Obesity as a risk factor in cancer: A national consensus of the Spanish Society for the Study of Obesity and the Spanish Society of Medical Oncology

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SPECIAL ARTICLE

Obesity as a risk factor in cancer: A national consensus of the Spanish Society for the Study of Obesity and the Spanish Society of Medical Oncology

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Abstract In the last few years, many prospective studies have demonstrated a clear association between obesity and cancers of the colon and rectum, breast in post-menopausal women, endometrium, kidney, oesophagus and pancreas. Obesity is also associated with a high risk of recurrence and cancer-related death. The pathophysiology of obesity involves various changes that may be implicated in the relationship between obesity and cancer, such as excess inflammatory cytokines and chronic inflammation, hyperinsulinaemia, insulin resistance, and raised leptin and oestrogens. The Spanish Society for the Study of Obesity and the Spanish Society of Medical Oncology have signed a cooperation agreement to work together towards reducing the impact of obesity in cancer. Preventing obesity prevents cancer.

Keywords Fatty acids · Adipokines · Inflammatory cytokines · IGF1 and 2 · BMI · Insulin

Introduction

The high prevalence of obesity worldwide and its direct implication in increased mortality from all causes, as well as the development of hypertension, type 2 diabetes, cardiovascular disease and some types of cancer, makes it one of the greatest public health challenges in the world [1, 2]. Body mass index (BMI), which relates weight (in kg) to height (in m^2) (BMI = kg/m^2), is the simplest way to work out an individual's degree of adiposity in clinical practice. Adults with a BMI of 25.0–29.9 kg/m^2 are overweight, and those with a BMI of 30.0 kg/m^2 or above are obese. Worldwide, the proportion of adults with a BMI of 25.0 kg/m^2 or above rose between 1980 and 2013 from 28.8 to 36.9 % in men, and from 29.8 to 38.0 % in women [3]. In Europe, obesity has reached epidemic proportions, and Spain is in the lead, with a prevalence of about 25 % in the adult population [4, 5].

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In the last few years, many prospective studies have demonstrated a clear association between obesity and cancers of the colon and rectum, breast in post-menopausal women, endometrium, kidney, oesophagus and pancreas [6]. A recent population-based cohort study involving more than 5 million British adults showed, after an observation period of 7.5 years, an association between BMI and the presence of 17 of the 22 most common cancers. Every 5 kg/m^2 rise in BMI was associated with an increase in the risk of developing cancer of the uterus, kidney, liver or colon, among others [7]. Obesity is also associated with a high risk of recurrence and cancer-related death, interferes with the effectiveness of systemic therapies, contributes to treatment morbidity and increases the risk of secondary tumours [8].

The time when a cancer is diagnosed and treated provides an excellent opportunity to tackle obesity in a comprehensive manner. A cancer patient's motivation makes it easier to adopt healthy changes in lifestyle and eating habits [8]. On the other hand, the excellent prognosis of patients who survive early-stage cancer of the breast, prostate or other sites means that obesity and its comorbidities (e.g. cardiovascular disease and diabetes) are responsible for over half of deaths among these long-term survivors [8].

Obesity is one of the main preventable causes of cancer. One of the most effective ways of reducing cancer risk is to prevent overweight and obesity. The Spanish Society for the Study of Obesity (SEEDO) and the Spanish Society of Medical Oncology (SEOM) have signed a cooperation agreement to work together towards reducing the impact of obesity in cancer by (1) raising awareness among professionals and patients about the strong association between obesity and cancer; (2) promoting substantial changes in lifestyle towards sustained healthy eating patterns and regular physical activity; (3) encouraging research into the pathophysiology of obesity and cancer development, and assessing the impact of lifestyle changes on the course of the disease; (4) drawing up guidelines for action in patients with obesity and cancer; and lastly (5) getting public institutions, the food industry and society actively involved in fighting obesity, employing all possible means of health promotion. As a result of this consensus statement, both societies have agreed 'The ten commandments of obesity and cancer' (Table 1).

Definition of obesity as a chronic disease

Obesity is a multi-factorial chronic metabolic disease resulting from the interaction between genotype and environment, characterised by excess body fat [9]. One of the key concepts is that diagnosis based solely on anthropometric measurements, such as BMI, is insufficient to establish an appropriate treatment plan. In 2014, following the Consensus Conference on Obesity, the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) established, using evidence-based criteria, that obesity is a chronic disease, and that these criteria could be used to develop a comprehensive plan to combat this disease [10].

AACE/ACE define obesity as a chronic disease characterised by pathophysiological processes that result in increased adipose tissue mass, which can lead to increased morbidity and mortality. The diagnostic algorithm for obesity incorporates two components, i.e. an assessment of body mass, including ethnicity-adjusted anthropometric data and the presence and severity of obesity-related complications. Each complication is evaluated for severity and impact on the patient's health as (1) 'Stage 0' when no complication is present, (2) 'Stage 1' when mild-moderate complication exists or (3) 'Stage 2' in cases of severe complication, using complication-specific criteria.

Four steps are recommended on diagnosis: (i) ethnicity-adjusted BMI; (ii) clinical evaluation for the presence of obesity-related complications using a checklist; (iii) assessment of the severity of complications using criteria to define them and (iv) selection of preventive and/or interventional strategies targeted at specific complications. Obesity-related complications include prediabetes, metabolic syndrome and type 2 diabetes, hypertension, hypertriglyceridaemia/dyslipidaemia, sleep apnoea, non-alcoholic fatty liver disease, polycystic ovary syndrome, osteoarthritis, urinary incontinence, gastro-oesophageal reflux disease, disability/immobility and psychological disorder/stigmatisation. Other complications and challenges to be resolved may include idiopathic intracranial hypertension, primary cancer prevention in high-risk individuals and families, secondary breast-cancer prevention, congestive heart failure, etc.

Epidemiology of obesity and overweight

Obesity, defined as a BMI $\geq$30 kg/m^2, is a chronic disease of epidemic tendency in the Western world, which has become a major public health issue, both because of its high prevalence, and because of the number and severity of comorbidities with which it is associated. In the USA, obesity affects 34.9 % of people over 20-year old. Although this figure has remained relatively stable during the last decade, there has been a marked increase among women over 65-year old, from 31.5 % in 2003–2004 to 38.1 % in 2011–2012 [11]. In Spain, the most recent data come from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA) [12], a cross-sectional study carried

Table 1 The ten commandments of obesity and cancer

1	Obesity, regarded as an epidemic disease, affects 22.9 % of the population when BMI (weight/height^2) is used. Using waist circumference, the figure rises to 36.5 %
2	Obesity (BMI >30 kg/m^2) represents an additional risk factor in patients with cancer
3	An epidemiological association has been found between obesity and cancer, with a HR >1.5 for breast cancer in post-menopausal women, endometrial cancer and renal carcinoma
4	A weaker positive association has also been found, with a HR of 1–1.5, for colorectal cancer, oesophageal/gastric cancer, thyroid cancer, meningiomas, prostate cancer, pancreatic cancer and hepatocellular carcinoma
5	Although poorly understood, the aetiopathogenic mechanisms are related to increased oestrogens from aromatisation of androgens and the proliferative activity of inflammatory cytokines, adipokines, insulin, IGF1, IGF2 and fatty acids
6	Increased body fat, particularly in the trunk, behaves as an independent risk factor for the development of certain cancers. It also worsens prognosis, reduces survival and increases the risk of secondary tumours
7	Greater survival among cancer patients means that obesity and its complications, mainly diabetes and cardiovascular disease, are responsible for over half of deaths in such patients
8	The time when a patient is diagnosed with cancer provides the ideal opportunity to raise his or her awareness about lifestyle changes and tackle obesity in a comprehensive manner. Protocols for assessing and treating obesity in cancer patients need to be implemented
9	It is estimated that 50 % of cancers could be prevented by lifestyle changes, such as not smoking, reducing exposure to the sun, preventing obesity, eating a healthier diet low in saturated fat and high in fruit and vegetables, and doing more physical exercise
10	Active policies aimed at preventing obesity and cancer need to be put in place. The various people involved (politicians, managers, educators, patients' associations and health professionals) should strive to achieve this

out between 2008 and 2010 in a non-institutionalised population aged 18 years or above. According to this study, the mean BMI of the Spanish population is in the overweight range, at 26.9 kg/m^2 (27.4 kg/m^2 in men and 26.3 kg/m^2 in women). Overall, 39.5 % of the Spanish population is overweight (BMI between 25 and 29.9 kg/m^2), while 22.9 % can be classed as obese.

These figures, impressive as they are, become even worse if one accepts that the BMI formula [weight in kg/(height in metres)^2] is an imperfect way to identify obesity, because it does not faithfully reflect the amount of body fat. In terms of percentage body fat, obesity is defined as ≥25 % in men and ≥35 % in women. Thus, 29 % of individuals with a BMI in the 'normal weight' range (between 20.0 and 24.9 kg/m^2) are obese when classified by their body fat, while 80 % of individuals with a BMI in the 'overweight' range are obese when assessed by body fat [13]. This explains why using waist circumference instead of BMI, the percentage of obese Spanish people rises to 36.5 % (31.7 % in men and 39.2 % in women) [12]. Waist circumference is a more faithful reflection of the amount of fat deposited in the abdomen, hence the percentage of visceral fat, which is the most metabolically active fat.

As a health issue, a rise in BMI is correlated with increased prevalence of not only type 2 diabetes mellitus, hypertension and hyperlipoproteinaemia, but also sleep apnoea/hypopnoea syndrome (SAHS), heart failure, cardiac arrhythmia due to atrial fibrillation, gout, left ventricular hypertrophy, cerebrovascular disease, pulmonary hypertension, venous insufficiency and degeneration of load-bearing joints. Likewise, it is also correlated with a major increase in various cancers. All this disease means obese individuals have not only higher rates of overall mortality, but also cardiovascular and cancer-related mortality. In fact, obesity has become the second most important cause of preventable death after tobacco use [14].

Molecular basis and mechanisms linking obesity and cancer

The molecular mechanisms linking cancer and obesity are poorly understood. Either they relate directly to the effects of increased adipose tissue itself, and the presence of inflammatory cytokines (a state of low-grade metabolic inflammation), and adipokines such as leptin, adiponectin, etc., or they relate to the consequences of obesity such as hyperinsulinism or hyperlipidaemia [15]. Figure 1 illustrates the mechanisms linking obesity to cancer.

Effects due to increased adipose tissue

Inflammatory cytokines such as tumour necrosis factor (TNFα) bind to the TNF receptor and activate nuclear factor-κB (NF-κB), which works by inhibiting apoptosis and promoting cell proliferation and metastases [16]. This pathway may activate proliferation of cell cycle regulation pathways, including cyclin D1 and cyclin-dependent kinase 2 (CDK2). Interleukin 6 (IL-6) sends signals to the nucleus via signal transducer and activator of transcription 3 (STAT3), an oncoprotein activated in a wide range of tumours [17].

Fig. 1 Molecular mechanisms between obesity and cancer. *IGF1* insulin-like growth factor 1
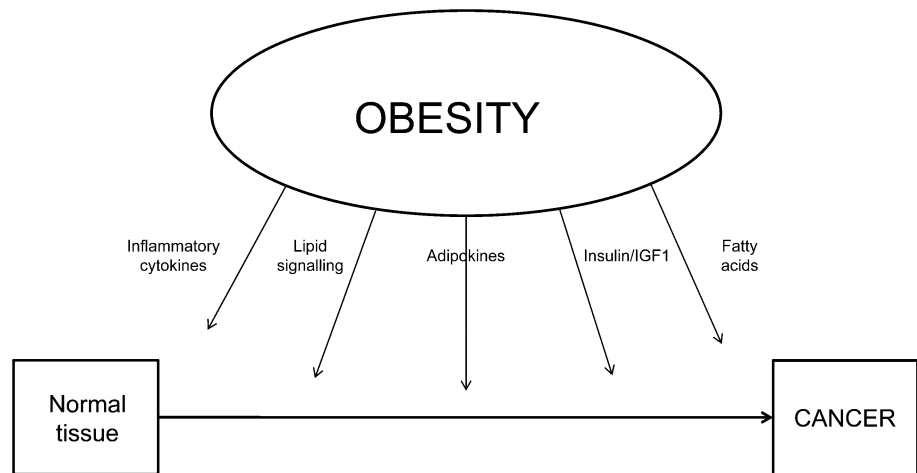
Leptin possesses proliferative activity mediated by various signalling pathways. On one hand, it induces the PI3K/Akt pathway that activates protein synthesis [18], and on the other hand, it activates the MAPK pathway, inducing protein phosphorylation [19]. Leptin also rapidly and directly stimulates the STAT3 pathway and may promote angiogenesis in breast cancer via vascular endothelial growth factor (VEGF) signalling.

Adiponectin inhibits cell proliferation and metastases. It also increases conversion of ceramide to sphingosine-1-phosphate [20], which has a variety of effects on apoptosis, possibly via MAPK. 'Adipocyte progenitor cells' may contribute to tumourigenesis through increased tumour angiogenesis or paracrine or endocrine signalling to malignant cells [21].

A higher incidence of hormone receptor-positive breast cancer has been linked to increased conversion of androgens to oestrogens in adipose breast tissue. Increased aromatase activity has been found in post-menopausal obese women, related to the presence of pro-inflammatory cytokines. This increased aromatase expression is associated with higher levels of cyclo-oxygenase 2 (COX-2) and prostaglandin E2 (PGE2) in breast tissue [22].

Effects due to obesity itself

As far as the presence of inflammatory cells is concerned, tumour-associated macrophages (TAMs) have been shown to play a key role in certain tumour types, contributing to tissue invasion, angiogenesis and metastasis [23]. Increased macrophage chemoattractant protein 1 (MCP1, also known as chemokine [C–C motif] ligand 2 [CCL2]) in breast tumour extracts is a predictor of relapses and metastasis.

With regard to increased signalling mediated by insulin and insulin-like growth factors 1 and 2 (IGF1 and IGF2), obesity associated with increased central fat is related to insulin resistance and higher concentrations of insulin and IGF1 and IGF2. Binding by insulin, IGF1 or IGF2 phosphorylates the insulin receptor (IRS), which sets off the signalling cascade by which the GRB2 and SOS factors activate the ERK pathway and induce increased cell proliferation [15]. ERK can activate oncogenic pathways via phosphorylation of MYC and members of the ETS family, such as ETS1 and ETS-like transcription factor 1 (ELK1).

Binding of insulin and receptor also activates the PI3 pathway, resulting in phosphorylation of AKT and activation of mammalian target of rapamycin (mTOR) [24]. PI3K activation can also activate other mediators of transformation involved in cell division control, including phosphorylation of protein 42 (CDC42). Moreover, PI3K activation can activate protein kinase B (PKB), which inhibits negative regulators of the cell cycle such as p27 (also known as KIP1) and p21 (also known as CIP1). Activation of mTOR can promote protein synthesis and affect cell growth. AKT inhibits BCL2-antagonist of cell death (BAD), an anti-apoptotic protein, and activates cyclin D1. Phosphorylation of FOXO proteins, such as FOXO3A, by AKT results in nuclear exclusion of FOXO, which promotes survival and cell division. AKT also activates MDM2, which degrades p53, thus preventing control of cell cycle activation and apoptosis [15].

High lipid levels also affect carcinogenesis. Exogenous lipids from diets high in saturated fats or fatty acids synthesised de novo in tumour cells or other cells can act as carcinogenic signalling factors via the paracrine or autocrine route. Fatty acid synthase (FASN) in cancer cells not only encourages phospholipid production, but is also involved in membrane production [25] and chemical inhibitors of FASN cause tumour cell death both in vitro and in vivo [26]. The increased FASN activity observed in cancer cells is consistent with up-regulation of enzymes that release fatty acids, mainly those in the monoacylglycerol

lipase (MAGL) pathway [27]. There is also an association between cholesterol and cancer. It has been suggested that one potential mechanism by which cholesterol may promote tumour growth and metastasis in breast cancer is through activation of the PI3K/Akt pathway [28].

Relationship between obesity and incidence of different types of cancer

Obesity and gastrointestinal cancer

Obesity and some related disorders, such as non-alcoholic fatty liver disease (NAFLD), metabolic syndrome and type 2 diabetes, increase the risk of developing various gastrointestinal cancers. Although the pathological mechanisms are not well understood, obesity-associated chronic inflammation is thought to be crucial in the development of these tumours. Other risk factors relate to immunity, adipokines (adiponectin and leptin), insulin, insulin-like growth factors and the gut flora [29]. Various studies in obese and diabetic animal models are investigating cancer chemoprevention by means of nutritional or pharmacological interventions [30], and by altering the flora.

The incidence of adenocarcinoma of the gastro-oesophageal junction and cardia has risen mainly in the West, in parallel with the increase in obesity. In a meta-analysis of 16 cohort and case–control studies, obesity was associated with a higher risk of gastric cancer [hazard ratio (HR) 1.13; 95 % confidence interval (CI) 1.03–1.24] [31].

Obesity is also a risk factor for the development of pancreatic cancer. As regards its prognostic value, Kasenda et al. observed, in 483 patients with locally advanced/metastatic pancreatic cancer [32] that high BMI ($p = 0.012$) and raised carbohydrate antigen 19-9 (CA19-9) ($p = 0.003$) were significantly associated with worse survival. They suggest using BMI as a stratification factor for clinical trials in advanced pancreatic cancer.

Viral hepatitis, alcohol abuse and exposure to hepatotoxic substances are the main risk factors for hepatocellular carcinoma. NAFLD is also a recognised factor, especially in the West. Hereditary factors that might favour liver cancer are being investigated, because NAFLD only progresses to hepatocellular carcinoma in a minority of patients.

Genetic and environmental factors, such as diet and lifestyle, including high BMI, obesity and little physical activity, contribute to the onset of colorectal adenomas and cancer [33]. Patients who are overweight/obese before being diagnosed with colorectal cancer are at greater risk of a second obesity-related cancer, and BMI ≥ 35 kg/m^2 may be associated with increased recurrence and mortality from

colorectal cancer [34]. Sinicrope et al. found that colorectal cancer in obese patients was less likely to show deficient mismatch repair (dMMR) [35], suggesting obesity-related differences in the pathogenesis of colon cancer. Although obesity was independently associated with a worse prognosis, the favourable prognostic impact of dMMR was maintained in obese patients. In conclusion, to reduce the incidence of gastrointestinal cancers and optimise the course of the disease, it is advisable to take steps to reduce obesity, encourage physical exercise and foster a healthy lifestyle.

Obesity and gynaecological cancer

Obesity is a recognised risk factor in the development of tumours of gynaecological origin, especially endometrial cancer. According to the UK Million Women Study, raised BMI was associated with a higher incidence of endometrial cancer (HR 2.89; 95 % CI 2.62–3.18) and ovarian cancer (HR 1.14; 95 % CI 1.03–1.27) [36]. The relationship between obesity and other types of gynaecological cancer (cervical, vulval, vaginal) is less well established, although studies exist to support it. Moreover, a recent publication suggests that obese patients recently diagnosed with gynaecological cancer have worse baseline quality of life than those of the right weight, even before they start any treatment. Obesity is also associated with worse treatment outcomes, both medical and surgical [37].

Various biological mechanisms linking obesity and endometrial cancer risk are recognised. In pre-menopausal women, obesity is associated with the development of polycystic ovary syndrome, characterised by anovulation, progesterone deficiency and hyperandrogenism. In post-menopausal women, excess weight results in increased circulating oestrogens due to peripheral conversion of androgens. As this is unopposed by progesterone production, it raises mitogenic activity in the endometrium. Obesity associated with hyperinsulinaemia and diabetes mellitus also plays a role in the development of both type 1 and type 2 endometrial carcinoma, regardless of whether the woman is pre- or post-menopausal. The mechanisms of carcinogenesis may be direct, such as stimulation of endometrial cell proliferation, or indirect, via the signalling cascade set off by insulin-like growth factor.

It is also suggested that excess weight may be associated with a state of systemic inflammation, characterised by a rise in circulating pro-inflammatory cytokines, thus promoting angiogenesis, cell proliferation and the production of free radicals, which would damage the deoxyribonucleic acid (DNA), leading to pre-cancerous changes [38].

Various studies have evaluated the relationship between obesity and development of ovarian carcinoma, with inconsistent results. While some firmly support its being a

risk factor, others find this relationship less clear. Although the EPIC study showed no differences in ovarian cancer risk among pre- and post-menopausal women [39], an analysis of cohort studies demonstrated a relative risk of 1.3 for developing ovarian cancer in pre-menopausal women, not seen in post-menopausal women [40].

There is extensive scientific evidence of the relationship between obesity and gynaecological cancer, especially of the endometrium. Weight gain, especially during a woman's adult life, is an important risk factor for developing this type of cancer, particularly after the menopause and in women not exposed to exogenous hormones.

Obesity and breast cancer

Obesity and overweight are related to the onset of tumours. They are associated with worse overall survival and worse breast cancer-related survival in pre- and post-menopausal women diagnosed with this cancer. In a 2006 study of obesity-associated deaths conducted in Spain [41], cancer mortality attributable to obesity was 16 % in males and 13.5 % in females. In the case of women with a BMI of 25–50 kg/m^2, the relative risk of dying from cancer related to obesity was 1.15 (95 % CI 1.02–1.31) for breast cancer in women over 60-year old.

A meta-analysis of 82 studies relating BMI and breast cancer mortality was recently published [42]. The relative risk of mortality analysing BMI at the time of diagnosis, compared with women of normal weight, was 1.41 (95 % CI 1.29–1.53) for obesity and 1.07 (95 % CI 1.02–1.12) for overweight. In obese women, the relative risk was 1.75 (95 % CI 1.26–2.41) before the menopause and 1.34 (95 % CI 1.18–1.53) for post-menopausal women. As regards the association between mortality risk and time of cancer diagnosis, this same study concludes that, for every 5 kg/m^2 of BMI, the increased risk for total mortality is 17 % before diagnosis, 11 % within the following 12 months and 8 % more than 12 months afterwards. These values are 18, 14 and 29 % in the case of breast cancer mortality.

The biological mechanisms behind this association between carcinogenesis and obesity are not completely established. Obesity generates a micro-environment in the adipose tissue and alterations in the endocrine system that favour the processes of malignant change and proliferation, with the interaction of hormones, adipokines and inflammation-related cytokines, involved in cell survival and apoptosis [43]. In obese women, aromatisation of androgens in adipose tissue favours high oestrogen levels. Furthermore, high insulin levels are also related to processes of malignant change. The interaction between insulin, leptin and obesity-related inflammation markers has been studied too [44]. Weight control and the avoidance of overweight and obesity are exceptionally important prevention measures. Evidence from randomised studies suggests that diet and weight control might reduce the risk of developing breast cancer [45].

Obesity and urological cancer

There are many factors related to the development of urological tumours. Obesity is one of the most extensively studied, given its increasing prevalence and its relationship to other factors involved, such as hypertension and diabetes mellitus [8]. Obesity-related urological cancers are those of the kidney, prostate and bladder [46, 47].

The incidence of renal cancer has risen gradually in the last few years. Approximately 30 % of new cases are attributed to obesity, and the risk of suffering kidney cancer rises by 24 % in males and 34 % in females for every 5 kg/m^2. The relative risk of suffering renal cancer in the obese is 2.3 for women and 1.8 for men [46–48]. The presence of other obesity-associated comorbidities, such as diabetes and hypertension, is also related to the development of kidney cancer. Among the pathogenic mechanisms linking obesity to the development of renal cancer, a major role is played by obesity-induced hormonal changes, especially raised levels of insulin and steroids associated with oxidative stress and lipid peroxidation, which can cause DNA damage [47]. In overweight individuals, a reduction has also been seen in adiponectin, an anti-angiogenic cytokine derived from adipose tissue, related to larger renal carcinomas and metastatic disease [49].

Prostate cancer is the second most common cancer in men and the sixth in terms of deaths caused. There are many studies linking obesity and prostate cancer. Meta-analysis data demonstrate that obesity is associated with a very slight but consistent increased risk of this cancer [47, 50]. It has been shown that obese patients are more likely to develop more aggressive tumours and have a higher recurrence rate after radical treatments. This might be related to lower than normal progesterone levels and higher oestrogens. Increased adipose tissue produces excessive amounts of oestrogens and higher blood concentrations of insulin and IGF1, stimulating the growth of androgen-independent prostatic cell lines by exerting a mitogenic and anti-apoptotic effect on cells. Fat tissue produces hormones called adipokines, which can stimulate or inhibit cell growth [51]. It has been shown that, in obese patients, periprostatic adipose tissue displays hypercellularity and reduced immune surveillance, promoting a favourable environment for the development of prostate cancer [52].

It is important to note that prostate cancer is more difficult to detect in obese patients, because they have lower prostate-specific antigen (PSA) values and fewer abnormalities on digital rectal examination, making it less likely that diagnostic prostate biopsies will be performed [53].

Also, prostate volume is greater, so a biopsy is less reliable. Some experts suggest lowering the cut-off value for PSA as a biopsy criterion in obese patients and increasing the number of cores, to reduce the false negative rate [54].

Studies carried out in the last decade have shown a relationship between obesity and bladder cancer, the risk being 15 % higher in overweight patients and 28 % higher in the case of obesity [55]. Excess body fat is associated with high insulin production and an increase in insulin-like growth factor receptor 1 (IGFR-1), which stimulates cell proliferation and suppresses apoptosis, all of which has been linked to bladder cancer. Type 2 diabetes is an established risk factor in bladder cancer [56]. Adipose tissue generates a mild systemic inflammatory reaction that may play a role in bladder cancer carcinogenesis, as seen in the link between levels of inflammatory mediators such as C-reactive protein and interleukin-6 and bladder cancer mortality [57].

Obesity and other types of cancer

Obesity and lung cancer

Various studies have examined the relationship between BMI and the risk of lung cancer, and one or two of them have suggested that patients with higher BMI have a lower incidence of lung cancer. A meta-analysis examining a total of 31 published studies demonstrated a clear inverse relationship between excess weight (BMI >25 kg/m^2) and lung cancer in patients who smoke [58] (relative risk 0.79), whereas that relationship appeared to be lost in non-smokers. Therefore, it can be concluded from this meta-analysis that overweight and obesity have a preventive effect on the development of lung cancer in patients who smoke.

Obesity and thyroid cancer

Observational studies examining the relationship between thyroid cancer incidence and overweight or obesity have been inconclusive and inadequate, so a systematic analysis was done of the seven most important cohort studies published, involving 5154 patients [59]. In that meta-analysis, it was concluded that a relative risk of thyroid cancer of 1.13 exists in overweight patients, rising to 1.18 for overweight and obesity combined. When the results were analysed according to patients' sex, there was no relationship between overweight and thyroid cancer in women, but for obesity, a relationship was found.

Obesity and haematological malignancies

A meta-analysis of 16 epidemiological studies examining the relationship between obesity and non-Hodgkin's lymphoma concluded that the relative risks were 1.07 for overweight people and 1.20 for obese individuals [60]. When the analysis differentiated between lymphoma subtypes, obesity was found to be significantly associated with diffuse large B cell lymphoma, with a relative risk of 1.40, but not follicular lymphoma. On the other hand, a meta-analysis of nine studies evaluating the relationship between obesity and leukaemia demonstrated a relative risk of 1.14 for overweight individuals and 1.39 for obese patients, concluding that a 5 kg/m^2 increase in BMI meant a 13 % rise in leukaemia risk.

Obesity and tumours of the central nervous system

The available data are highly inconsistent in terms of the association between obesity and glioma incidence, because studies are few and variable. However, data are more consistent in patients with meningioma. Everything seems to suggest that obesity in women is related to a higher risk of meningioma, with a relative risk ranging from 1.67 to 2.01, depending on the study [61].

Obesity control as a cancer prevention factor

As seen above, there is increasing evidence that obesity is not just an independent risk factor for the development of certain types of cancer, but also a poor prognostic factor and indicator of lower survival in patients who have already been diagnosed [8]. However, society in general still has little awareness of the relationship between obesity and cancer, no doubt partly because both these diseases were stigmatised for a long time.

Moreover, although there have been marked improvements in the last few decades in detection, treatment options and cancer patients' survival, there are still large gaps in our knowledge about preventing the occurrence of cancer. Such knowledge is needed, because about 50 % of cancers are thought to be preventable [62]. The balance between each person's genetic predisposition and the interaction between genome and obesity determines individual susceptibility to developing certain types of cancer to a greater or lesser extent. Lifestyle interventions, i.e. a healthier diet, greater physical activity and weight control, thus appear to be a safe, physiological approach to preventing cancer.

To date, no prospective, randomised studies have evaluated the impact of voluntary weight loss on the incidence of new cancers, or the prognosis of patients who have already been diagnosed. It is known that, beyond a certain BMI, weight gain over a period of time leads to higher cancer risk. For example, among women of pre-menopausal age diagnosed with breast cancer, all-cause mortality, including cancer mortality, is twice as high in those who

gained over 16 kg between 20 years of age and the year prior to diagnosis than in those whose weight remained stable. Similarly, among post-menopausal women with breast cancer, mortality is up to three times higher in those who put on more than 12.7 kg between the age of 50 years and 1 year before being diagnosed [63]. Moreover, weight gain over a short period of time, of 2–4 years, and more gradual weight gain, over 10 years, are both significantly associated with a higher incidence of colon cancer [64].

Studies in patients diagnosed with cancer are also available showing that weight loss achieved by lifestyle changes, such as a more balanced diet and greater physical activity, can improve feelings of tiredness, self-perceived body image and lung capacity, reduce the incidence of comorbidities, and achieve favourable changes in the profile of biomarkers linked to cancer risk and prognosis [65, 66]. In this sense, diagnosis should be seen as an ideal time to raise patients' awareness of their obesity problem and suggest that they lose weight to improve their prognosis [8].

Conclusions

Obesity, defined as a BMI of over 30 kg/m^2, is a highly prevalent disease in Spain. This prevalence has increased in the last two decades, and currently 23 % of the adult population and 15 % of children and adolescents are affected. Abdominal obesity, defined by waist circumference, affects 36 % of the Spanish population. It is well known that excess weight carries a greater risk of suffering type 2 diabetes mellitus, hypertension, dyslipidaemia, non-alcoholic fatty liver disease, degenerative joint disease and obstructive sleep apnoea. In addition to these classical associations, it also increases the risk of suffering various types of cancer. The pathophysiology of obesity involves various changes that may be implicated in the relationship between obesity and cancer, such as excess inflammatory cytokines and chronic inflammation, hyperinsulinaemia, insulin resistance, and raised leptin and oestrogens.

The current evidence reveals differences in the relationship between obesity and various types of cancer. Among cancers of the gastrointestinal tract, there is clear evidence of increased risk of, for example, gastric cancer (HR 1.13), or of the relationship to prognosis in malignancies such as pancreatic cancer, in which high BMI entails worse survival, or colorectal cancer, in which BMI >35 kg/m^2 is associated with increased recurrence and mortality. In the gynaecological field, raised BMI is associated with a higher risk of endometrial (HR 2.89) and ovarian (HR 1.14) cancer, although the link is more debatable in the latter case. Obese women with breast cancer have worse survival, irrespective of whether they are pre- or post-menopausal. As far as urological cancers are concerned, it is worth noting the relationship between obesity and increased incidence of renal cancer (an increase of 1.8–2.3 in relative risk). Likewise, diseases such as prostate or bladder cancer have also been correlated with overweight, in terms of both incidence and worse prognosis.

Health professionals and the general public both need to be informed and educated about the relationship between obesity and cancer. This means taking preventive action. Preventing obesity prevents cancer. On the other hand, the treatment strategy should be adjusted for excess weight, and patients recovering from cancer should be treated for obesity.

References

1. WHO World Health Statistics. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf
2. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377:557–
3. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–81.
4. Recomendaciones nutricionales basadas en la evidencia para la prevención y el tratamiento del sobrepeso y la obesidad en adultos (Consenso FESNAD-SEEDO). Rev Esp Obes. 2011; 10 Suppl 1.http://www.seedo.es/images/site/documentacionConsenso/Guia_obesidad_SEEN_Endocrinologia_2003.pdf.
5. Berghöfer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review. BMC Public Health. 2008;8:200.
6. González SCA, Goday AA. Obesidad y cáncer : "las amistades peligrosas". Med Clin (Barc). 2014. Available at: http://dx.doi.org/10.1016/j.medcli.2014.05.026. Accessed Dec 2014.
7. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014;384:755–65.
8. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, et al. American society of clinical oncology position statement on obesity and cancer. J Clin Oncol. 2014;32:3568–74.
9. Rubio Miguel A, Salas-Salvadó Jordi, Barbany Montserrat, Moreno Basilio, Aranceta Javier, Bellido D, et al. Consenso SEEDO 2007 para la evaluación del sobrepeso y la obesidad y el establecimiento de criterios de intervención terapéutica (versión íntegra). Rev Esp Obes. 2007; 7–48. http://www.seedo.es/images/site/documentacionConsenso/Consenso_SEEDO_2007.pdf.
10. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American association of clinical endocrinologists and american college of

endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. Endocr Pract. 2014;20:977–89.

11. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311:806–14.

12. Gutierrez-Fisac JL, Guallar-Castillon P, Leon-Munoz LM, Graciani A, Banegas JR, Rodriguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008-2010: the ENRICA study. Obes Rev. 2012;13:388–92.

13. Gomez-Ambrosi J, Silva C, Galofre JC, Escalada J, Santos S, Millan D, et al. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. Int J Obes (Lond). 2012;36:286–94.

14. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363:2211–9.

15. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011;11:886–95.

16. Orosz P, Echtenacher B, Falk W, Ruschoff J, Weber D, Mannel DN. Enhancement of experimental metastasis by tumor necrosis factor. J Exp Med. 1993;177:1391–8.

17. Bromberg JF, Wrzeszczynska MH, Devgan G, Zhao Y, Pestell RG, Albanese C, et al. Stat3 as an oncogene. Cell. 1999;98:295–303.

18. Nkhata KJ, Ray A, Schuster TF, Grossmann ME, Cleary MP. Effects of adiponectin and leptin co-treatment on human breast cancer cell growth. Oncol Rep. 2009;21:1611–9.

19. Fusco R, Galgani M, Procaccini C, Franco R, Pirozzi G, Fucci L, et al. Cellular and molecular crosstalk between leptin receptor and estrogen receptor-{alpha} in breast cancer: molecular basis for a novel therapeutic setting. Endocr Relat Cancer. 2010;17:373–82.

20. Ogretmen B, Hannun YA. Biologically active sphingolipids in cancer pathogenesis and treatment. Nat Rev Cancer. 2004;4:604–16.

21. Zhang Y, Bellows CF, Kolonin MG. Adipose tissue-derived progenitor cells and cancer. World J Stem Cells. 2010;2:103–13.

22. Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Zhou XK, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res (Phila). 2011;4:1021–9.

23. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature. 2011;475:222–5.

24. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009;9:550–62.

25. Kuhajda FP, Jenner K, Wood FD, Hennigar RA, Jacobs LB, Dick JD, et al. Fatty acid synthesis: a potential selective target for antineoplastic therapy. Proc Natl Acad Sci USA. 1994;91:6379–83.

26. Alli PM, Pinn ML, Jaffee EM, McFadden JM, Kuhajda FP. Fatty acid synthase inhibitors are chemopreventive for mammary cancer in neu-N transgenic mice. Oncogene. 2005;24:39–46.

27. Nomura DK, Long JZ, Niessen S, Hoover HS, Ng SW, Cravatt BF. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. Cell. 2010;140:49–61.

28. Li YC, Park MJ, Ye SK, Kim CW, Kim YN. Elevated levels of cholesterol-rich lipid rafts in cancer cells are correlated with apoptosis sensitivity induced by cholesterol-depleting agents. Am J Pathol. 2006;168:1107–18 quiz 404–5.

29. Tilg H, Moschen AR. Mechanisms behind the link between obesity and gastrointestinal cancers. Best Pract Res Clin Gastroenterol. 2014;28:599–610.

30. Shirakami Y, Shimizu M, Kubota M, Araki H, Tanaka T, Moriwaki H, et al. Chemoprevention of colorectal cancer by targeting obesity-related metabolic abnormalities. World J Gastroenterol. 2014;20:8939–46.

31. Lin XJ, Wang CP, Liu XD, Yan KK, Li S, Bao HH, et al. Body mass index and risk of gastric cancer: a meta-analysis. Jpn J Clin Oncol. 2014;44:783–91.

32. Kasenda B, Bass A, Koeberle D, Pestalozzi B, Borner M, Herrmann R, et al. Survival in overweight patients with advanced pancreatic carcinoma: a multicentre cohort study. BMC Cancer. 2014;14:728.

33. Scarpa M, Ruffolo C, Erroi F, Fiorot A, Basato S, Pozza A, et al. Obesity is a risk factor for multifocal disease and recurrence after colorectal cancer surgery: a case-control study. Anticancer Res. 2014;34:5735–41.

34. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB 3rd, Macdonald JS, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer. 2003;98:484–95.

35. Sinicrope FA, Foster NR, Yoon HH, Smyrk TC, Kim GP, Allegra CJ, et al. Association of obesity with DNA mismatch repair status and clinical outcome in patients with stage II or III colon carcinoma participating in NCCTG and NSABP adjuvant chemotherapy trials. J Clin Oncol. 2012;30:406–12.

36. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335:1134.

37. Doll KM, Kalinowski AK, Snavely AC, Irwin DE, Bensen JT, Bae-Jump VL, et al. Obesity is associated with worse quality of life in women with gynecologic malignancies: an opportunity to improve patient-centered outcomes. Cancer. 2015;121:395–402. doi:10.1002/cncr.29061.

38. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer. 2010;17:1007–19.

39. Lahmann PH, Cust AE, Friedenreich CM, Schulz M, Lukanova A, Kaaks R, et al. Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;126:2404–15.

40. Schouten LJ, Rivera C, Hunter DJ, Spiegelman D, Adami HO, Arslan A, et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev. 2008;17:902–12.

41. Martin-Ramiro JJ, Alvarez-Martin E, Gil-Prieto R. Mortality attributable to excess weight in Spain. Med Clin (Barc). 2014;142:526–30.

42. Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014;25:1901–14.

43. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer—mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol. 2014;10:455–65.

44. Goodwin PJ, Ennis M, Fantus IG, Pritchard KI, Trudeau ME, Koo J, et al. Is leptin a mediator of adverse prognostic effects of obesity in breast cancer? J Clin Oncol. 2005;23:6037–42.

45. Advani P, Moreno-Aspitia A. Current strategies for the prevention of breast cancer. Breast Cancer (Dove Med Press). 2014;6:59–71.

46. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–38.

47. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.

48. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000;343:1305–11.

49. Zigeuner R. Editorial comment on: lower plasma adiponectin levels are associated with larger tumor size and metastasis in clear-cell carcinoma of the kidney. Eur Urol. 2008;54:873–4.

50. Buschemeyer WC 3rd, Freedland SJ. Obesity and prostate cancer: epidemiology and clinical implications. Eur Urol. 2007;52:331–43.

51. Mistry T, Digby JE, Desai KM, Randeva HS. Obesity and prostate cancer: a role for adipokines. Eur Urol. 2007;52:46–53.

52. Ribeiro R, Monteiro C, Catalan V, Hu P, Cunha V, Rodriguez A, et al. Obesity and prostate cancer: gene expression signature of human periprostatic adipose tissue. BMC Med. 2012;10:108.

53. Pruthi RS, Swords K, Schultz H, Carson CC 3rd, Wallen EM. The impact of obesity on the diagnosis of prostate cancer using a modern extended biopsy scheme. J Urol. 2009;181:574–7 discussion 8.

54. Motamedinia P, Korets R, Spencer BA, Benson MC, McKiernan JM. Body mass index trends and role of obesity in predicting outcome after radical prostatectomy. Urology. 2008;72:1106–10.

55. Koebnick C, Michaud D, Moore SC, Park Y, Hollenbeck A, Ballard-Barbash R, et al. Body mass index, physical activity, and bladder cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev. 2008;17:1214–21.

56. Zhao H, Grossman HB, Spitz MR, Lerner SP, Zhang K, Wu X. Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. J Urol. 2003;169:714–7.

57. Hilmy M, Bartlett JM, Underwood MA, McMillan DC. The relationship between the systemic inflammatory response and survival in patients with transitional cell carcinoma of the urinary bladder. Br J Cancer. 2005;92:625–7.

58. Yang Y, Dong J, Sun K, Zhao L, Zhao F, Wang L, et al. Obesity and incidence of lung cancer: a meta-analysis. Int J Cancer. 2013;132:1162–9.

59. Zhao ZG, Guo XG, Ba CX, Wang W, Yang YY, Wang J, et al. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. J Int Med Res. 2012;40:2041–50.

60. Larsson SC, Wolk A. Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis. Int J Cancer. 2007;121:1564–70.

61. Wiedmann M, Brunborg C, Lindemann K, Johannesen TB, Vatten L, Helseth E, et al. Body mass index and the risk of meningioma, glioma and schwannoma in a large prospective cohort study (The HUNT Study). Br J Cancer. 2013;109:289–94.

62. Khan N, Afaq F, Mukhtar H. Lifestyle as risk factor for cancer: evidence from human studies. Cancer Lett. 2010;293:133–43.

63. Cleveland RJ, Eng SM, Abrahamson PE, Britton JA, Teitelbaum SL, Neugut AI, et al. Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:1803–11.

64. Thygesen LC, Gronbaek M, Johansen C, Fuchs CS, Willett WC, Giovannucci E. Prospective weight change and colon cancer risk in male US health professionals. Int J Cancer. 2008;123:1160–5.

65. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104:815–40.

66. Goodwin PJ, Segal RJ, Vallis M, Ligibel JA, Pond GR, Robidoux A, et al. Randomized trial of a telephone-based weight loss intervention in postmenopausal women with breast cancer receiving letrozole: the LISA trial. J Clin Oncol. 2014;32:2231–9.