,16,20,44,56,359,360-363].
50. The intracellular capture of iron not only alters the cancer cell, but also affects its inflammatory microenvironment: If we want to fight cancer, we must modify the "carcinogenic" biology of iron, checked histologically, given its powerful role of metal in stimulating and maintaining the most common carcinogenic signaling; otherwise, all chemotherapy or radiotherapy will increase the resistance of the tumor by increasing the inflammatory signaling that feeds the cancer; and this because it powerfully increases the bioavailability of free iron [1,66,202,287,362,364-368]. Iron in charge potentially induces seizures due to its high neuroinflammatory power and must be proscribed in epilepsy and in the entire field of neuro-oncology [370,371].
51. The progression of the cell cycle that occurs in normal tissues, and particularly during the development of tumorigenesis is finely controlled by the anti-apoptotic signaling of iron, an essential nutrient for the aberrant and uncontrollable cell proliferation that occurs in cancer [372].
52. Optimal immune function is initiated and determined by an optimal cellular metabolism; the continuous or excessive intake of iron, alters it negatively, reducing the physiological immunoprotection against the cancer disease, besides altering the axis of Insulin, the master hormone that regulates the immunity –neoplastic [63,160,328,373,374].
53. The energy that feeds the cancer cells (glycolysis) increases in the presence of the inactivation of the anticancer gene p53, which increases strongly due to dietary iron overload: thus, iron binds, interferes and degrades the blood [375]. Main tumor suppressor protein P53; while its deprivation, by stabilizing it, suppresses the dependent tumor formation, constituting the best coadjuvant treatment of the isolated and obsolete current

chemotherapy [376,377]. This shows that free iron (or its dietary overload) IS DIRECTLY CARCINOGENIC, strongly promotes neoplastic cell survival, and the molecular mechanisms that initiate, promote and they support cancer, because the oxidative damage of DNA -8-OHdG- is controlled by iron body deposits [1,10,356,378-386].

54. Blood extraction decreases the incidence of visceral cancer, as well as its mortality, in humans [387]. Repeated phlebotomies are demonstrating in vivo to reduce the size of the cancerous tumor, its histology and its malignancy, as well as the extent of its extension (induced asbestos mesothelioma) Figure 13 [388]. If cancer cells require higher amounts of iron than normal cells, phlebotomy will be the best complement not only to prevent but to reduce the spread of cancer, by improving the redistribution of iron and its circle vicious that perpetuates the systemic inflammation that perpetuates cancer, and accelerates the presentation of its main risk factor, diabetes mellitus [138,184,187,388,389].
55. Iron oral or pharmacological intravenous promotes death and apoptosis of beta cells and causes diabetes or accelerates and aggravates its complications (105, rev), because the powerful effect Mutagenicity of excess free iron only occurs in the presence of stable and normal concentrations of oxygen, unlike its unique necro-apoptotic cytotoxic effect, before hypoxia-hyperoxia patterns [89,101,105,114,197,256,390-398].
56. For all the extensively documented, serial phlebotomies - better since adolescence - will be a magnificent therapeutic weapon (isolated or together with iron chelation) to avoid complications and the severity of chronic metabolic- and oculogyodegenerative diseases, from diabetes to cancer [1,10,31,39,94,106,399].
57. All chronic anemia is of Inflammatory cause, and it is mainly due to the excess of Hepcidin, which tissue "sequesters" Fe: therefore, anemia it is not due to the lack of iron, but to its poor distribution promoted by inflammation and / or hidden infection [1,400-402]. The doctor is at great risk of worsening the disease by administering iron: e.g. to higher intracellular iron deposits, higher serum ferritin –not nuclear, which protects DNA-, the greater the resistance of the cancer cell to its total eradication [403,404]. It is incredible that, until five years ago, the numerous physiological damages that free iron causes by itself and in combination have not been appreciated, Kell, 2009: extensive review 2469 references [401]. Dietary iron and Insulin Resistance (hidden hyperinsulinemia) together constitute the greatest risk for cancer, which, however, can be prevented with a phlebotomy or frequent blood donation [405].
58. It is essential to correct the altered metabolism of cancer cells that initiate cancer (Cancer Stem-Cells), even before the genomic alterations -promoted by the inflammatory microenvironment, originated and sustained by the excess of iron or glucose- to eradicate the disease [406]. That is to say: If we do not control in all the stages of the carcinogenic process the metabolic alteration that precedes, sustains and feeds the permanence of the stem cells (Cancer Stem-Cells), the cancerous disease will never be eradicated, and it will always recur, since it is the cellular iron that allows the survival of these cancer root cells [406-409].

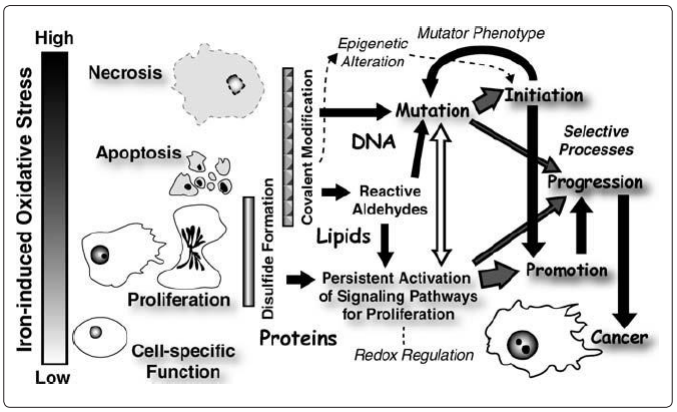


Figure 1: Meaning of the Potent Oxidation Effect Induced by Iron in the Genesis of Cancer.
Schematic View (Taken from: Tokoyuni S, 2009) [1].

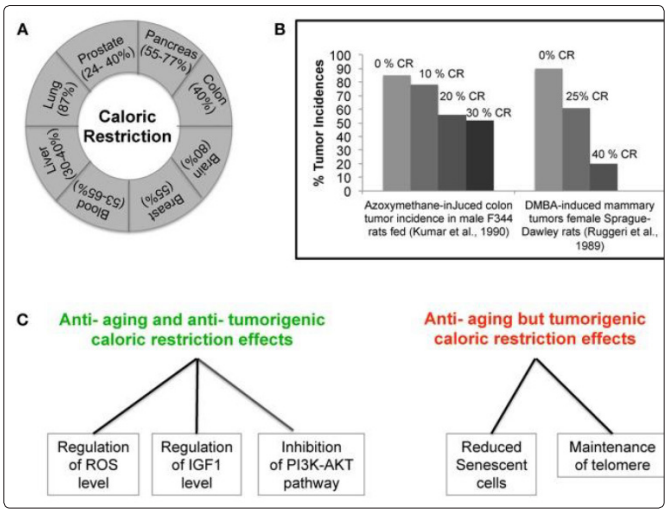


Figure 2: Restriction of Calories and Cancer
A) Caloric Restriction (CR) effectively inhibits several types of cancer in animal models;
B) Correlation between the lower incidence of Tumor and the degree of Caloric Restriction;
C) Demonstration of parallel and opposite effects of CR on cancer and aging: the ability of CR to decrease the axis Insulin-IGF-1 (strongly enhanced by iron), and the inhibition of insulin signaling PI3K-AKT, protect, simultaneously, the cells of aging and cancer. (Taken and modified from: Pallavi S, 2012) [268].

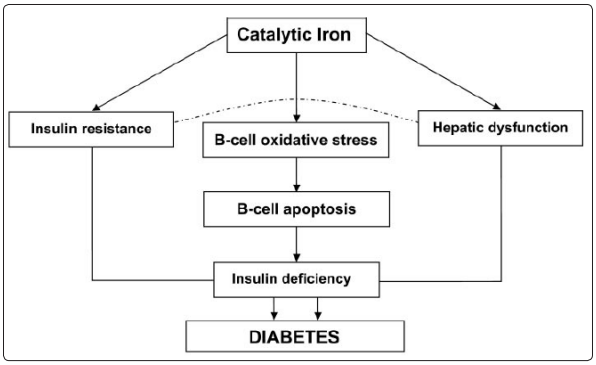


Figure 3: Simplified Scheme of the Pathways by Which Iron Induces Diabetes (Taken from Swaminathan S, 2007) [106].

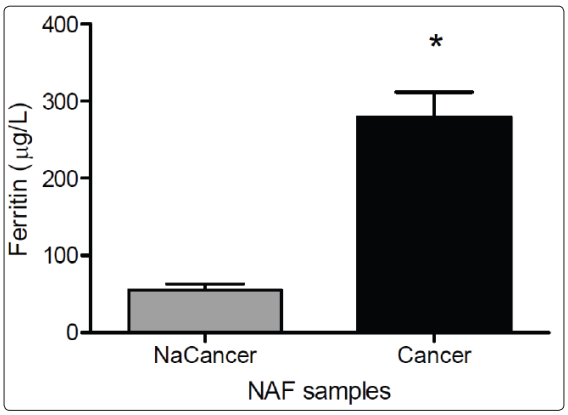


Figure 4: Concentrations of Ferritin in Breast Aspirate (areola). Substantive differences between the breast fluids of Women without or with Cancer (Taken from: Mannello F, 2012) [273].

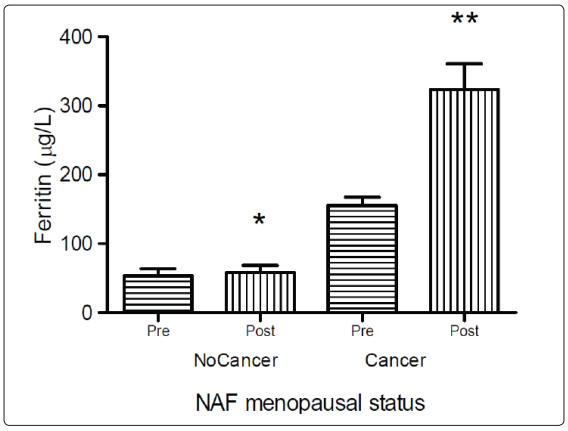


Figure 5: Ferritin Concentrations in Areolar Aspirated Fluids from Mama In Women without or with cancer, according to their menopausal status (pre or post-menopausal).
(Taken from: Mannello F, 2012) [273].

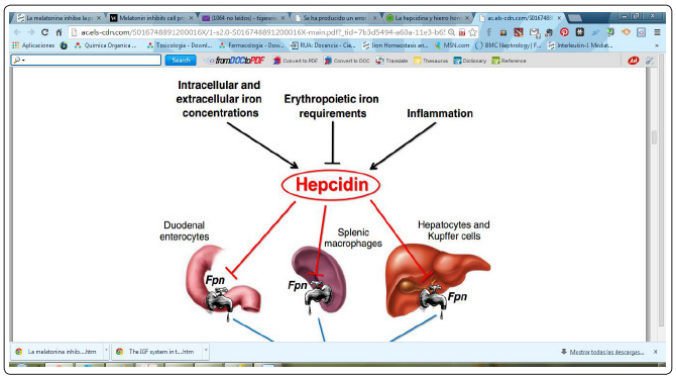


Figure 6: Scheme that demonstrates the actions of the Hepcidin hormone on the metabolism (sequestration) of Iron in tissues: When Hepcidin is elevated -before any inflammation / infection or advanced cancer- it is responsible for Chronic Anemia Resistant to Iron Contribution Modified by: Ganz, 2012 [168].

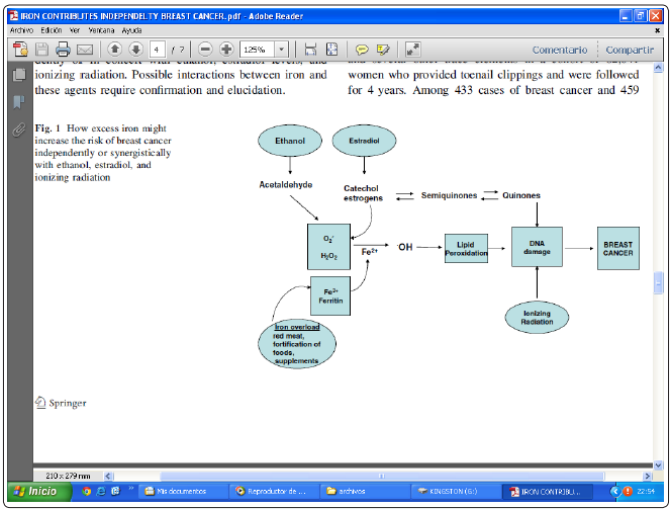


Figure 7: How Excess Iron Potentially Increases Breast Cancer Risk Independently; or enhancing the carcinogenic effects of ethanol, estradiol and ionizing radiation
Taken from: Kabat, 2007 [132].

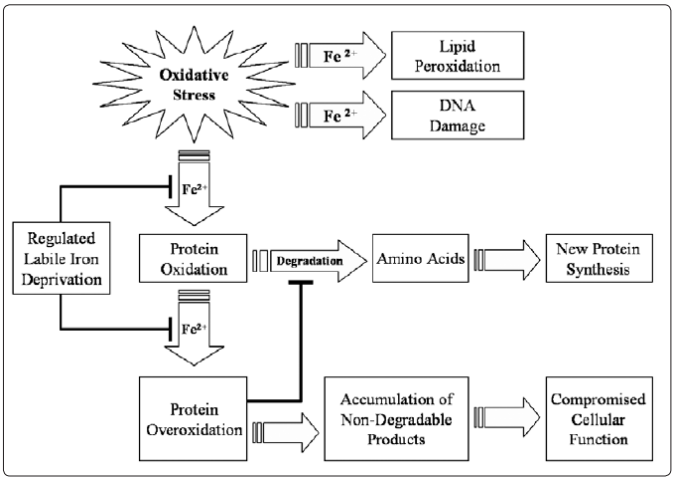


Figure 8: Scheme that shows the different mechanisms by which iron promotes oxidative stress that accelerates in particular the diseases of aging; generating an accumulation of non-degraded toxic products (denatured proteins) and lipid peroxidation; and its direct damage to cellular and mitochondrial DNA, all of which could be stopped (left side of the figure) in case of a deprivation of free iron or catalytic -labile- which will be achieved through a regular extraction of iron (by donation , chelation or restriction). Otherwise, excessive oxidation to proteins (which leads to their alteration and accumulation) will cancel any natural mechanism of DNA repair.
Modified from: Galaris, 2008 [300].

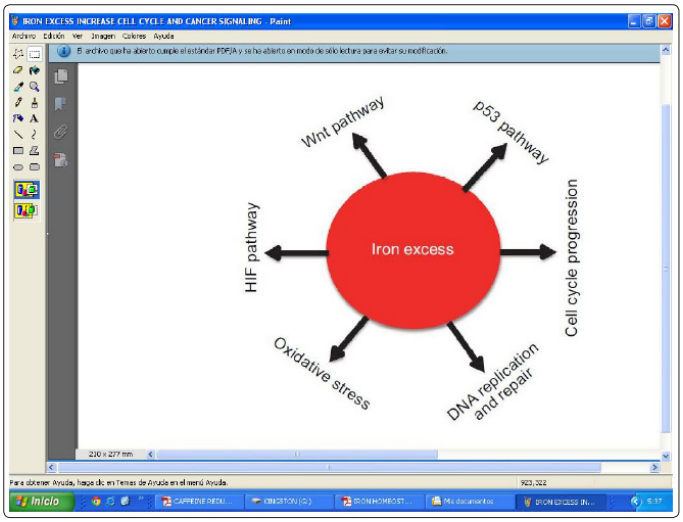


Figure 9: Image showing the Signaling Patterns Activated in the different types of Cancer caused by the excess of Iron
We will mention only 2: the Cell Cycle Progression that immortalizes the malignant cells, and the inhibition of the P53 gene that activates the apoptosis (and "kills" the cancer cells).
Taken from: Zhang, 2015 [321].

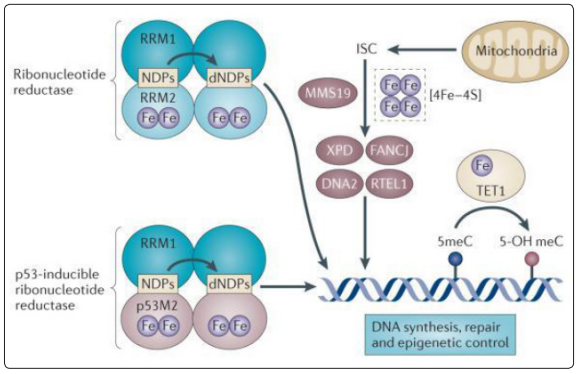


Figure 10: Molecular diagram showing how cellular iron determines metabolism and chromosomal integrity and genome (explanation in the text: Torti, 2013) [337].

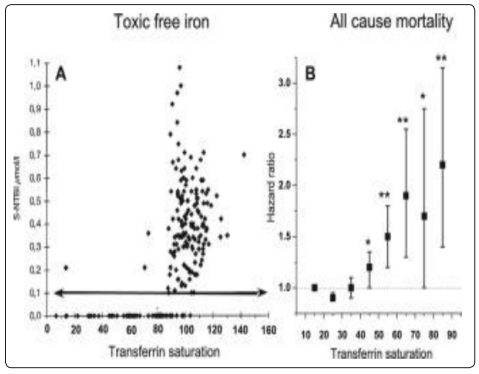


Figure 11: In the general population, it is shown that all causes of mortality increase significantly with higher transferrin saturations (panel B): and it is the largest increase in toxic iron not bound to transferrin (transferrin saturation> 60%). that increases this radius in mortality (Taken from: Puliyel, 2015) [335].

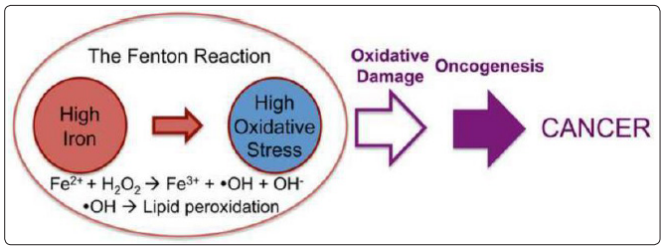


Figure 12: Scheme that shows how the Oncogenesis and the Cancer are generated through an intense mutagenic oxidative damage that promotes a genomic instability, and all this generated by iron overloads, which, through the Fenton reaction, turn the Iron into its Ferrous state (Fe ++) to its ferric state (Fe +++).
(Diagram taken with modified text from: Bystrom, 2015) [362].

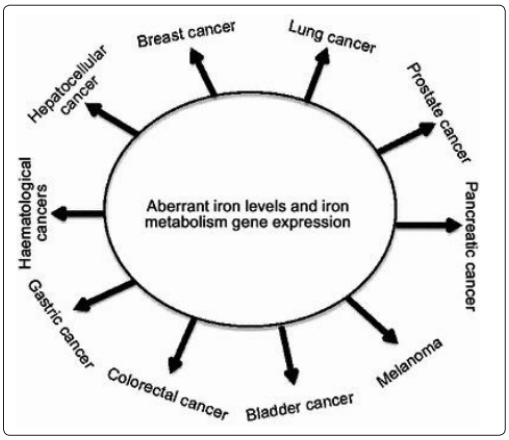
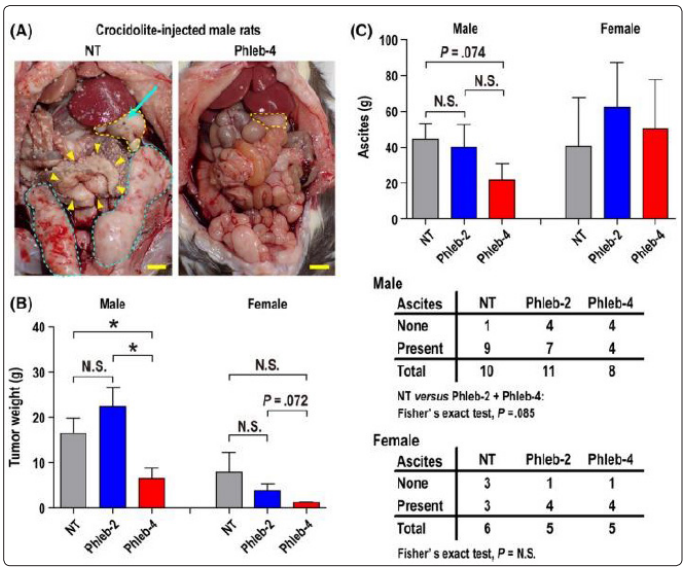


Figure 13: Iron involved in the genesis, progression or maintenance of Cancer Taken from: Zhang, 2015 [321].



Male

Ascites	NT	Phleb-2	Phleb-4
None	1	4	4
Present	9	7	4
Total	10	11	8

NT *versus* Phleb-2 + Phleb-4:
Fisher's exact test, $P = .085$

Female

Ascites	NT	Phleb-2	Phleb-4
None	3	1	1
Present	3	4	4
Total	6	5	5

Fisher's exact test, P = N.S.

Figure 14: We show the reduction of peritoneal tumor dissemination of mesothelioma induced by asbestos, in rats: disappearance of metastasis in rats with 4 phlebotomies, in comparison with the control group (Phleb-4 vs NT).
(Taken from: Ohara, 2018) [388].

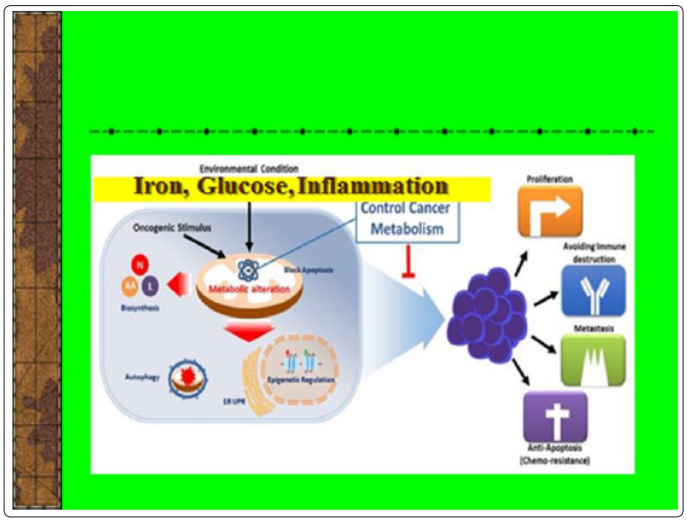


Figure 15: Schematic showing that it is the metabolic decontrol of cancer stem cells (Stem-Cell) that precedes their proliferation, spread and resistance to treatment (insulin-mediated anti-apoptosis) (Taken and Modified from: Chae, 2018) [408].

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