Published in final edited form as:
Mol Carcinog. 2012 January ; 51(1): 53–63. doi:10.1002/mc.20778.

Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms

Paige M. Bracci, PhD, MPH
Department of Epidemiology & Biostatistics, School of Medicine, University of California San Francisco, San Francisco, CA

Abstract

In the U.S. pancreatic cancer is characterized by a low 5-year survival rate of approximately 6%, fewer than 10% of patients diagnosed with localized disease and thus candidates for "curative" surgical resection, increasing incidence and few established risk factors. Similar statistics are observed for other industrialized nations. With new evidence to suggest that pancreatic cancer develops over a number of years, markers that can better identify high risk patients and are applicable to earlier diagnosis hold promise for improving these dire statistics. Obesity is one of the few modifiable risk factors that has been associated with increased risk of pancreatic cancer and also is related to increased risk of diabetes, a condition that in turn has been associated with pancreatic cancer development. Given recent data that nearly 70% of U.S. adults are overweight or obese, a clarification of the complex association between obesity and pancreatic cancer may disclose targets for prevention and intervention to decrease incidence and improve prognosis of this highly fatal disease. An overview of the current epidemiology and hypothesized biological mechanisms involved in the obesity-pancreatic cancer association are presented.

Keywords

body mass index; etiology; risk factor

Introduction

Pancreatic cancer is one of the most fatal cancers in adult men and women in the U.S. Most patients are diagnosed with advanced disease; 75% die within one year of diagnosis and the current 5-year survival is estimated to be 6% [1,2]. Non-specific and vague symptoms are hallmarks of the disease and have contributed to the typical advanced stage at diagnosis along with a lack of highly sensitive and specific screening tests for early diagnosis. Surgical resection offers the best prognosis but typically is considered an option only for the small proportion of patients who are diagnosed with localized disease (<10% [1]). Treatment of patients with advanced disease (>50% [1]) is largely palliative. Established risk factors explain only a small proportion of pancreatic cancer cases and include smoking, diabetes, heavy alcohol consumption, family history, increasing age, and rare inherited genetic conditions such as Peutz-Jeghers, familial melanoma and hereditary pancreatitis. There is mounting evidence that risk of pancreatic cancer is increased among those who are obese or have high body mass index (BMI). In fact, the World Cancer Research Fund Panel concluded in a 2007 report that based on current evidence from 38 published studies there is a "convincing increased risk" of pancreatic cancer related to body fatness and a "probable

Paige M. Bracci, PhD, MPH, Department of Epidemiology & Biostatistics, University of California, San Francisco, 3333 California Street, Suite 280, San Francisco, CA 94118-1944, Fax: (415) 563-4602; paige.bracci@ucsf.edu.

increased risk" with abdominal fatness[3]. Given the increase in obesity in the U.S [4], the elucidation of an association between pancreatic cancer and obesity may provide an opportunity to exploit a personally modifiable risk factor that is amenable to prevention and intervention measures. Plausible mechanisms that have been proposed to explain the complex relationship between obesity and cancer development include tumor promoting inflammatory and hormonal effects associated with adiposity and adipose tissue, and the energy-balance related factors of increased exposure to carcinogens due to increased food consumption and diminished physical activity. As there are few known risk factors, a lack of specific markers for early detection and diagnosis, and new data to suggest that pancreatic tumors are slow-growing[5] (thus a target for early detection and intervention), clarification of the role of modifiable risk factors for pancreatic cancer such as BMI may provide new insights about pancreatogenesis that can be translated to efforts to reduce incidence and improve prognosis in high risk populations.

Epidemiology

Obesity

Overweight and obesity in adults is defined by BMI, the ratio of weight in kilograms (kg) to height in meters squared (m^2), where a BMI of 18.5 to <25 is normal, 25 to <30 is overweight and ≥30 is obese. The most recent statistics from the 2007-2008 National Health and Nutrition Examination Survey (NHANES) that used measured height and weight indicated that 33.8% of adults ≥20 years old were obese and an additional 34.2% were overweight [4]. Compared with the statistics for 1976-1980 this reflects a 2-fold increase in the prevalence of adult obesity whereas prevalence of overweight adults was unchanged[4]. In addition, obesity prevalence varied by sex, race and ethnicity with greater percents of obese women than men (35.5% vs. 32.2%) and obese non-Hispanics blacks (44.1%) compared with other race/ethnic groups [4]. Interestingly, trend statistics suggested that the rate of increase from 1999-2008 was less than in previous time periods, especially for women [4]. The implications of these increases are many as obesity has been associated with numerous negative health effects including increased mortality from all causes and increased risks of hypertension, diabetes, cardiovascular disease, stroke, liver disease, apnea and some cancers (including pancreatic). Therefore, as a potentially modifiable risk factor, a reduction in the prevalence of obesity among adults could have a substantial impact on mortality and incidence of pancreatic cancer and related chronic diseases.

Pancreatic Cancer

Pancreatic cancer ranks 10th in incidence of all cancers in U.S. men and women with approximately 43,000 new cases expected in the U.S. in 2010 [2]. However, as the 4th leading cause of cancer mortality the annual number of pancreatic cancer deaths are nearly equivalent to the number of new cases with >36,000 deaths expected in 2010 [2]. Pancreatic cancer also is among the few cancers for which the average annual percent change in incidence and mortality have been increasing in recent time periods [1]. Smoking, excessive alcohol consumption, increasing age, family history, obesity, diabetes and several rare genetic syndromes are factors known to be associated with increased pancreatic cancer risk. Other exposures and conditions such as some dietary factors, gallbladder and other gastrointestinal conditions, and regular use of specific medications e.g. non-steroidal anti-inflammatory drugs and statins, have been less consistently associated with pancreatic cancer risk. Recent genome-wide association studies also have identified variants in ABO blood group [6], cleft lip and palate transmembrane 1-like (*CLPTM1L*)-telomerase reverse transcriptase (*TERT*) and nuclear receptor subfamily 5A2 (*NR5A2*) [7] genes that may alter susceptibility to pancreatic cancer.

Pancreatic cancer risk and obesity/BMI

Cachexia is a known characteristic of pancreatic cancer with estimates as high as 80% of patients cachexic at diagnosis [8]. Therefore to determine whether BMI is a risk factor for rather than a result of pancreatic cancer, recent epidemiological case-control and cohort studies of pancreatic cancer frequently have used self-reported data for usual adult weight and height, or weight and height at specific ages to assess obesity and associations with increasing BMI[9-19]. Prospective cohort studies also used weight and height at baseline (self-reported or measured) to compute BMI and frequently excluded cases who were diagnosed shortly after study enrolment, typically ≤2 years, to ensure that weight was not a result of the disease. Few studies have collected data for other measures of adiposity such as waist circumference and waist to hip ratio (WHR).

Overall, results have suggested a positive association between obesity/high BMI and pancreatic cancer risk that has been confirmed in three recent large pooled analyses [20-22] and in two of three meta-analyses [23-25]. These analyses provide the basis for the discussion presented here as they encompass a range of well-designed independent observational epidemiological studies that investigated BMI and pancreatic cancer risk. As summarized below, risk estimates from these pooled and meta-analyses usually were reported as associations with a 5 kg/m^2 increase in BMI and with BMI categorized using WHO cutpoints (overweight: 25≤BMI <30; obese 30≤BMI<35, extreme/severe obesity: 35≤BMI.). Effects were relatively consistent across studies with approximate 10% or greater increases in risk for a 5 kg/m^2 unit increase in BMI, or a 20%-50% increased risk among obese relative to normal BMI participants. Several studies that assessed measures of adiposity in addition to BMI also were included in these pooled and meta-analyses with results supporting positive associations with WHR [20,21]. Effect modification and confounding associated with known pancreatic cancer risk factors (e.g. smoking, diabetes), geographic location, sex, and for study design/methodology (self-reported vs. measured anthropometrics) were assessed when possible and provided further insight into the BMI and pancreatic cancer relationship that was not possible in many independent studies.

The first of the published meta-analyses[23] included 14 studies, 6 of which were case-control studies thereby allowing for a formal evaluation of effect estimates by study design. The summary estimate for case-control studies was slightly attenuated compared with cohort studies (RR=1.02, RR=1.03 respectively), despite that BMI was computed based on pre-diagnostic weight values [usual adult weight (1 study), weight 2 years before interview (4 studies), unknown (1 study)][23]. Given that most of these case-control studies assessed BMI based on anthropometric characteristics 2 years before enrollment, a time frame that many prospective cohort studies used to exclude newly diagnosed cancer cases from their analyses, results suggest that use of self-reported data, recall or selection bias in case-control studies may have contributed to the observed differences. Further evaluations of effect by type of study design were not conducted in the five subsequently published pooled/meta-analyses as only prospective cohort studies were included in these analyses (with one exception; one case-control study was included in the pooled PanScan analyses after sensitivity analyses showed no undue influence on study estimates[20]).

Another fundamental study design characteristic that also was investigated for its effect on the association between BMI and pancreatic cancer risk was the type of anthropometric factor assessment, self-reported or measured. Analysis by type of assessment is of interest because although measured and self-reported anthropometric data are well-correlated, reporting biases exist by sex, age and weight which can affect measures of association, such as estimates of mortality risk[26]. BMI from self-reported compared with measured factors was evaluated best by the pooled and meta-analyses that included prospective cohort studies with weight and height data collected at baseline prior to diagnosis. Summary estimates for

BMI based on self-reported data were either somewhat attenuated[24,25,27] or similar[20,22] to summary risk estimates from studies that measured anthropometric factors. Importantly, in studies that noted a variation in estimates the overall inference that obesity/high BMI is associated with increased pancreatic cancer risk was not altered.

Other key factors that were evaluated in most studies as potential confounders or effect modifiers of the association between BMI and pancreatic cancer risk included sex and age, the established risk factors smoking and diabetes, and geographic region although few studies formally tested statistical interactions. All studies assessed differences by sex with any observed differences in estimates statistically non-significant and no one sex having consistently higher risk estimates. Interestingly, in the PanScan[20] study the greatest differential in risks by sex were observed for those severely obese (BMI≥35) as estimated in models that excluded smokers, diabetics and cases diagnosed within two years of follow-up and included BMI categorized using WHO cutpoints (women: RR=1.98, men: RR=0.90). Age was similarly included in all models in all studies and was not found to be an effect modifier in the studies that stratified by age at study entry/diagnosis[21,22].

Smoking and long-standing diabetes are among the few known risk factors for pancreatic cancer and as both also are associated with weight they conceivably can alter the association between BMI and pancreatic cancer risk. Nearly all studies considered smoking as a confounder whereas statistical interaction or effect modification due to smoking was determined in a subset of these pooled and meta-analyses. There was some evidence that risk estimates were slightly increased when smoking was adjusted for in models[23] although most studies did not provide effect estimates from models without smoking included. In analyses stratified by smoking, results provided support for an increased risk of pancreatic cancer with increased BMI mainly among nonsmokers[20] and never/former smokers [21,22] (p for interaction= 0.08 to 0.12), but not current smokers. This intriguing result requires further study as smoking status reflects baseline behavior in these cohort studies and if smokers are thinner than the rest of the population then power may be low to detect a joint effect of current smoking and obesity.

The role of diabetes as a potential confounder is complicated as diabetes may be in the causal pathway between BMI and pancreatic cancer. Despite this possibility many studies adjusted for diabetes history in their models but similar to smoking characteristics, few studies evaluated effect modification/statistical interaction with diabetes. In a comparison of models that did and did not include adjustment for diabetes, adjustment for diabetes resulted in higher risk estimates in several studies[22-24] (highest risk was found in non-diabetics although statistical interaction was non-significant),[22] attenuated risk in one large pooled analysis[20] and no substantial difference in risk in another[21]. Given the analytic concerns that diabetes is not independently associated with both obesity and pancreatic cancer, and the mixed results that have been reported in some large studies, further carefully designed research that can clarify the interplay among obesity/high BMI, diabetes and pancreatic cancer risk are needed.

Although most studies did not consider the effect of geographic region in their analyses, pooled and meta-analyses that included studies from different continents provided an opportunity to investigate whether risk of pancreatic cancer associated with BMI differed across continents. Study data confirmed obesity statistics across populations with the highest median or average BMIs observed among participants from North American studies, followed by Europeans and Asians[21,22]. In the studies that stratified analyses by region, BMI was modeled as a continuous variable and results showed positive associations between BMI and pancreatic risk in North American and European populations, with the highest RRs observed among North American groups[23,24] and no association in Asian

study populations[24]. The lack of an association in the Asian study populations was based on two studies and is inconsistent with data suggesting that the negative effects of obesity/high BMI on disease occur at lower BMI values in Asian populations. Although compelling, further pooled and meta-analyses that include a larger number of Asian studies and that also can compare the effect estimates to those obtained for assimilated Asians in non-Asian countries will help to clarify this association.

Two recently published prospective cohort study pooling projects [20-22] are noteworthy as analyses included evaluation of other important characteristics of obesity/high BMI that have not been investigated in earlier pooled analyses; measures of central adiposity, BMI as a young adult, change in BMI overtime, and the effect of physical activity. Both studies assessed central adiposity and in analyses of men and women combined[21] or separately, [20] results showed that hip circumference[21] and waist circumference[20,21] were not associated with pancreatic cancer risk. In contrast, WHR was associated with a statistically significant 20-30% increased risk for those with the highest ratios[20,21]. Further analyses of WHR by sex were less consistent with data from one study suggesting similar risk by sex[21] and the other showing a stronger effect among women (4^{th} vs. 1^{st} quartile: RR=1.6 (1.03-2.50)) although risk also was elevated among men (RR=1.50 (0.77-2.93))[20]. Central adiposity is a marker of visceral body fat that is metabolically active, secreting adipokines that have a downstream effect on insulin resistance, a risk factor for pancreatic cancer. Storage of body fat is hormonally driven and among women the tendency for centrally stored fat is more pronounced after menopause. Because BMI can be misleading measure of 'fatness' for those who are very fit or for those who are very thin, central adiposity has been shown to be a better marker of disease risk for some conditions, e.g. cardiovascular disease and metabolic syndrome. Given the accumulating evidence and biologic relevance of central adiposity in disease development, continued study of central adiposity that also includes waist-to-height ratio, evaluation of defined risk cutpoints, and consideration of pre and post-menopausal status among women are needed to improve our understanding of body fat in risk of pancreatic cancer.

Results for other obesity-related factors that were pooled for analyses in these two recent studies suggested that obesity was associated with earlier onset and that timing of obesity may be important[20,21]. Obese participants were found to be diagnosed on average 1 year earlier than those of normal-weight [20] which is consistent with results reported from a recent independent study [16]. Participants who reported being overweight/obese as young adults (ages 18-21 years) had an approximate 1.2-fold increased risk of pancreatic cancer compared with those with normal BMI[21]. Further, those whose BMI had increased >10 kg/m^2 over their adult life had a 1.4-fold increased risk of pancreatic cancer compared with those whose BMI had changed no more than 2 kg/m^2 [21]. Finally, although physical activity is a critical component of energy balance, it was evaluated in only one pooled analysis with results suggesting a statistically significant interaction between physical activity and BMI (p for interaction =0.02)[21]. Those who were obese and highly active were at the greatest risk of pancreatic cancer (RR=1.29).[21]. These results were based on subsets of studies within these pooled analyses and although they contribute new data that may help refine our study of obesity and pancreatic cancer, additional research is required to clarify these associations.

Based on data described above, obesity/high BMI has been consistently associated with increased risk of pancreatic cancer. However, as implied by results from these large pooled and meta-analyses, effects have been influenced by study design characteristics and are likely to vary by subgroups of at-risk patients. Therefore, although the wealth of evidence indicates that obesity increases risk of pancreatic cancer, the additional refinement of hypotheses and continued study of adiposity and obesity-related factors will increase our

understanding of the underlying biological mechanisms relevant to pancreatogenesis and help to better define an at-risk population.

Pancreatic cancer survival and obesity/BMI

Studies that have assessed obesity/BMI associated with pancreatic cancer survival include those among patients who had undergone surgical resection[28-32] as well as in observational case-control and cohort study populations [16,33,34]. Reported results have been inconsistent with some studies reporting decreased survival associated with obesity/ increased BMI [16,28,30,33,34], others finding no association [29,31] and one study finding longer survival duration [32].

The studies of surgical resection patients typically used BMI at time of surgery (from medical records) to assess primary hypotheses related to specific surgical complications/ outcomes in obese compared with non-obese patients, in addition to the more general question of whether obesity was related to survival in these patients. Two studies reported no association with obesity [29,31] whereas another also found no association with BMI but a poor survival for those with high intra-abdominal fat as measured by CT [28]. Poorer survival also was reported for extremely obese patients (BMI≥35) compared with all others in a study of consecutive patients seen for curative resections at a cancer referral center [30]. The single study that reported improved survival was a relatively large series (795 cases) of surgical-resection patients where both overweight (HR=0.68) and obese patients (HR=0.72) had improved survival relative to normal BMI patients [32].

In contrast to studies of surgical patients, the observational case-control and cohort studies tested whether obesity prior to diagnosis was associated with survival. In these studies BMI was computed based on usual adult weight, weight at specific ages or weight at baseline (prospective cohort studies) before diagnosis. Obesity/high BMI was associated with poor survival in three case-control or case series studies[16,33,34].

Despite some suggestion that pre-diagnostic obesity/high BMI may be associated with poor pancreatic cancer survival, overall results are inconclusive. Additionally, the differences in study designs, study populations, measures and classifications of obesity, and slight differences in hypotheses being tested prevent generalization of study results. Because surgical-resection studies computed BMI based on weight at time of surgery and are likely to have included only those patients with localized disease who tend to have a better prognosis compared to other pancreatic cancer patients, results and inferences from these populations may not reflect associations in patients with more advanced inoperable disease. Also, underlying differences in populations of surgically resected patients that were related to varying medical practices between countries and types of treatment centers may be a concern when interpreting results. Finally, as the negative effects of increased BMI may occur at lower levels in Asian compared with non-Asian populations, inferences based on results from studies of largely Asian populations may not be applicable to other racial groups. Because of the low variability in survival duration, and confounding by indication and clinical prognostic factors, large pooled analyses of case-control and cohort studies are needed to have sufficient sample size and power to test the association between obesity/high BMI determined at different times, and pancreatic cancer survival. Case-control studies can be affected by survival bias but will have a larger number of patients and pre-diagnostic data specific to pancreatic cancer. In contrast, prospective cohort studies will have fewer cases and events, but by design are more likely to include a greater proportion of the sickest patients who tend to be under-represented in case-control studies, and can directly measure anthropometric factors and adiposity before diagnosis. Integration of complementary information from both case-control and cohort studies will provide a more comprehensive evaluation of survival-related associations.

Pancreatic cancer mortality and obesity/BMI

Results from studies of pancreatic cancer mortality associated with obesity/high BMI also have been inconsistent. Obesity/high BMI at baseline was not associated with pancreatic cancer mortality in three large prospective cohorts[35-37]. In contrast, obesity/high BMI was associated with increased mortality in a series of patients after pancreatectomy[30], in the Million Women Study (a large cohort of middle aged-women) [38], in a large cohort of U.S. adults [39] where later follow-up showed the magnitude of risk was greatest in nonsmoking men [40], and in a prospective cohort of men in Chicago, U.S. area [41]. An analysis of individual data from 30 cohort studies in the Asia Pacific showed an increase in pancreatic cancer mortality with weight change that was measured as a 2cm increase in waist circumference [42]. Although several of these studies found that BMI and other known risk factors were positively associated with pancreatic cancer risk, there was insufficient evidence to conclude that obesity/high BMI was associated with pancreatic cancer mortality. Mortality results may have been affected by type of assessment of BMI as shown in a recent study[26]. However, similar to the determination of pancreatic cancer risk and survival associated with BMI, the inconsistency in results from these studies also may be related to the potential for misclassification of obesity related to assessing BMI at baseline only and possible inadequate adjustment for potential confounders. Assessment of other obesity-related characteristics with pancreatic cancer mortality including measures of adiposity, use of measured anthropometrics, and more detailed data about timing of obesity may help to clarify and increase our understanding of a possible association between BMI and pancreatic cancer mortality.

Overview of Biologic Mechanisms

Hypotheses that have been put forth to explain the association between obesity and pancreatic cancer risk have focused on: 1) hormonal and inflammatory effects of adipose tissue; 2) increased exposure to carcinogens as a result of increased food consumption and; 3) diminished physical activity. Given that obesity often reflects an energy imbalance, it is likely that some aspect of each of the proposed mechanisms and pathways contribute to create an environment that promotes pancreatogenesis. The mechanisms described below are further complicated by accumulating evidence that potentially involved biological markers are modified by variants in genes involved in the synthesis, metabolism, binding and cell signaling of many of these compounds and factors.

Hormonal effects

Obesity and high BMI have been associated with increases in circulating insulin and C-peptide, hyperglycemia, insulin resistance and diabetes, factors that have been associated with pancreatic cancer. Insulin and insulin growth-factor pathways that potentially influence tumor promotion and development largely through apoptosis and cell proliferation have been a focus of research to clarify the obesity-pancreatic cancer association. Increased circulating insulin leads to a decrease in circulating insulin growth-factor binding-proteins (IGFBP) -1 and -2 and subsequent increased levels of bioavailable insulin growth factor (IGF)-1. IGF-1 binding to its receptor, IGF-1R, also can contribute to tumor promotion through resultant activation of cell proliferation, apoptosis and angiogenesis. Although results from epidemiological studies of pancreatic cancer that investigated serum and plasma IGF-1 and IGFBPs have been inconsistent, studies have consistently shown an increased risk with markers of increased glucose levels [43-45]. Obesity also has been associated with sex steroid hormone levels and synthesis that are differential among men, pre- and post-menopausal women. Although obesity-related sex-steroid effects have been associated with risk of hormone-related cancers, no association between sex steroids and pancreatic cancer risk has been identified.

Adipokines in obesity and cancer: leptin, adiponectin

Adipose tissue, particularly visceral adipose tissue, has been shown to be metabolically active, producing adipokines including those most frequently studied in relation to cancer, leptin and adiponectin. Additionally, obesity is a characterized by low-grade chronic inflammation that may be driven by macrophage infiltration of adipose tissue that also drives insulin resistance[45,46]. Cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 are released by infiltrating macrophages and/or adipocytes, are elevated in obese individuals and have been associated with risk or progression of several cancers through their effects on angiogenesis, apoptosis and cell proliferation[45,46]. Leptin, is positively correlated with adiposity, in general is higher in women than in men regardless of BMI and plays a role in appetite control and in transcription of aromatase, an enzyme key to estrogen synthesis. Adiponectin has been inversely correlated with obesity and is involved in glucose and fatty acid metabolism, insulin regulation and resistance. Adiponectin, considered anti-inflammatory, and leptin, considered proinflammatory, can influence carcinogenic processes through decreased (adiponectin) or increased (leptin) secretion of IL-6 and of TNF-alpha[45,46]. In a model of pancreatic cancer using strains of obese mice, leptin was not associated with cell proliferation or tumor progression whereas circulating adiponectin was inversely associated with tumor progression [47]. Results from the few studies that investigated leptin and adiponectin associated with pancreatic cancer provide some suggestion that high levels of circulating adiponectin may be associated with pancreatic cancer risk[48] and differentiate pancreatic cancer from other pancreatic conditions [49-51] whereas associations with leptin were inconsistent [49-51]. Given the limited, somewhat conflicting data in pancreatic cancer and additional data to suggest that the relationship between adiponectin and inflammation driven by adiposity contradicts that driven by classic inflammatory conditions i.e. autoimmunity [52], continued research is required to clarify a role of adiponectin in the association between obesity and pancreatogenesis.

Other biological mechanisms

Obesity induced hypoxia that results in increased vascular endothelial growth factor (VEGF) also has been suggested to play a role in the association between obesity and cancer. Higher circulating VEGF levels have been reported in persons with high BMI [53] although a relationship with pancreatic cancer has not been explored. As an angiogenic factor, increased VEGF could play a role in tumor progression and growth.

Carcinogens from food

Increased exposure to carcinogens in food is a plausible factor in obesity-related risk of pancreatic cancer. Dietary intake of heterocyclic amines (HCA) was positively associated with increased BMI [54] in one study whereas a study of circulating DNA adducts for benzo(a)pyrene were inversely associated with body fat stores likely due to their storage in fat [55]. Although it has been suggested that for the average person, carcinogens and mutagens in foods contribute significantly to the total body burden of these compounds [56], current methods are inadequate to measure biological markers for these epidemiologic exposures. Results from epidemiologic studies that have assessed average typical consumption of specific types of foods have provided most of the evidence to support an association with dietary carcinogens. Risk of pancreatic cancer has been evaluated for diets high in meat, especially meats fried and grilled at high temperatures, preserved foods, and some grains and vegetables that are sources of cancer causing HCAs, polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds. In general studies suggest an increased pancreatic cancer risk with higher exposure to these compounds as estimated from food intake [57-62].

Physical activity

Obesity as a result of energy imbalance can be modified by increasing physical activity levels and decreasing caloric consumption. Chronic moderate physical activity has been associated with increased anti-inflammatory cytokines, increased natural killer cell activity, increased CYP activity, increase DNA repair activity, altered insulin sensitivity, and reduced tumor angiogenesis[63]. Most studies have been conducted in animal models and results have been inconclusive including a murine study of pancreatic cancer that reported no effect of exercise on IGF-1 levels (as reviewed in [63]). Physical activity is difficult to investigate as a risk factor in epidemiologic studies as it is prone to inaccurate measurement, misclassification, healthy worker type effects and the inherent heterogeneity in the variety of daily physical activities in which individuals partake. Thus, although there has been some suggestion from epidemiologic studies that exercise may be associated with reduced risk for some cancers the current overall evidence suggests a weak inverse association between overall physical activity and pancreatic cancer risk [64]. As physical activity directly impacts obesity and by implication obesity-related carcinogenesis, improved methods to elucidate the role of physical activity in pancreatic cancer risk are needed.

Conclusion

Obesity increases risk of pancreatic cancer and may contribute to poor prognosis and survival compared with non-obese patients. Pathways and mechanisms to clarify this association are not well elucidated but a single mechanism is unlikely to explain how obesity alters pancreatic cancer risk. The effects of adipose tissue on insulin and insulin resistance, release and synthesis of hormones, cytokines and chemokines, in addition to environmental exposure to carcinogens and mutagens in foods, the biological effects of physical activity that contribute to energy imbalance and functional genetic variants in potentially relevant biological pathways, all are likely to play a role in the obesity-pancreatic cancer association. As obesity is a modifiable factor, it is possible that with a better understanding of this complex relationship, pancreatic cancer incidence and prognosis can be improved by reducing the prevalence of obesity in the population and through prevention and intervention that promote energy balance and target specific key biologic pathways that can be affected by adipose tissue. However, further research studies including randomized controlled trials that are able to assess causation, are needed to establish whether interventions that modify obesity or hypothesized obesity-related mechanisms, alter pancreatic cancer development, risk and prognosis.

Acknowledgments

Funding: This work was supported in part by National Cancer Institute grants CA59706, CA108370, CA109767, CA89726 and by the Rombauer Pancreatic Cancer Research Fund.

References

1. Altekruse, S.; Kosary, C.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2007. Bethesda, MD: National Cancer Institute; 2010.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. Ca. 2010; 60(5):277–300. Epub 2010 Jul 2017. [PubMed: 20610543]
3. World Cancer Research Fund A. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
4. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. Jama. 2010; 303(3):235–241. Epub 2010 Jan 2013. [PubMed: 20071471]
5. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature. 2010; 467(7319):1114–1117. [PubMed: 20981102]

6. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009; 41(9):986–990. Epub 2009 Aug 2002. [PubMed: 19648918]
7. Petersen GM, Amundadottir L, Fuchs CS, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010; 42(3):224–228. Epub 2010 Jan 2024. [PubMed: 20101243]
8. Fearon KC, Baracos VE. Cachexia in pancreatic cancer: new treatment options and measures of success. HPB. 2010; 12(5):323–324. [PubMed: 20590907]
9. Bueno de Mesquita HB, Moerman CJ, Runia S, Maisonneuve P. Are energy and energy-providing nutrients related to exocrine carcinoma of the pancreas? Int J Cancer. 1990; 46(3):435–444. [PubMed: 2394510]
10. 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(9):2490–2501. [PubMed: 12015775]
11. Eberle CA, Bracci PM, Holly EA. Anthropometric factors and pancreatic cancer in a population-based case-control study in the San Francisco Bay area. Cancer Causes Control. 2005; 16(10): 1235–1244. [PubMed: 16215874]
12. Ghadirian P, Simard A, Baillargeon J, Maisonneuve P, Boyle P. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. Int J Cancer. 1991; 47(1):1–6. [PubMed: 1845960]
13. Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. Int J Cancer. 2001; 94(1):140–147. [PubMed: 11668489]
14. Howe GR, Jain M, Miller AB. Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case-control study. Int J Cancer. 1990; 45(4):604–608. [PubMed: 2157670]
15. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer. 2005; 93(11):1310–1315. [PubMed: 16288300]
16. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. Jama. 2009; 301(24):2553–2562. [PubMed: 19549972]
17. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. Jama. 2001; 286(8):921–929. [PubMed: 11509056]
18. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. Cancer Causes Control. 2007; 18(2):165–175. Epub 2007 Jan 2011. [PubMed: 17219012]
19. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. J Natl Cancer Inst. 1998; 90(22):1710–1719. [PubMed: 9827525]
20. 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(9):791–802. [PubMed: 20458087]
21. 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. 2010; 23
22. 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(8):1305–1314. [PubMed: 20383573]
23. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer. 2003; 89(3):519–523. [PubMed: 12888824]
24. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer. 2007; 120(9):1993–1998. [PubMed: 17266034]
25. 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(9612):569–578. [PubMed: 18280327]

26. Keith SW, Fontaine KR, Pajewski NM, Mehta T, Allison DB. Use of self-reported height and weight biases the body mass index-mortality association. Int J Obes. 2010 advance online publication:8.
27. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev. 2006; 15(5):879–885. [PubMed: 16702364]
28. Balentine CJ, Enriquez J, Fisher W, et al. Intra-abdominal fat predicts survival in pancreatic cancer. J Gastrointest Surg. 2010; 14(11):1832–1837. [PubMed: 20725799]
29. Benns M, Woodall C, Scoggins C, McMasters K, Martin R. The impact of obesity on outcomes following pancreatectomy for malignancy. Ann Surg Oncol. 2009; 16(9):2565–2569. Epub 2009 Jun 2526. [PubMed: 19557479]
30. Fleming JB, Gonzalez RJ, Petzel MQ, et al. Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. Arch Surg. 2009; 144(3):216–221. [PubMed: 19289659]
31. Khan S, Sclabas G, Reid-Lombardo K, et al. Does body mass index/morbid obesity influence outcome in patients who undergo pancreatoduodenectomy for pancreatic adenocarcinoma? J Gastrointest Surg. 2010; 14(11):1820–1825. [PubMed: 20676790]
32. Tsai S, Choti MA, Assumpcao L, et al. Impact of obesity on perioperative outcomes and survival following pancreaticoduodenectomy for pancreatic cancer: a large single-institution study. J Gastrointest Surg. 2010; 14(7):1143–1150. [PubMed: 20431978]
33. McWilliams RR, Matsumoto ME, Burch PA, et al. Obesity adversely affects survival in pancreatic cancer patients. Cancer. 2010; 116(21):5054–5062. [PubMed: 20665496]
34. Olson SH, Chou JF, Ludwig E, et al. Allergies, obesity, other risk factors and survival from pancreatic cancer. Int J Cancer. 2010; 127(10):2412–2419. [PubMed: 20143395]
35. Batty GD, Kivimaki M, Morrison D, et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomarkers Prev. 2009; 18(2):673–675. Epub 2009 Feb 2003. [PubMed: 19190162]
36. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS Jr. Physical activity, body weight, and pancreatic cancer mortality. Br J Cancer. 2003; 88(5):679–683. [PubMed: 12659113]
37. Nakamura K, Nagata C, Wada K, et al. Cigarette Smoking and Other Lifestyle Factors in Relation to the Risk of Pancreatic Cancer Death: A Prospective Cohort Study in Japan. Jpn J Clin Oncol. 2010; 2010:12.
38. Stevens RJ, Roddam AW, Spencer EA, et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. Int J Cancer. 2009; 124(10):2400–2405. [PubMed: 19165860]
39. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control. 2000; 11(10):915–923. [PubMed: 11142526]
40. 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(17):1625–1638. [PubMed: 12711737]
41. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. Jama. 2000; 283(19):2552–2558. [PubMed: 10815119]
42. Ansary-Moghaddam A, Huxley R, Barzi F, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomarkers Prev. 2006; 15(12):2435–2440. [PubMed: 17164367]
43. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. Arch Physiol Biochem. 2008; 114(1):63–70. [PubMed: 18465360]
44. Douglas JB, Silverman DT, Pollak MN, Tao Y, Soliman AS, Stolzenberg-Solomon RZ. Serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer. 2010; 19(9):2298–2306. Epub 2010 Aug 2210.
45. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu. 2010; 61:301–316.

46. Berger, N., editor. Cancer and Energy Balance, Epidemiology and Overview. New York, NY: Springer; 2010. p. 312
47. Zyromski NJ, Mathur A, Pitt HA, et al. Obesity potentiates the growth and dissemination of pancreatic cancer. Surgery. 2009; 146(2):258–263. [PubMed: 19628082]
48. Stolzenberg-Solomon RZ, Weinstein S, Pollak M, et al. Prediagnostic adiponectin concentrations and pancreatic cancer risk in male smokers. Am J Epidemiol. 2008; 168(9):1047–1055. Epub 2008 Sep 1018. [PubMed: 18801887]
49. Chang MC, Chang YT, Su TC, et al. Adiponectin as a potential differential marker to distinguish pancreatic cancer and chronic pancreatitis. Pancreas. 2007; 35(1):16–21. [PubMed: 17575540]
50. Dalamaga M, Migdalis I, Fargnoli JL, et al. Pancreatic cancer expresses adiponectin receptors and is associated with hypoleptinemia and hyperadiponectinemia: a case-control study. Cancer Causes Control. 2009; 20(5):625–633. Epub 2008 Dec 2003. [PubMed: 19051043]
51. Krechler T, Zeman M, Vecka M, et al. Leptin and adiponectin in pancreatic cancer: connection with diabetes mellitus. Neoplasma. 2011; 58(1):58–64. [PubMed: 21067267]
52. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol. 2008; 121(2):326–330. Epub 2007 Dec 2003. [PubMed: 18061654]
53. 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. 5(9):e12610.
54. Ericson U, Wirfalt E, Mattisson I, Gullberg B, Skog K. Dietary intake of heterocyclic amines in relation to socio-economic, lifestyle and other dietary factors: estimates in a Swedish population. Public Health Nutr. 2007; 10(6):616–627. Epub 2007 Mar 2023. [PubMed: 17381880]
55. Rundle A, Madsen A, Orjuela M, et al. The association between benzo[a]pyrene-DNA adducts and body mass index, calorie intake and physical activity. Biomarkers. 2007; 12(2):123–132. [PubMed: 17536763]
56. Ferguson LR. Natural and human-made mutagens and carcinogens in the human diet. Toxicology. 2002:181–182. 79–82. [PubMed: 11893417]
57. Anderson KE, Kadlubar FF, Kulldorff M, et al. Dietary intake of heterocyclic amines and benzo(a)pyrene: associations with pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14(9):2261–2265. [PubMed: 16172241]
58. Li D, Day RS, Bondy ML, et al. Dietary mutagen exposure and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(4):655–661. [PubMed: 17416754]
59. Anderson KE, Sinha R, Kulldorff M, et al. Meat intake and cooking techniques: associations with pancreatic cancer. Mutat Res. 2002:506–507. 225–231.
60. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT, et al. Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. Cancer Epidemiol Biomarkers Prev. 2007; 16(12):2664–2675. [PubMed: 18086772]
61. Zhu J, Rashid A, Cleary K, et al. Detection of 2-amino-1-methyl-6-phenylimidazo [4,5-b]-pyridine (PhIP)-DNA adducts in human pancreatic tissues. Biomarkers. 2006; 11(4):319–328. [PubMed: 16908439]
62. Zhang J, Dhakal IB, Gross MD, et al. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. Nutr Cancer. 2009; 61(4):457–465. [PubMed: 19838917]
63. Rogers CJ, Colbert LH, Greiner JW, Perkins SN, Hursting SD. Physical activity and cancer prevention: pathways and targets for intervention. Sports Med. 2008; 38(4):271–296. [PubMed: 18348589]
64. O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis. Int. 2010; 126(12):2957–2968.

Abbreviations

BMI body mass index

HR	hazard ratio
HCA	heterocyclic amines
IGFBP	insulin growth-factor binding-proteins
IGF	insulin growth-factor
IL	interleukin
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PanScan	The Pancreatic cancer Cohort Consortium
PAHs	polycyclic aromatic hydrocarbons
RR	relative risk
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
WHR	waist to hip ratio

Table 1

Characteristics of pooled and meta-analyses of body mass index associated with risk of pancreatic cancer

1st Author, publication year	Follow-up (FU)	Study design	Number of studies, participants, regions	BMI factors, covariates	Effect estimates
Arslan et al., 2010	Mean FU 0-21 years	Pooled analysis	13 prospective cohort studies using a nested case-control design, 1 case-control study; 2170 cases, 2209 controls; U.S., Europe, Finland, China	BMI at baseline (quartiles, WHO groups), weight, height waist circumference, waist to hip ratio (WHR) Multivariable modeling of smoking diabetes, BMI assessment, age, sex, follow-up >2 yrs	BMI 4th quartile: 1.33 (1.12-1.58) Severely obese: 1.55 (1.16-2.07) WHR 4th quartile M: 1.41 (0.83-2.40) W: 1.87 (1.31-2.69)
Genkinger et al., 2010	FU 7-20 years	Pooled analysis	14 prospective cohorts; 2135 cases, 846,340 participants; US, Canada, Finland, Sweden, Australia, Netherlands	BMI at baseline, BMI in young adulthood (continuous, WHO groups); WHR (7 studies), waist circumference, hip circumference, (continuous and quartiles) Effect modification by sex Multivariable adjustment, age sex, diabetes, smoking, physical activity, alcohol and energy intake	Baseline Obese: 1.47 (1.23-1.75, ptrend<0.001 Early adulthood overweight:1.30 (1.09-1.56), ptrend<0.0001 Overweight in early adulthood and obese at baseline: 1.54 (1.24-1.93) WHR 4th quartile1.35 (1.03-1.78) ptrend=0.06 BMI*smoking p=0.12
Jiao et al, 2010	Mean FU 7-17 years	Pooled analysis	7 prospective cohorts;2,639 cases 952,494 participants; US, Finland, China	BMI at baseline (continuous, WHO groups) Multivariable adjustment Effect modification by age, baseline calendar year, smoking status, physical activity, diabetes	BMI continuous 5kg/m2 M: 1.06 (0.99-1.13) W: 1.12 (1.05-1.19) BMI*Smoking p=0.08 BMI WHO group obese: M: 1.10 (0.94-1.28) ptrend=0.05 W: 1.29 (1.06-1.57) ptrend=0.04
Larsson et al. 2007	Mean FU 6-33 years	Meta-analysis	21 prospective cohorts; 8,062 cases, 3,495,981 participants; US, Sweden Finland, Japan, UK, Korea, Europe	BMI at baseline (continuous) All adjusted for smoking Effect modification by region, follow-up time, self-report vs. measured height and weight, diabetes	BMI continuous 5kg/m2 1.12 (1.06-1.17) BMI*BMI assessment Self-report: 1.17 (1.13-1.22) Measured: 1.05 (0.99-1.12) p=0.003 Diabetes adjustment Yes: 1.15 (1.08-1.23) No: 1.06 (1.0-1.13) p=0.07
Renehan et al.2008	Mean FU 5-19 years	Meta-analysis	16 prospective studies; 4,443 cases, 3,338,001 participants; North America, Europe, Australia, Asia	BMI continuous standardized to 5kg/m2 Adjusted for 2 to 5 additional covariates in individual studies Stratified by geographic region, BMI assessment type, age, follow-up duration	BMI continuous 5kg/m2 M: 1.07 (0.93-1.23, p=0.23 W: 1.12 (1.08-1.16), p<0.0001 Differences by geographic region (men) Differences by BMI assessment (self-report higher in women)
Berrington de Gonzalez et al 2003	NA	Meta-analysis	14 studies (6 case-control, 8 cohort), 6,391 cases total; US, Canada, Poland, Netherlands, Finland	BMI continuous standardized to 1kg/m2 unit increase Effect of study design, BMI assessment type, geographic region, diabetes adjustment, smoking adjustment, sex, proxy interview	BMI continuous 1kg/m2 All: 1.02 (1.01-1.03) M: 1.03 (1.01-1.06) W: 1.02 (1.00-1.03) Case-control: 1.02 (1.00-1.03) Cohort: 1.03 (1.01-1.04) BMI Assessment: Measured: 1.02 (0.97-1.07) Self-report: 1.03 (1.02-1.03) Smoking adjustment Yes: 1.03 (1.02-1.03) No: 1.00 (0.96-1.03) p=0.04