CURRENT TREND

Obesity, type 2 diabetes and risk of digestive cancer

Obésité, diabète de type 2 et risque de cancer du tube digestif

P. Hillon\textsuperscript{a,*,c}, B. Guiu\textsuperscript{b}, J. Vincent\textsuperscript{c}, J.-M. Petit\textsuperscript{d}

\textsuperscript{a} Université de Bourgogne, CHU de Dijon, rue de l’église, 21220 Dijon, France
\textsuperscript{b} Inserm U866, service d’hépatogastro-entérologie, département de radiologie, hôpital universitaire, 2, boulevard Mal-De-Lattre-De-Tassigny, BP 77908, 21079 Dijon, France
\textsuperscript{c} Inserm U866, service d’hépatogastro-entérologie, département d’hépatologie, hôpital universitaire, 2, boulevard Mal-De-Lattre-De-Tassigny, BP 77908, 21079 Dijon, France
\textsuperscript{d} Département d’endocrinologie, CHU de Dijon, 21000 Dijon, France

Summary  The frequency of obesity has been increasing worldwide for 20 years. Many epidemiological studies support a correlation between obesity and increased risk of cancer, particularly digestive cancers in both genders, and gynaecological cancer in women. Currently, about 5% of cancers could be directly related to overweight. Carcinogenesis mechanisms induced by obesity involve insulin resistance, adipokine and angiogenic factor secretions, and inflammation. Experimental and clinical evidence suggest that insulin resistance plays a major role in carcinogenesis. Insulin and non-protein banded IGF-1, whose levels are increased in type 2 diabetes, stimulate cellular growth and inhibit apoptosis. Abnormalities in adipokine secretion by the central adipose tissue play a role at different stages of obesity-induced carcinogenesis. Excess of leptin and PAI-1, associated with a decrease in adiponectin secretion in obese people, contributes to carcinogenesis through cellular growth and angiogenesis stimulation. Remodelling of the extracellular matrix due to metalloproteinase stimulation by PAI-1 is also able to promote cell migration. Obesity not only increases cancer frequency, but is also liable to modify the prognosis and the response to antiangiogenic therapy of digestive cancers. This data suggests the need for clinicians to take into account overweight in cancer risk evaluation and to consider obesity and metabolic disorders as confounding factors in designing therapeutic studies.

Introduction

Obesity, which is increasing worldwide, is correlated with high mortality due to cardiovascular events and cancer risk \cite{1}. Epidemiological data suggests that about 5% of new cancer cases could be directly related to overweight \cite{2}, and this could reduce recent progress induced by public health prevention policies.

Knowledge about mechanisms involved in carcinogenesis, associated with obesity, is important in terms of prevention and treatment. These mechanisms are beginning to be better understood, and involve insulin resistance, inflammation and adipokine secretion disturbances. All these mechanisms result from adipose visceral tissue dysfunctioning \cite{3}, which induces metabolic disorders caused by central overweight.
Metabolic disorders induced by excess of visceral fat are involved in carcinogenesis

Physiological functions of visceral fat are seriously disturbed in obesity

Contrary to peripheral obesity caused by lipocyte hyperplasia, visceral obesity results from intra-abdominal lipocyte hypertrophy [4] associated with major changes in the physiological functions of fat tissue (Fig. 1). These changes include disturbances in adipokine secretion, excess of endogenous sex steroid secretion, storage impairment of free fatty acid (FFA) excess, and secretion of pro-inflammatory cytokines (IL6, TNFα). Excesses of pro-inflammatory cytokines and FFAs contribute, with an adiponectin level decrease, to the development of insulin resistance which reduces the insulin inhibition of lypolysis, leading to a vicious circle of events. Under normal conditions, adiponectin increases insulin sensitivity and fatty acid oxidation, thus reducing FFA levels, but adiponectin secretion decreases paradoxically in obese patients [3].

Insulin resistance plays a major role in obesity-induced carcinogenesis

Insulin resistance is responsible for compensative insulin hypersecretion by beta pancreatic cells [5] leading to high blood levels of insulin and free insulin-like growth factor-1 (IGF-1). Using cell growth and antiapoptotic mTOR signaling pathway which could be less altered than metabolic pathways by insulin resistance, insulin and IGF-1 properties focalize functionally to cell growth and apoptosis inhibition.

Adipokine secretion and carcinogenesis

Leptin resistance could explain high leptin levels reported in obese patients [6]. Some studies suggest a relationship between systemic leptin level and colorectal cancer risk, where cells often overexpress leptin receptors [7,8]. Leptin mitogenic and antiapoptotic effects described for colon cancer cell lines are reduced by MAP kinase and PI3-K inhibitors [9]. Adiponectin has opposite protective properties with a proapoptotic effect [10].

Plasminogen Activator Inhibitor-1 (PAI-1) is a serine protease inhibitor produced by visceral adipose tissue. PAI-1 overexpression has been reported to be associated with the progression of many obesity-related cancers, among them colorectal cancer [11]. PAI-1 inhibition prevents adenoma formation in APC gene-deficient mice [12].

PAI-1 may indirectly contribute to tumor cell invasion and metastasis by activating matrix metalloproteinase which is a family of enzymes implicated in extracellular matrix (ECM) remodeling. Severity of colon cancer has been found to be correlated with high levels of certain metalloproteinases (MMP-2, MMP-7, MMP-9 and MMP-13) [13–15]. Serum and tissue MMP-9 are increased in pancreatic cancer patients compared to pancreatitis patients or healthy controls [16]. Upregulation of MMP-2 has also been reported in pancreatic juices from pancreatic cancer patients, but not juices from benign pancreatic disease patients [17]. Increased expression of MMP7 [18] and ADAM9 [19] predict poor survival in pancreatic cancer.

The alterations of the ECM induced by PAI-1 activation lead to growth factor secretion, angiogenesis, loss of cell adhesion contributing also to local growth cancer and cell migration. According to these carcinogenic effects, PAI-1 could be in the future an interesting target for cancer therapy [20].

Inflammatory cytokines and risk of cancer

Obesity reflects low-grade systemic inflammation [21]. Increased inflammation factors like C reactive protein, IL6 [22], and TNFα [23] associated with a decrease of anti-inflammatory factors like adiponectin, are correlated to an elevated risk of cancer. An excess of pro-inflammatory adipokine secretion by lipocytes could be involved in obesity-induced carcinogenesis, through the inhibition of apoptosis resulting from an activation of NF-kB pathway and increase of oxidative stress [24].

Obesity and digestive cancers: epidemiological data

Epidemiological data demonstrating an increase of cancer risk in obese patients

Many cohort studies have been published worldwide on the increase of cancer risk due to obesity and its metabolic consequences, particularly type 2 diabetes. A cohort of male health workers published in 1995 revealed an increased relative risk of colorectal cancer of 4.9 in obese people with low level physical activity compared to normal weight people with high level physical activity [25]. In a female cohort [26], cancer mortality increased with body mass index (BMI) in nonsmokers. In this study, physical activity partially protected against the risk of cancer induced by overweight [27] (Box 1). One year later, Calle et al. [28] published the results of a large cohort of 900,000 Americans, showing a 1.50 to 1.60 cancer risk in people suffering from morbid obesity compared to normal weight people. In this paper, the authors reported the risks attached to different locations of cancers according to gender (Table 1). In 2008,
Box 1: Beneficial effects of physical exercise for cancer risk reduction [27]

The reduction of cancer risk through physical activity might be due to the reduction of fat excess but also to direct metabolic, immunological and hormonal properties.

**Physical activity and metabolic disorders**

Physical activity improves insulin sensitivity and glucose uptake by skeletal muscles, but does not decrease the IGF-1 level in obese patients. Resistance training seems to have better metabolic effects compared to aerobic activity.

**Physical activity and immune function improvement**

Moderate chronic physical activity seems to enhance the anti-tumour effects of natural killer.

**Physical activity also decreases sex hormone levels** which could be beneficial in risk reduction and prognosis improvement of gynaecological cancers.

Renehan et al. pooled 67 cohort studies, three case-control studies nested in a cohort, and three randomized interventional studies, out of 142 studies published between 2000 and 2007 on the risk of cancer in overweight people [29]. The authors reported the increased risk of cancer by 5 kg/m² BMI according to location and gender. Digestive cancer incidence increased with BMI in both genders, and so did kidney and thyroid cancers, malignant melanomas and multiple myeloma. In women, endometrial, cervix and post-menopausal breast cancer incidences also increased with weight.

Overall, overweight and obesity account yearly for 5 to 6% of all cancers in European Union (73,000 cases) and USA (84,000 cases) [30—32].

**Type 2 diabetes and risk of cancer**

The frequency of type 2 diabetes increases with BMI [33]. Type 2 diabetes has been shown to be associated with a high risk of cancer [34,35], contrary to type 1 diabetes [36] confirming the carcinogenic role of a high insulin level.

The risks of liver [37,38], pancreatic [39], colon [40] and esophageal cancers [34] are increased in type 2 diabetic. The increased risk of pancreatic cancer remained significant after the exclusion of cases in which the diagnosis of cancer was made within 1 to 5 years following the diagnosis of type 2 diabetes [41].

**Visceral fat (VFA), type-2 diabetes and prognosis of digestive cancers**

Type-2 diabetes and visceral fat are associated with elevated risk of recurrence after HCC curative treatment

In untreated patients, tumour growth doubling time was highly correlated with the level of fasting insulin [42]. In a surgical survey [43] type-2 diabetes was associated with a more than two-fold increased risk of cancer recurrence at 5 years. The same result was reported by Okhi et al. [44] who found also an increased recurrence rate after HCC treatment by radiofrequency in high visceral fat area (VFA) patients compared with low VFA patients. In this study, VFA was evaluated by CT scan measuring retroperitoneal fat square. The differences between high and low VFA corresponded to the upper limits above which the risk of metabolic syndrome becomes significant: 130 cm² in males and 90 cm² in females [45].

<table>
<thead>
<tr>
<th>Location of digestive cancer</th>
<th>Women</th>
<th>p</th>
<th>Men</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digestive cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.59</td>
<td>[1.02—2.47]</td>
<td>0.04</td>
<td>1.09</td>
</tr>
<tr>
<td>Oesophageal adenocarcinoma</td>
<td>1.51</td>
<td>[1.31—1.74]</td>
<td>&lt;0.0001</td>
<td>1.52</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.12</td>
<td>[1.02—1.22]</td>
<td>0.01</td>
<td>1.07</td>
</tr>
<tr>
<td>Colon</td>
<td>1.09</td>
<td>[1.05—1.13]</td>
<td>&lt;0.0001</td>
<td>1.24</td>
</tr>
<tr>
<td>Liver</td>
<td>1.07</td>
<td>[0.55—2.08]</td>
<td>—</td>
<td>1.24</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.02</td>
<td>[1.00—1.05]</td>
<td>0.26</td>
<td>1.09</td>
</tr>
<tr>
<td><strong>Other cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.14</td>
<td>[1.06—1.23]</td>
<td>0.001</td>
<td>1.33</td>
</tr>
<tr>
<td>Renal</td>
<td>1.34</td>
<td>[1.25—1.43]</td>
<td>&lt;0.0001</td>
<td>1.24</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.11</td>
<td>[1.07—1.15]</td>
<td>&lt;0.0001</td>
<td>1.11</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>0.96</td>
<td>[0.92—1.01]</td>
<td>0.05</td>
<td>1.17</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.07</td>
<td>[1.00—1.14]</td>
<td>0.05</td>
<td>1.06</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.59</td>
<td>[1.50—1.68]</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Postmenopausal breast</td>
<td>1.12</td>
<td>[1.08—1.16]</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Prostate</td>
<td>—</td>
<td>—</td>
<td></td>
<td>1.03</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>[0.66—0.97]</td>
<td>0.03</td>
<td>0.76</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>0.47</td>
<td>[0.47—0.69]</td>
<td>&lt;0.0001</td>
<td>0.71</td>
</tr>
<tr>
<td>Premenopausal breast</td>
<td>0.92</td>
<td>[0.88—0.97]</td>
<td>0.001</td>
<td>—</td>
</tr>
</tbody>
</table>
Visceral fat and response to antiangiogenic therapy in colon cancer

The first paper reporting an evaluation of anticancer treatment response in high visceral fat patients was published recently [46]. This paper studied time to progression in 120 patients suffering from metastatic colon cancers. Two groups of patients were studied according to type of treatment: 40 patients received chemotherapy only, and 80 patients received antiangiogenic therapy by bevacizumab as well. In the bevacizumab group, the time to progression was shorter in high VFA patients compared to low VFA patients. At the same time, no difference was observed in the chemotherapy only group according to the level of VFA. This result could be explained by decreased antiangiogenic therapy effectiveness, due to a high level of angiogenic factors well known in obese patients [47], particularly in cases of visceral obesity [48]. The same authors found also a decreased effectiveness of kidney cancer antiangiogenic therapy in high VFA patients (submitted).

Conclusion

Increased obesity incidence may induce in the near future many digestive cancers which could be for some more difficult to treat than for normal weight patients. So, any progress achieved by public health prevention policies may be dramatically reduced. This underlines the need for clinicians to take the increasing weight of patients into consideration very early on, in order to prevent not only cardiovascular events but also cancer, particularly digestive cancers. Addressing the overweight issue as soon as possible may be particularly important in patients at risk of cancer: those suffering from precancerous diseases, or those with a family history.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

References


