Clinical Journal of Gastroenterology (2019) 12:285–291
https://doi.org/10.1007/s12328-019-00953-3

CLINICAL REVIEW

Pancreatic cancer and obesity: epidemiology, mechanism, and preventive strategies

Prashanth Rawla[1] · Krishna Chaitanya Thandra[2] · Tagore Sunkara[3]

Received: 21 January 2019 / Accepted: 14 February 2019 / Published online: 20 February 2019

Abstract
The prevalence of obesity has seen a global increase in the past decades, escalating to one of the major epidemiological challenges today. Global economic growth has caused changes in dietary and physical activity patterns fueling obesity across age, gender, and income groups. The implications are many, as obesity has been associated with numerous serious health conditions, ultimately affecting morbidity and mortality. There is a growing recognition of the risk a high body mass index confers on the development and outcome of several malignancies, including pancreatic cancer. Pancreatic cancer is a highly lethal disease with exceptionally poor outcome, with incidences rising worldwide. Due to vague symptoms and no screening recommendations, a vast majority of patients are diagnosed at late stages, with already advanced disease and no opportunity for surgical intervention. Obesity mediates risk for pancreatic cancer through insufficiently understood mechanisms, possibly including inflammation and hormonal misbalance. As excess abdominal adiposity is among the few modifiable risk factors for pancreatic cancer onset, enduring weight loss could manifest an effective preventive measure. Lifestyle modifications on a population level aimed to reduce obesity could also scale down the grim pancreatic cancer rates. In cases when these measures alone are insufficiently effective, bariatric surgery can be an advantageous alternative. Extremely obese patients exhibit many health benefits following bariatric surgery along with weight loss, consequently reducing the chances of pancreatic cancer, especially if additionally adopting healthy lifestyle habits.

Keywords Obesity · Pancreatic cancer · Epidemiology · Weight loss · Bariatric surgery

Introduction

Obesity and pancreatic cancer are posing a considerable health burden across the globe, with alarming incidences that show no sign of dropping. As obesity results from an imbalance between calorie consumption and expenditure, while pancreatic cancer arises from malignant transformation of pancreatic cells, the link between the two was long overlooked, and they were viewed as unrelated medical conditions. However, new emerging evidence is bringing together a different picture. Chronic obesity has far-reaching consequences depicted in its many comorbidities, pancreatic cancer probably being the most lethal one. Evidence integrated from different fields, including prospective epidemiological studies, animal models and pre-clinical studies reveal a close relationship between obesity and pancreatic cancer, making it apparent that a trans-disciplinary approach is a key to comprehend this link. It is crucial to understand the biological and non-biological factors standing behind the rising incidences of these conditions to enable healthcare providers to implement more effective preventive strategies. Therefore this review was aimed to shed light on the interconnection between obesity and pancreatic cancer on a population scale, but also the physiological mechanisms by which obesity supports pancreatic cancer advancement. We also consider the possibility that weight loss, either through lifestyle modifications or bariatric surgery, could be the most sensible approach for pancreatic cancer prevention in the obese population at risk.

✉ Prashanth Rawla
rawlap@gmail.com

[1] Department of Internal Medicine/Hospitalist, SOVAH Health, 320 Hospital Dr, Martinsville, VA 24115, USA

[2] Department of Pulmonary and Critical Care Medicine, Sentara Virginia Beach General Hospital, Virginia Beach, VA, USA

[3] Division of Gastroenterology and Hepatology, Mercy Medical Center, Des Moines, IA 50314, USA

Epidemiology of obesity

Obesity is a metabolic syndrome that poses a major contemporary clinical and healthcare challenge. It is a complex and multifactorial condition arising from an interplay between genetic, epigenetic, and environmental factors epitomized by the accumulation of excess adipose tissue. Obesity is highly heritable, and it varies by age, sex, and race-ethnicity [1]. The rapid economic development of the modern world accompanied by urbanization has resulted in profound lifestyle changes, both in nutrition and physical activity levels, which have led obesity to be considered a worldwide epidemic. It is a forerunner and a major risk factor for a wide range of pathological conditions including type 2 diabetes, cardiovascular disease, and depression, but is also associated with increased risk of several malignancies [2]. It is estimated that between 4% and 7% of all diagnosed cancers are attributable to obesity [3].

The most commonly used criterion for determining obesity is the body mass index (BMI). BMI is calculated as the ratio between the person's weight, expressed in kilograms, and height, expressed in square meters. According to the World Health Organization, a BMI of or 30 kg/m^2 or greater is defined as obesity.

Available data from the World Health Organization indicate that in 2016 39% of adults aged 18 years and over were overweight and 13% obese [4]. Current trends predict that by 2030 nearly 40% of the world's adult population will be overweight and about 20% obese [5]. Estimates of obesity in the Western world indicate a rising trend since the middle of the twentieth century, with significant differences between racial, ethnic, and socioeconomic groups. Data from America indicate a prevalence of obesity of about 35% with a somewhat higher rate between Hispanics (43%) and African Americans (48%) [2]. Europe displays more modest statistics of about 17%, with higher rates in southern regions like Spain and Italy, but also Eastern Europe [6]. These variations could be traced to disproportional genetic susceptibility between ethnicities or local populations, but socioeconomic disparities may also play a prominent role. Nations going through economic transitions and/or with a lower average income are in general exposed to inexpensive low-quality food with high-calorie content additionally influencing obesity risk. Gender is also an independent risk factor, as women develop significantly higher BMI than men [7]. It also appears that women are inclined to develop obesity later in life [8]. Data from regions outside of the US and Europe are limited. A study from China demonstrated that in a period between 1993 and 2009 obesity saw a steady rise, doubling in women and almost quadrupling in men [9]. Data acquired by the International Obesity Task Force show rising trends also in Central and South America, as well as sub-Saharan Africa [10]. In sum, the past decades of research have provided evidence that the prevalence of obesity rises over time in most countries with very few exceptions. According to the Global Database on BMI, trends of obesity saw a decline only in Denmark and Saudi Arabia in men, and Denmark, Ireland, Saudi Arabia, and Finland in women [11].

Epidemiology of pancreatic cancer

Pancreatic cancer has an extremely poor prognosis and survival rate. The estimated 5-year survival rate ranges between 2 and 9% [12, 13]. The Global Cancer Observatory (GLOBOCAN) reports indicate a similar number of cases and deaths caused by pancreatic cancer in 2018, making it one of the most lethal malignancies in the world [14]. It is the seventh leading cause of cancer death in both males and females. The highest rates are reported in the US, Europe, and Australia, while the lowest are in Middle Africa and South–Central Asia. It is the 4th lethal cause of cancer death in America and the 6th in Europe [15]. The incidence is higher in blacks than whites and slightly higher in men than women [15]. The most important risk factor that repeatedly comes up in all epidemiological studies is a history of smoking as it increases the risk of pancreatic cancer by 75% [16]. Other predisposing factors include positive family history, diabetes, pancreatitis, obesity, alcohol abuse, and inactivity [12, 17, 18]. Based on trends from European Union pancreatic cancer is anticipated to supersede breast cancer as the third lead cause of cancer death, given that breast cancer rate will continue to decline [19]. The incidence rates increase with age, with almost 90% of affected diagnosed after the age of 55 [20]. Although surgical resection significantly improves prognosis, most pancreatic cancer patients are diagnosed at late stages of disease with local advancement disease or metastatic spreading and only a small portion of patients is considered to be surgical candidates. Only about 20% of patients are presented with localized disease at diagnosis [21].

Epidemiology of obesity associated with pancreatic cancer

It has long been recognized that obesity-related conditions increase the risk of several malignancies including pancreatic cancer. As mentioned earlier, obesity along with smoking is one of the very few modifiable risk factors that increase the likelihood of developing pancreatic cancer. There is a wealth of literature including pooled and meta-analyses that well document this link [22–27]. A recent study used Mendelian randomization analysis on data obtained from genome-wide association studies to assess the

significance of a range of metabolic factors on pancreatic cancer risk. The analysis singled out only BMI and fasting insulin levels, but not type 2 diabetes or dyslipidemia to be causally associated with an increased risk of pancreatic cancer [28]. In 2011, a study was conducted by Parkin et al. [29] which assessed that around 12% of all pancreatic cancers could be attributed to elevated body mass index. Another cohort study estimated that women with a BMI > 27.5 had a 20–37% higher risk of acquiring this condition [30]. In a joint analysis conducted by London Imperial College and the University of Leads similar prediction was made for both men and women emphasizing an even higher risk for persons with a BMI over 35 [31]. The American Cancer Society also associated the increased BMI with mortality from the cancer of the pancreas in both men and woman. Obese participants also had, on average, an earlier onset of the disease as well as worse survival rates [32].

It is worthy to note that several studies underlined the importance of the location of the excess adipose tissue. It appears that persons who carry the majority of fatty tissue in the abdominal region are 70% more likely to develop pancreatic cancer compared to those who bear it around the hips [33]. It is estimated that a 10 cm increase in waist circumference enhances the pancreatic cancer risk by about 11%. Two independent studies assessed the impact of central adiposity on pancreatic cancer development. They concluded that hip circumference and waist circumference alone were not associated with pancreatic cancer risk. However, a high waist-to-hip ratio was correlated with a 20–30% increased risk [22, 23]. Finally, results of a pooled analysis conducted on 1,564,218 participants demonstrated that high waist circumference and high waist-to-hip ratio correlate with increased pancreatic ductal adenocarcinoma (PDAC) mortality regardless of BMI [22]. This association was even stronger if the onset of obesity was acquired relatively early, between the ages of 18 and 21. These findings highlight the prominent role of visceral fat in the disease process [34].

That said, it is worthy to look back on the current epidemiological status of central adiposity per se. A recent study evaluated the prevalence of central adiposity in five high-income and five low-income countries in men and woman separately. The results showed a higher prevalence of central adiposity in low-income countries, reaching as much as 74% in Mexico and 68.9% in South Asia, while high-income countries like the US demonstrated a lower prevalence of 54%, Canada 35%, and Germany 33.9%. Data also indicated a higher prevalence in women than men regardless of income [35].

Mechanism of obesity and pancreatic cancer

Molecular mechanisms and signaling pathways contributing to clinical events that lead to pancreatic cancer are poorly understood, but it seems likely that multiple biological processes may be involved (Fig. 1) [36].

One explanation argues that the expansion of adipose tissue causes the accumulation of connective tissue, or desmoplasia which in turn promotes the survival and movement of malignant cells [37]. The desmoplasia is composed of extracellular matrix proteins, pancreatic stellate cells, and immune cells, making it a metabolically active tissue that secretes an abundance of cytokines and growth factors and promotes cancer growth. Desmoplasia causes changes in overall tissue structure, along with accompanying interstitial fluid pressure, thereby also contributing to chemoresistance. The role of desmoplasia in pancreatic cancer is still a matter of ongoing research. However, data suggest that obesity plays an important part. For example, a study on patients suffering from pancreatic ductal carcinoma (PDAC) revealed elevated desmoplasia only in obese patients. A comprehensive study conducted by Incio et al., encompassed both mouse models and human subjects to effectively demonstrate the mechanism by which obesity impacts PDAC through desmoplasia aggregation. The authors argue that adipocyte-induced inflammation activates pancreatic stellate cells and tumor-associated neutrophils causing desmoplasia formation. Desmoplasia mechanically compresses local blood vessels impairing drug delivery, inducing local hypoxia and promoting tumor advancement [37].

Another proposed mechanism underpinning the role of obesity on pancreatic cancer progression implicates the overproduction of circulating insulin by obese individuals [38]. Hyperinsulinemia causes a rise in insulin growth factor (IGF)-1 which, after binding with its receptor, or the insulin-like growth factor receptor (IGFR), activates the mTOR, PI3K, and MAPK pathways. These are well-known pathways in cancer biology that promote cell proliferation and angiogenesis and inhibit apoptosis, thus fueling cancer growth. Many studies have repeatedly associated pancreatic cancer risk with markers of elevated glucose levels.

Increased food consumption by obese individuals often combined with poor dietary habits also increment the consumer's exposure to carcinogens. Although the published studies have been somewhat inconsistent, a meta-analysis encompassing 11 studies recognized an association between pancreatic cancer incidence and processed meat consumption, meat fried or grilled at high temperatures and preserved food [39]. Nitrites are commonly used additives in most processed meat products that have been positively associated with risk of pancreatic cancer in both men and women. Processed meat may also contain other potent carcinogens like N-nitroso compounds [40]. An animal model study conducted by Risch et al. demonstrated the effect of these compounds on pancreatic cancer formation [41].

Apart from adipocytes, the adipose tissue consists of a myriad of different metabolically active cell types like

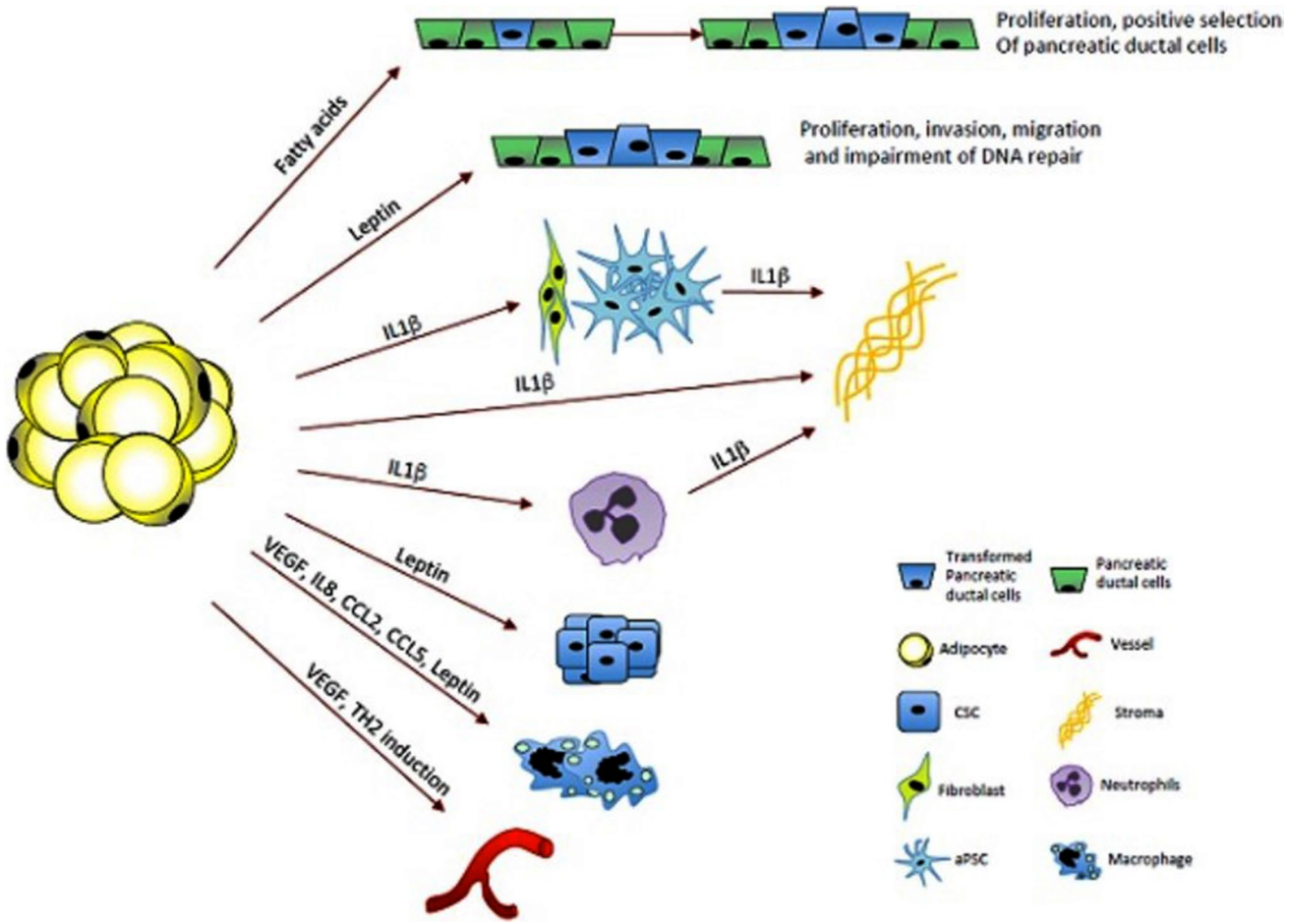

Fig. 1 Molecular mechanisms linking obesity to pancreatic cancer initiation and progression (Reproduced with permission from [36])

immune cells, fibroblasts, endothelial cells, and stem/progenitor cells. The production of adipokines like leptin and cytokines like TNF-alpha and interleukin-6 by the adipose tissue may also play a role in susceptibility to pancreatic cancer [42]. Obese individuals express ten times higher leptin levels, which activate the Notch pathway signaling many tumors, including PDAC [43]. The disturbance of balance between these finely tuned pro-inflammatory and anti-inflammatory biologically active molecules cause modifications in tissue microenvironment which in turn exhibit their effects on cell proliferation, apoptosis, cell invasion, and angiogenesis.

Obesity also induces local hypoxia which causes the overexpression of vascular endothelial growth factor (VEGF). Persons with high BMI are reported to display higher levels of VEGF [44]. Although published data are not entirely consistent, as an angiogenic factor, increased VEGF levels could play a role in tumor progression and growth.

Further evidence on the aftermaths of obesity comes from a mouse model of pancreatic cancer. When fed with normal chow, only 10% of mice developed pancreatic neoplasia, while when these mice were placed on a high-fat, high-calorie diet and became obese, about 45% of ductal cells developed neoplastic transformations [45].

Apart from the impact obesity displays on pancreatic cancer development, it has also been shown that excess body weight was correlated with reduced responses to chemotherapy in patients suffering from PDAC. However, the link between obesity and pancreatic cancer is further complicated as the manifestation of previously described pathways is highly dependent on the individual genetic background and exposure to various environmental factors.

Bariatric surgery effect on pancreatic cancer

There are only a handful of reports and case studies elaborating on the effects of physical activity on pancreatic cancer management. Most authors report positive effects of orderly exercise attributing them mostly to neovascularization rather than weight loss [46, 47]. An ongoing randomized control trial named PancFit currently recruits 128 participants to address this question more thoroughly.

However, due to harsh symptoms, most pancreatic cancer patients find it difficult to tolerate a regular exercise schedule. As weight loss can be difficult to achieve and maintain for these patients during their medical treatment, bariatric surgery may prove to be a more effective approach [48].

Bariatric surgery includes a number of surgical procedures that facilitate enduring weight loss in severely obese patients when exercise and diet fail to produce satisfying effects. Forms of bariatric surgery reported substantial weight loss even after a 20-year follow-up [49]. A study conducted in Sweden recruited more than 4000 obese patients, 2010 of them subjected to bariatric surgery, and 2036 controls. After a 10-year follow-up, the bariatric surgery group was associated with a 40% lower incidence of malignancies associated with obesity compared to the control group [50]. A similar study was carried out in Utah, with nearly 8000 gastric bypass surgery patients and a comparable number of controls. After a follow-up period of 7 years, researchers reported a 60% reduction in cancer mortality in the bariatric surgery cohort [51]. These promising results suggest that pancreatic patients may also benefit from bariatric surgery.

A study from Canada reported that 0.1% of surgery patients developed pancreatic cancer, compared to 0.33% in the control group [52]. A study from 2016 on patients suffering from severe obesity (BMI > 40 kg/m^2) showed a significantly lower risk of PDAC in patients who underwent bariatric surgery compared to the control group [53]. In addition to this, patients who underwent bariatric surgery also have many health benefits like reduction of tissue inflammation and insulin resistance, a decrease of inflammatory markers like C-reactive protein and interleukin-6. However, apart from these advantages, the effect of bariatric surgery on pancreatic cancer risk is a matter of debate. Possibly due to limited sample sizes and short follow-up periods, a number of published retrospective studies failed to provide evidence that bariatric surgery decreases pancreatic cancer risk. At present, credible studies establishing the effects of bariatric surgery on pancreatic cancer prevention or outcome are still lacking. Prospective multicenter studies with a large number of patients and long-term follow-ups should be undertaken in future to obtain more convincing results.

Meanwhile, the effectiveness of bariatric surgery can be evaluated using animal pancreatic cancer models. A recent study by He et al. [54] demonstrated that gastric bypass surgery prevents the occurrence of pancreatic cell acinar carcinoma in mice genetically engineered to recapitulate human pancreatic neoplasia. An earlier study on a Goto-Kakizaki rat model reported antidiabetic effects of gastric bypass surgery, but also signs of improved pancreatic functions like β-cell functional recovery [55].

Conclusion

Pancreatic cancer is an exceptionally aggressive malignancy portrayed by very poor prognosis and low survival rates. Although the incidence varies across regions and ethnicities, it typically affects the elderly population of developed countries. Due to vague symptoms and no current screening recommendations, the illness is usually diagnosed at late stages, when surgical removal is no longer an option. Low responsiveness to radiotherapy and chemotherapy additionally afflicts treatment and outcome. Therefore, there is a critical need to pinpoint the causes of susceptibility to pancreatic cancer and to concentrate future efforts on finding adequate preventive strategies.

Available epidemiologic studies have revealed many potential predisposing factors to pancreatic cancer. A smaller portion of affected subjects report a positive family history or bear an underlying germline disorder. The majority of patients, however, disclose unfavorable lifestyle habits. Smoking, poor diet and lack of physical activity, along with their chronic aftermaths like obesity and diabetes enhance the chances of pancreatic cancer development. Obesity is of particular interest, as it is a principally preventable trait, yet it affects a significant portion of the world's population today. The global upward trend it has seen in the past decades can be attributed to lifestyle changes that accompany rapid industrialization and economic growth. The contemporary way of life, portrayed by increased consumption of processed food and insufficient physical activity, both during working hours and leisure time, skyrocketed obesity into a global epidemic.

This opens up the possibility that lifestyle interventions could reduce pancreatic cancer risk. A diet low in saturated fat and sugars along with regular exercise on a population scale could be a useful prevention strategy that would ultimately scale down pancreatic cancer incidence. A strong confirmation for this proposition comes from a study on more than 48,000 postmenopausal women that were randomly selected to be placed on a low-fat diet or maintain their previous dietary routine. Over the course of 7 years, a low-fat dietary intervention significantly reduced pancreatic cancer incidence [56]. What remains uncertain is to what extent could weight loss influence the course of the disease after the diagnosis of illness had been made.

The clinical utility of bariatric surgery in pancreatic cancer management is also an open question. Available data clearly show a multitude of health benefits for bariatric surgery patients, including reduced levels of most markers of elevated glucose levels. Follow-up studies report significant reductions both in incidence and mortality of obesity-related cancers. Research on pancreatic cancer is still scarce but promising. Future studies should

be designed to overcome the challenges of investigating pancreatic cancer and ultimately address the question of applicability of bariatric surgery in pancreatic cancer treatment.

Pancreatic cancer and obesity are posing a growing health burden across the globe. The identification of new modifiable factors that mediate risk for these conditions is also of importance and may play a prominent role in constructing effective preventive strategies in the future.

Author contributions Conception and design, analysis and interpretation, drafting of the article, critical revision of the article and final approval of the article: PR, KCT, TS.

Funding No funding to disclose.

Compliance with ethical standards

Conflict of interest None of the authors have a conflict of interest.

Ethics approval No ethics approval needed.

References

1. Arroyo-Johnson C, Mincey KD. Obesity epidemiology worldwide. Gastroenterol Clin North Am. 2016;45:571–9.
2. Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics. 2015;33:673–89.
3. Polednak AP. Estimating the number of U.S. incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. Cancer Detect Prev. 2008;32:190–9.
4. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 15 Jan 2019.
5. Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008;32:1431–7.
6. von Ruesten A, Steffen A, Floegel A, et al. Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. PLoS One. 2011;6:e27455.
7. 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.
8. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377:13–27.
9. Liang YJ, Xi B, Song AQ, et al. Trends in general and abdominal obesity among Chinese children and adolescents 1993–2009. Pediatr Obes. 2012;7:355–64.
10. Biadgilign S, Mgutshini T, Haile D, et al. Epidemiology of obesity and overweight in sub-Saharan Africa: a protocol for a systematic review and meta-analysis. BMJ Open. 2017;7:e017666.
11. Nishida C, Mucavele P. Monitoring the rapidly emerging public health problem of overweight and obesity: the WHO global database on body mass index. SCN News 2005;29:5–11.
12. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016;22:9694–705.
13. Michaud DS. Obesity and pancreatic cancer. Recent Results Cancer Res. 2016;208:95–105.
14. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
15. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
16. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;126:2394–403.
17. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir. 2004;59:99–111.
18. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252–61.
19. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol. 2016;55:1158–60.
20. Bosetti C, Bertuccio P, Negri E, et al. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog. 2012;51:3–13.
21. Fogel EL, Shahda S, Sandrasegaran K, et al. A multidisciplinary approach to pancreas cancer in 2016: a review. Am J Gastroenterol. 2017;112:537–54.
22. Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010;170:791–802.
23. Genkinger JM, Spiegelman D, Anderson KE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer. 2011;129:1708–17.
24. Jiao L, Berrington de Gonzalez A, Hartge P, et al. Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. Cancer Causes Control. 2010;21:1305–14.
25. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer. 2003;89:519–23.
26. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. Int J Cancer. 2007;120:1993–8.
27. Pang Y, Holmes MV, Kartsonaki C, et al. Young adulthood and adulthood adiposity in relation to incidence of pancreatic cancer: a prospective study of 0.5 million Chinese adults and a meta-analysis. J Epidemiol Community Health. 2017;71:1059–67.
28. Carreras-Torres R, Johansson M, Gaborieau V, et al. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a mendelian randomization study. J Natl Cancer Inst 2017;109:djx012.
29. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105(Suppl 2):77–81.
30. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million women study: cohort study. BMJ. 2007;335:1134.
31. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23:843–52.
32. Calle EE, Rodriguez C, Jacobs EJ, et al. The American cancer society cancer prevention study II nutrition cohort: rationale, study design, and baseline characteristics. Cancer. 2002;94:2490–501.
33. Luo J, Margolis KL, Adami HO, et al. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). Br J Cancer. 2008;99:527–31.

34. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol. 2015;26:2257–66.
35. Olinto MTA, Theodoro H, Canuto R. Epidemiology of abdominal obesity. 2017. https://doi.org/10.5772/65342. https://www.intechopen.com/books/adiposity-epidemiology-and-treatment-modalities/epidemiology-of-abdominal-obesity.
36. Cascetta P, Cavaliere A, Piro G, et al. Pancreatic cancer and obesity: molecular mechanisms of cell transformation and chemoresistance. Int J Mol Sci. 2018;19:3331.
37. Incio J, Liu H, Suboj P, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discov. 2016;6:852–69.
38. Aleman JO, Eusebi LH, Ricciardiello L, et al. Mechanisms of obesity-induced gastrointestinal neoplasia. Gastroenterology. 2014;146:357–73.
39. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106:603–7.
40. Coss A, Cantor KP, Reif JS, et al. Pancreatic cancer and drinking water and dietary sources of nitrate and nitrite. Am J Epidemiol. 2004;159:693–701.
41. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst. 2003;95:948–60.
42. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013;2013:139239.
43. Harbuzariu A, Rampoldi A, Daley-Brown DS, et al. Leptin-Notch signaling axis is involved in pancreatic cancer progression. Oncotarget. 2017;8:7740–52.
44. Loebig M, Klement J, Schmoller A, et al. Evidence for a relationship between VEGF and BMI independent of insulin sensitivity by glucose clamp procedure in a homogenous group healthy young men. PLoS One. 2010;5:e12610.
45. Chang HH, Moro A, Takakura K, et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. PLoS One. 2017;12:e0184455.
46. Cormie P, Spry N, Jasas K, et al. Exercise as medicine in the management of pancreatic cancer: a case study. Med Sci Sports Exerc. 2014;46:664–70.
47. Niels T, Tomanek A, Schneider L, et al. Exercise improves patient outcomes in advanced pancreatic cancer patient during medical treatment. Pancreat Disord Ther. 2018;8:193.
48. M. D. Anderson Cancer Center. PancFit: multimodal exercise during preoperative therapy for pancreatic cancer. 2019. https://clinicaltrials.gov/ct2/show/NCT03187951. NLM identifier: NCT03187951. Accessed 1 Feb 1 2019.
49. Puzziferri N, Roshek TB III, Mayo HG, et al. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934–42.
50. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol. 2009;10:653–62.
51. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357:753–61.
52. Christou NV, Lieberman M, Sampalis F, et al. Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis. 2008;4:691–5.
53. Schauer DP, Feigelson HS, Koebnick C, et al. Bariatric surgery and the risk of cancer in a large multisite cohort. Ann Surg. 2019;269:95–101.
54. He R, Yin Y, Yin W, et al. Prevention of pancreatic acinar cell carcinoma by Roux-en-Y gastric bypass surgery. Nat Commun. 2018;9:4183.
55. Zhou X, Qian B, Ji N, et al. Pancreatic hyperplasia after gastric bypass surgery in a GK rat model of non-obese type 2 diabetes. J Endocrinol. 2016;228:13–23.
56. Jiao L, Chen L, White DL, et al. Low-fat dietary pattern and pancreatic cancer risk in the women's health initiative dietary modification randomized controlled trial. J Natl Cancer Inst 2018;110:49–56.