J R Coll Physicians Edinb 2020; 50: 392–7 | doi: 10.4997/JRCPE.2020.408 REVIEW

Obesity and the Risk of Malignancy: An Evolving Saga

Sophie Wilcock[1], Nadim Haboubi[2]

Abstract

Worldwide, the prevalence of both obesity and cancer are rising. So far, there is an association between obesity and an increased risk of at least 20 different cancers and this number is increasing. The mechanism behind obesity increasing the risk of cancer varies. The importance of looking at all aspects of obesity, such as hip to waist ratio, body fat distribution and waist circumference, in addition to BMI has been acknowledged in order to further understand these mechanisms. The duration of time a person is obese for, and whether their weight gain was in childhood or adulthood can also affect risk of cancer, however this can be hard to distinguish as obese children and adolescents frequently remain obese into adulthood.

Keywords: Obesity, cancer, carcinoma, BMI, oncology, malignancy, fat

Financial and Competing Interests: No conflict of interests declared

Correspondence to:
Professor Nadim Haboubi
Department of Clinical Nutrition and Obesity
University of South Wales
Pontypridd
UK

Email:
nadim.haboubi@wales.nhs.uk

Introduction

The World Health Organisation (WHO) have recognised obesity, defined as a body mass index (BMI) ≥ 30kg/m^2, as a widespread epidemic and a disease within itself, which is chronic and progressive in nature with potential for relapse.[1,2] In 2016 an excess of 1.9 billion individuals aged 18 plus were overweight (with a BMI of ≥25kg/m^2), of which more than 650 million had a BMI ≥ 30kg/m^2. World-wide rates of obesity have increased almost three fold between 1975 and 2016.[2] If this trend is to continue, it is predicted that between 2016 and 2025, worldwide obesity levels will increase from 11% to 18% in men and from 15% to exceed 21% in women.[2,3]

Being overweight or obese and having an excess adiposity is known to increase the risk of many diseases, including several cancers. In the 'Father of Medicine', Hippocrates depicted cancer as a crab like structure, and highlighted the risks associated with excessive food consumption.[4] An observational UK based study which involved 3.6 million people, demonstrated that both cardiovascular disease and cancer are significant causes of mortality in those who are overweight or obese.[5] Additionally, obesity is one of the biggest preventable causes of cancer in the UK, second only to smoking.[6]

Adequate evidence has become available to support the association between excess body fat and the development of 14 different cancers.[7] These include, but are not limited to, some of the most common cancers, such as breast and colorectal, as well as some of those with the poorest prognoses, such as oesophageal and pancreatic.[7,8] Risk of other cancers (Table 1), including more recently advanced prostate cancer, have also been found to be increased with obesity.[9,10,11,12]

In this narrative review we have looked at current epidemiology for both obesity and cancer and we have appraised the current understanding of how obesity can increase the risk of certain cancers. In doing so, we have primarily focused on how body fat distribution and the duration and onset of obesity can possibly affect the cancer risk.

Search Strategy

We collated and compared the relevant literature for papers published in English between 1997 and 2020, searched using PubMed. Key words used in the search include, but are not limited to, 'cancer', 'obesity', 'oncology', 'BMI' and 'malignancy', whilst key terms included 'body fat distribution' and 'onset of obesity'. Some papers were identified from the reference lists of articles found in the initial search. No study was excluded, whilst studies with a long follow up time were favoured.

Incidence of Obesity and Cancer with Associated Mortality

Cancer in itself is one of the primary causes of death across the globe causing 9.56 million deaths worldwide in 2017, second only to cardiovascular diseases, which obesity also increases the risk of.[13] Published work identified that in the same year, obesity led to 4.7 million premature deaths.[14] Trends have shown that the number of obese and overweight

[1]4th year Medical Student, Cardiff University School of Medicine, Cardiff, UK; [2]Professor, Department of Clinical Nutrition and Obesity, University of South Wales, Pontypridd, UK

Table 1 Cancers linked with obesity

*Breast cancer (post-menopausal)	*Colon	*Oesophageal (adenocarcinoma)	*Thyroid	*Kidney (Renal cell carcinoma)
*Liver	*Rectum	*Pancreatic	*Gall bladder	*Multiple myeloma
*Gastric cardia	*Ovarian	*Endometrium	*Meningioma	Leukemia
Non-Hodgkin's lymphoma	Prostate	Cervical	Glioma	Malignant melanoma

*Those recognized by the International Agency for Research on Cancer (IARC)

adults in the world, and in the UK are increasing annually as are the number of individuals with cancer.[13,15]

The number of individuals dying from cancer worldwide is increasing. Approximately 5.7 million people worldwide died as a result of cancer in 1990 and by 2017 there had been almost a 68% increase, however this is not taking population expansion into account. When population growth is taken into account, there has still been a 17% increase in deaths due to cancer, which is shown as death rate (deaths per 100,000). When looking at the UK in isolation, from the 1.7 million deaths in 1990, there was a general reduction in death rates from cancer up until the year 2014, but there has been a steady increase since then.[13]

Extremes of BMI have been associated with an increase in overall mortality risk, which increases exponentially when BMI is greater than or equal to 30 kg/m^2. Furthermore, overweight and obese individuals who currently have cancer were found to have worse survival rates, and those who have had it previously, were found to have a greater risk of recurrence for multiple cancers including colorectal and breast.[3] Collectively, this highlights the rationale behind this literature review.

How Obesity Can Increase the Risk of Cancer – What we know so far

The relationship between obesity and cancer is not fully understood, whilst the exact mechanisms of carcinogenesis will vary between cancers, alluding to the complexities of the relationship.[3] In some cases, it is the direct effect of having excessive adipose tissue that will increase risk, as having more adipose tissue can enhance the metabolism of sex hormones. This is particularly relevant to hormone sensitive cancers, including those of the breast, endometrium and prostate.[3,16]

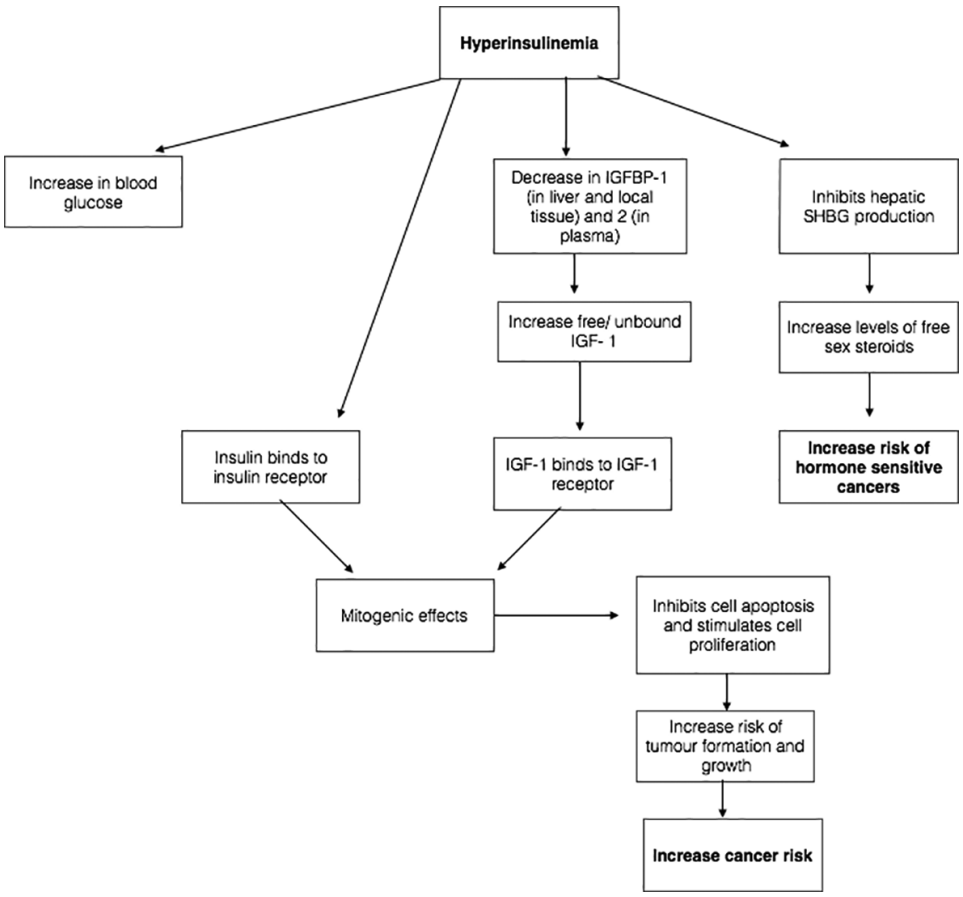

Figure 1 Hyperinsulinemia and cancer risk
IGFBP-1 = insulin like growth factor binding protein 1; IGF- 1 = insulin like growth factor 1; SHBG = sex hormone binding globulin

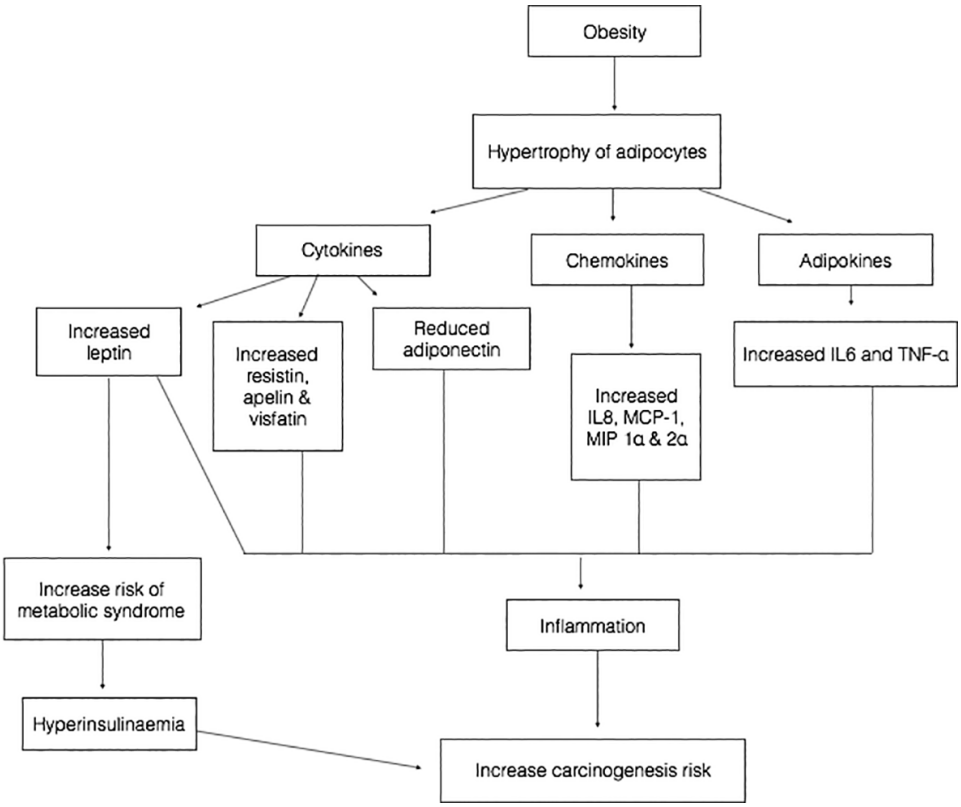

Figure 2 Biochemical pathways linking obesity to cancer
IL6 = interleukin 6; IL8 = interleukin 8; MCP-1 = monocyte chemoattractant protein -1; MIP 1α/ 2α = macrophage inflammatory protein 1 alpha/ 2 alpha; TNFα = tumour necrosis factor alpha

In other cases, the risk is increased secondary to the diseases that can result from obesity, such as type 2 diabetes mellitus (T2DM), which has been shown to increase the likelihood of certain cancers.[3,7] Aside from its role in energy metabolism, insulin has mitogenic properties meaning it can induce cell division.[17] This is apparent in obesity, when the number of pancreatic beta cells increases to produce more insulin to overcome insulin insensitivity (a consequence of obesity). This results in chronic hyperinsulinemia, the effects of which can be seen in Figure 1.

Colorectal cancer is amongst the top three causes of cancer deaths and evidence suggests hyperinsulinemia is a key mechanism for its development. Individuals who are obese have a 30% higher risk of developing colorectal cancer compared to those who's BMI is less than 30 kg/m^2. [18,19]

Genetics also play a role. The fat mass and obesity associated (FTO) gene plays a role in appetite control and whilst overexpression of this gene is linked with increased food uptake, there is evidence to suggest there is a high risk variant of this gene that increases risk of obesity, but the gene has also been linked directly to breast, endometrial, pancreatic and colon cancer.[20,21]

Human melanocortin 4 receptor (MC4R) is involved in appetite control and the mutation of the gene has been associated with obesity, including up to 6% of cases of severe early onset obesity.[22,23] A large evaluation study looking at obesity related genes showed that MC4R has been linked with a greater chance of developing colorectal cancer.[21]

Leptin, visfatin, adiponectin and resistin are adipokines released from adipocytes.[24] Biochemical pathways resulting from excess adiposity has been postulated as another mechanism which relates cancer to obesity. In obese individuals, the levels of pro-inflammatory adipokines are elevated, whilst the levels of anti-inflammatory adipokines are reduced. In addition, there are altered levels of chemokines and cytokines.[24,25] Collectively this resultant inflammatory environment promotes carcinogenesis as shown in Figure 2.

Some of the physical medical problems that result from obesity can also raise the likelihood of cancer. Gastro-oesophageal reflux disease (GORD) is more prevalent in obese individuals. Erosive oesophagitis as well as Barrett's oesophagus (BO) could complicate GORD and increase the risk of adenocarcinoma of the oesophagus.[8]

Oesophageal adenocarcinoma that results from BO is considered a male predominant disease, with males at least four times more likely than their female counterparts to develop it.[26] Oestrogen receptors have been demonstrated in Barrett's mucosa, with certain subtypes deemed more protective than others.[27,28] Furthermore, studies involving animals have shown estradiol can have a protective role in rodents with oesophageal tumours.[29] Whilst the mechanism of protection is still not yet known, larger epidemiological studies have also demonstrated a potential protective effect in women taking long term hormone replacement therapy.[30]

Obesity related hypertension can influence the development of renal cancer, whilst low levels of iodine have been linked with increasing the likelihood of follicular thyroid cancer,

possibly due to increased thyroid stimulating hormone (TSH) levels, which are also commonly found in obese individuals.[31,32,33] In contrast, high iodine levels have been linked with higher levels of papillary thyroid cancer and hence the pathophysiology of obesity in thyroid cancer is complex and not yet fully understood.[34]

Bacteria has been reported to promote inflammation and cancer cell proliferation via cytokine production. The interaction between helicobacter pylori and interleukin 22 has been shown to promote tumour genesis in gastric cancer.[35]

While the risk between obesity and colorectal cancer has been well established, one proposed mechanism is alterations in the gut microbiome. Certain gut microbes such as streptococcus spp, bacteroides spp, escherichia coli, fusobacterium nucleatum and enterococcus faecalis which all have pro-oncogene components have been implicated.[36]

Body Fat Distribution in Obesity and Cancer

Whilst overall body fat is relevant to obesity, the distribution of it is equally important. Visceral fat/ adiposity, also known as central adiposity, has a greater link with adverse health than the fat which is distributed further away from vital organs, around the hips, thighs and buttocks, known as subcutaneous fat.[37]

Mendelian randomisation to analyse the relationship between adiposity and cancer was studied. Variables such as single nucleotide polymorphism associated with BMI, waist to hip ration (WHR) and birth weight were used. This has shown a strong causal relationship between obesity and colorectal cancer.[38]

Once women have gone through the menopause, distribution of body fat changes, increasing visceral adipose deposition, which is not reflected in BMI.[39,40]

A significant relationship has been identified which links a high visceral obesity with an increased risk of cancer of the gastrointestinal tract, female genital organs and lung, independent of smoking. The same study which recruited a large number of postmenopausal women noted a significant association between breast cancer and BMI, but fail to show a significant relationship with central obesity.[16] Furthermore, it was noted that obesity may be linked to some cancers independent of BMI. Gold standard measures such as dual energy X-ray absorptiometry (DXA) scanning should be used to determine the distribution of lean and fat masses throughout the body and would be more appropriate if available.[16]

Similarly, another study that looked at the size of individuals throughout life and endometrial cancer risk, identified a weakness in using BMI as a single marker for obesity. It recognised the importance of looking at other measurements, including waist circumference and WHR, in conjunction with BMI to identify links between obesity and lifetime cancer risk, which are also cheaper and more readily available than DXA scanning.[41]

Visceral fat was found to be associated with a higher risk of advanced prostate cancer in men with a BMI greater than 27, in a prospective male only study.[9] This further supports the importance of visceral fat independent of BMI. In this study, CT scanning was used to measure the distribution of body fat. According to Hills criteria the study provides sufficient evidence for a causal relationship.[42] The study recognised the importance of looking at body fat distribution, identifying that as men get older, muscle mass is lost and body fat is redistributed towards the visceral compartments. BMI therefore becomes a less reliable indicator in this age group than men of a younger age.[9] It also noted that body fat distribution could potentially be an indicator for some of the metabolic, hormonal and inflammatory changes linked with obesity that could have an integral role in prostate cancer development. In keeping with this, an increase in visceral fat has been associated with a lower level of free testosterone and has a stronger link to insulin resistance and proinflammatory cytokines than subcutaneous fat.[9]

Duration and Onset of Obesity and Cancer Risk

There are few studies so far which have investigated the timing and duration of weight gain and the consequent effects, or whether the vulnerability to cancer from obesity depends upon specific time periods in life.

A large longitudinal study which monitored 221,274 individuals over a mean of 17.6 years investigated BMI, weight and cancer risk associated with obesity. The study showed significant associations for men only, where the longer they were obese, the more likely they were to develop cancer.[43]

In support of this, Staunstrup et al concluded that the longer an individual was obese or overweight, the greater the risk of developing cancer. The severity of an individual's weight in adulthood also seemed to have a strong influence on the likelihood of cancer. This was significant for endometrial cancer, where cancer risk increases by 17% for every ten year period of being overweight in adulthood. This was the first study to investigate the impact of the duration of obesity has on the risk of developing cancer in a large population of postmenopausal women.[16] The link between obesity and endometrial cancer has been suspected for some time, with Robert Thomas hypothesising a link as early as 1811.[44]

The period in life in which an individual is overweight or obese is important, with the International Agency for Research on Cancer (IARC) acknowledging the increasing findings that those who are obese in childhood are more likely to develop at least one of several different cancers in adulthood.[7] It is also acknowledged that children and adolescents frequently remain obese into adulthood.[45]

The study investigating 'BMI and weight, and the risk of obesity related cancers' also identified individuals whose BMI was 25-29.9kg/m^2 before they reached 40 years of age, were at a 15% greater risk of developing an obesity related cancer (Table 1). The greatest risks were found to be for endometrial cancer, and in men, renal cell carcinoma and colon cancer. This paper finds a consistent association between both duration and onset of obesity, particularly to endometrial cancer.[43]

Morbidly obese patients who have undergone bariatric surgery have a reduced cancer incidence associated with sustained weight loss with reproducible results.[46,47] A meta analysis study using the data for over 600,000 individuals concluded that bariatric surgery reduced the overall likelihood of developing obesity related cancers, particularly breast cancer. Bariatric surgery has so far been found to be the most effective way to achieve and sustain a lower BMI in obese patients.[47]

There are two types of bariatric surgery for super or morbidly obese patients (those with a BMI ≥ to 40kg/m^2), or those with a BMI of 35-39.9kg/m^2 with a significant disease such as T2DM.[48,49] Despite their efficacy in reducing the risk of obesity related cancers, they each have an infrequent association with certain gastrointestinal cancers.

Restrictive surgery, also referred to as a sleeve gastrectomy, is highly effective for weight loss, however in very few cases it may increase the risk of oesophageal adenocarcinoma. Although weight loss can improve reflux symptoms in the majority, for some these symptoms may worsen with restrictive surgery.[50] GORD is a precursor to BO and consequently, increasing the frequency of reflux will increase risk of BO, which can progress to oesophageal adenocarcinoma. Preoperative endoscopy may help to identify signs and severity of GORD or BO to detect those who may be better suited for an alternative surgical method.[50,51]

The other surgical option is gastric bypass surgery. Although very rare, there have been a few case reports of cancer developing in the remnants of the stomach located mainly in the antrum/prepyloric region.[52]

Conclusion

The association between obesity and risk of cancer is complex with multiple proposed mechanisms. Most of the research has focused on hormone sensitive cancers. Duration and onset of obesity, along with distribution of body fat are important in the link between obesity and cancer. There is limited information regarding the impact of weight loss on cancer risk due to limited success in achieving weight loss using lifestyle modifications only. Studies have shown that bariatric surgery can reduce cancer risk in obese individuals who have sustained a healthier weight. Nevertheless, more research is required before definite conclusions can be drawn.

References

1 James W. WHO recognition of the global obesity epidemic. *International Journal of Obesity*. 2008; 32:120-126
2 World Health Organisation. Obesity and overweight. 2020. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed 17 March 2020]
3 Kyrou I, Randeva HS, Tsigos C, Kaltsas G, Weickert MO. Clinical problems caused by obesity. South Dartmouth (MA). *Endotext*. 2018. Found at www.ncbi.nlm.nih.gov/sites/books/NBK278973/ [Accessed 17 March 2020]
4 Hippocrates of Kos. http://www.platos-academy.com/archives/hippocrates.html. [Accessed 17 March 2020]
5 Bhaskaran K, dos-Santos-Silva I, Leon D, et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *The Lancet Diabetes & Endocrinology*. 2018; 6:944-953
6 Cancer research UK. Does obesity cause cancer? 2018. https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/obesity-weight-and-cancer/does-obesity-cause-cancer#Obesityrefs0 [Accessed 22 March 2020]
7 Lauby-Secretan B, Scoccianti C, Loomis D et al. Body fatness and cancer – viewpoint of the IARC working group. *New England Journal of Medicine*. 2016; 375:794-798
8 Braghetto I, Korn O, Csendes A et al. Laparoscopic treatment of obese patients with gastroesophageal reflux disease and Barrett's esophagus: a prospective study. *Obesity Surgery*. 2012;22:764-772
9 Dickerman B, Torfadottir J, Valdimarsdottir U et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES- Reykjavik study. *Cancer*. 2019; 125:2877-2885
10 Larsson SC, Wolk A. Obesity and risk of non-Hodgkin's lymphoma: A meta analysis. *International Journal of Cancer*. 2007; 121:1564-1570
11 Benson V, Pirie K, Green J, et al. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *British Journal of Cancer*. 2008; 99: 185- 190
12 Maruthur N, Bolen S, Brancati F, et al. The association of obesity and cervical cancer screening: a systematic review and meta-analysis. *Obesity*. 2009; 17:375-381
13 Roser M, Ritchie H. Cancer. Our World in Data. 2020. https://ourworldindata.org/cancer [Accessed 27 March 2020]
14 GBD 2017 Risk Factor Collaborators. Global, regional and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. *The Lancet*. 2018; 392:1923-1994
15 Ritchie H, Roser M. Obesity. Our World in Data. 2020. https://ourworldindata.org/obesity [Accessed 27 March 2020]
16 Staunstrup L, Nielsen H, Pedersen B et al. Cancer risk in relation to body fat distribution, evaluated by DXA-scans, in postmenopausal women – the Prospective Epidemiological Risk Factor (PERF) study. *Scientific Reports*. 2019;9: 5379
17 Ish-Shalom D, Christoffersen CT, Vorwerk P et al. Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. *Diabetologia*. 1997; 40:25-31
18 Frezza E, Wachtel M, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. *Gut*. 2006; 55:285-291

19 Liu J, Druta M, Shibata D et al. Metabolic syndrome and colorectal cancer: Is hyperinsulinemia/insulin receptor-mediated angiogenesis a critical process? *Journal of Geriatric Oncology*. 2014; 5:40-48
20 Chen J, Yang J, Zhoa KN. FTO gene, obesity and colon cancer: from epidemiological evidence to laboratory studies. *Translational Gastrointestinal Cancer*. 2013; 2:194-203
21 Yang B, Thrift A, Figueiredo K et al. Common variants in the obesity-associated genes FTO and MC4R are not associated with risk of colorectal cancer. *Cancer Epidemiology*. 2016; 44:1-4
22 Adan RA, Tiesjema B, Hillebrand JJ et al. The MC4 receptor and control of appetite. *British Journal of Pharmacology*. 2006;149:815-827
23 Doulla M, McIntyre A, Hegele R, et al. A novel MC4R mutation associated with childhood-onset obesity: a case report. *Paediatrics & Child Health*. 2014;19:515-518
24 Paz-Filho G, Lim E, Wong M, et al. Associations between adipokines and obesity related cancer. *Frontiers in Bioscience*. 2011; 16:1634-1650
25 Pischon T, Nimptsch K. Obesity and risk of cancer: an introductory overview. *Obesity and Cancer*. 2016; 208:1-15
26 Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence and the extent of columnar epithelium. *Gastroenterology*. 1999;116:277-285
27 Liu L, Chirala M, Younes M. Expression of estrogen receptor-beta isoforms in Barrett's metaplasia, dysplasia and esophageal adenocarcinoma. *Anticancer Res*. 2004;24(5A):2919 2924
28 Rashid F, Khan RN, Iftikhar SY. Probing the link between oestrogen receptors and oesophageal cancer. *World J Surg Oncol*. 2010;8:9
29 Ueo H, Matsuoka H, Sugimachi K, et al. Inhibitory effects of estrogen on the growth of a human esophageal carcinoma cell line. *Cancer Res*. 1990;50(22):7212 7215
30 Menon S, Nightingale P, Trudgill N. Is hormone replacement therapy in post-menopausal women associated with a reduced risk of oesophageal cancer? *United European Gastroenterol J*. 2014;2(5):374 382
31 Sanfilippo K, McTigue K, Fidler C et al. Hypertension and obesity and the risk of kidney cancer in 2 large cohorts of US men and women. *Hypertension*. 2014;63:934-941
32 Franceschi S. Iodine intake and thyroid carcinoma - a potential risk factor. *Experimental and Clinical Endocrinology & Diabetes*. 2009;106:38-44
33 Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: an intriguing link. *Indian Journal of Endocrinology and Metabolism*. 2016;20:554
34 Dong L, Lu J, Zhao B, et al. Review of the possible association between thyroid and breast carcinoma. *World Journal of Surgical Oncology*. 2018;16:130
35 McCracken KW, Cata EM, Crawford CM et al. Modelling human development and disease in pluripotent stem-cell derived gastric organoids. *Nature* 2014;516:400-4
36 Alexander GL, Scott AJ, Pouncey AL, et al. Colorectal carcinogenesis: an archetype of gut microbiota-host interaction. *Ecancermedicalscience*.2018;12:865
37 Kaess B, Pedley A, Massaro J et al. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia*. 2012;55:2622-2630
38 Jarvis D, Mitchell J, Law P et al. Mendelian randomisation analysis strongly implicates adiposity with risk of developing colorectal cancer. *British Journal of Cancer*. 2016;115:266-272
39 Song M, Hu F, Spiegelman D et al. Long-term status and change of body fat distribution, and risk of colorectal cancer: a prospective cohort study. *International Journal of Epidemiology*. 2015;45:871-883
40 Valencak T, Osterrieder A, Schulz T. Sex matters: The effects of biological sex on adipose tissue biology and energy metabolism. *Redox Biology*. 2017;12:806-813
41 Horn-Ross PL, Canchola A, Bernstein L et al. Body size over the life-course and the risk of endometrial cancer: the California Teachers Study. *Cancer Causes & Control*. 2016;27:1419-1428
42 Morabia A. On the Origin of Hill's Causal Criteria. *Epidemiology*. 1991;2:367-369
43 Bjørge T, Häggström C, Ghaderi S et al. BMI and weight changes and risk of obesity-related cancers: a pooled European cohort study. *International Journal of Epidemiology*. 2019;48:1872-1885
44 Thomas R. *The Modern Practice of Physic*. New York: Collins & Co. 1811
45 Weihrauch-Blüher S, Schwarz P, Klusmann J. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism*. 2019;92:147-152
46 Zhang K, Luo Y, Dai H, et al. Effects of bariatric surgery on cancer risk: evidence from meta-analysis. *Obesity Surgery*. 2019;30:1265-1272
47 Wiggins T, Antonowicz SS, Sheraz R Markar SR. Cancer risk following bariatric surgery – systematic review and meta-analysis of national population-based cohort studies. *Obesity Surgery.* 2019;29:1031-1039
48 NICE. Obesity treatment summary. 2020. Available from: https://bnf.nice.org.uk/treatment-summary/obesity.html [accessed 23 May 2020]
49 Cutolo P, Nosso G, Vitolo G et al. Clinical Efficacy of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Gastric Bypass in Obese Type 2 Diabetic Patients: a Retrospective Comparison. *Obesity Surgery*. 2012;22:1535-1539
50 El Khoury L, Benvenga R, Romero R et al. Esophageal adenocarcinoma in Barrett's esophagus after sleeve gastrectomy: Case report and literature review. *International Journal of Surgery Case Reports*. 2018;52:132-136
51 Sebastianelli L, Benois M, Vanbiervliet G et al. Systematic Endoscopy 5 Years After Sleeve Gastrectomy Results in a High Rate of Barrett's Esophagus: Results of a Multicenter Study. *Obesity Surgery*. 2019;29:1462-1469
52 Tornese S, Aiolfi A, Bonitta G et al. Remnant Gastric Cancer After Roux-en-Y Gastric Bypass: Narrative Review of the Literature. *Obesity Surgery*. 2019;29:2609-2613