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Primary and Secondary Prevention of Pancreatic Cancer

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Abstract

Purpose of Review Pancreatic cancer remains one of the most lethal of malignancies with 5-year survival of only 8%. A number of reasons account for the high fatality rate including few known modifiable risk factors, no effective screening tools, and lack of early diagnostic symptoms. Therefore, in this review, we aim to summarize existing evidence from major studies concerning (1) risk factors for risk assessment and risk stratification, and (2) screening modalities and early detection markers to better understand the ways to prevent pancreatic cancer or identify it at earlier stages. Improvements in primary and secondary prevention of pancreatic cancer are critical to reduce the morbidity and mortality of this deadly disease.

Recent Findings We searched the published literature and identified studies of pancreatic cancer risk published prior to September 30, 2018, with an emphasis on manuscripts publicized during the last 5–10 years. Known and suspected risk factors include familial and genetic risk, smoking, obesity, alcohol, poor diet including sugary sweetened beverages, diabetes, and periodontal disease. Recent advances have identified potential early detection markers (e.g., ctDNA, circulating cancer cells, metabolites, and miRNA).

Summary Currently, pancreatic cancer has few known and suspected risk factors, and risk assessment tools have limited utility given their modest discriminatory power. Although emerging evidence suggests blood-based biomarkers may be useful as early detection markers, findings need to be confirmed in prospective studies. Due to the rarity of disease, future studies should consider a two-tiered approach in which risk assessment is used to identify high-risk individuals for screening, and then effective imaging and biomarkers in pathways known to affect pancreatic cancer risk are employed; these combination approaches may reduce false positives and mortality compared with just risk assessment or screening alone.

Keywords Pancreatic cancer · Risk factors · Early detection

Introduction

Pancreatic cancer remains one of the most lethal of malignancies. An estimated 232,306 cases of pancreatic cancer occur globally each year, and 227,023 die from the disease [1]. Since 2004, incidence rates have increased by 1.5% per year in the USA [2]. This is extremely alarming given that half of the individuals diagnosed with pancreatic cancer die within 6 months and that the 5-year survival for pancreatic cancer is 8% [3]. While the 5-year survival rate improves to 37.4% in patients presenting with stage 1 or localized disease, only 10% of patients are identified at this early stage [4]. The majority of patients (53%) are diagnosed with distant, metastatic cancer, and have a 5-year survival of 2.9% [5]. A number of reasons exist for the late diagnosis and high fatality rate, including few known modifiable risk factors, no effective screening tools, and lack of early diagnostic symptoms unique to pancreas cancer. Thus, approaches to prevent disease or identify it at earlier stages (e.g., stage 1a) are critical to reduce the morbidity and mortality of this deadly disease. Therefore, in this review, we aim to review the recent literature with regard to the (1) identification for risk factors for risk assessment and risk stratification (Table 1 and Fig. 1) and (2) identification of screening modalities and early detection markers.

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Table 1 A summary of epidemiologic studies examining the association between risk factors and pancreatic cancer risk

Risk factor	Study, country, year	Study population	Study design	Main findings
Familial and genetic risk	Molina-Montes E et al., Europe, 2018	1431 cases and 1090 controls	Case-control	Pancreatic cancer is associated with 2 first degree relatives of pancreatic cancer (OR = 3.88; 95% CI 2.97–9.72)Pancreatic cancer is associated with family history of cancer (OR = 1.30; 95% CI 1.13–1.54)Pancreatic cancer is associated with family history of diabetes (OR = 1.24; 95% CI: 1.01–1.52)
	Ghadirian P et al., Canada, 2002	174 cases and 136 controls	Case-control	Pancreatic cancer is associated with family history of pancreatic cancer (relative risk = 5.0; $p = 0.01$)
	Fehringer G et al., Canada, 2014	690 cases and 736 control	Case-control	Pancreatic cancer is associated with family history of pancreatic cancer (OR = 1.68; 95% CI 1.03–2.72)Pancreatic cancer is associated with one sibling history of pancreatic cancer (OR = 5.22; 95% CI 2.03–13.41)
	Permuth-Wey J et al., 2009	2617 cases and 6284 controls in 7 case-control study 3951 cases and 1,104,508 participants in 2 cohort study	Meta-analysis	Pancreatic cancer is associated with family history of pancreatic cancer (summary RR = 1.80; 95% CI 1.48–2.12)
	Klein AP et al., Europe, 2018	11,537 cases and 17,107 controls from Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4)	Genome-wide meta--analysis	New genome-wide significant loci:rs13303010 at 1p36.33 (NOC2L, OR = 1.26; 95% CI 1.19–1.35, $P = 8.36 \times 10–14$)rs2941471 at 8q21.11 (HNF4G, OR = 0.89; 95% CI 0.85–0.93, $P = 6.60 \times 10–10$) rs4795218 at 17q12 (HNF1B, OR = 0.88; 95% CI 0.84–0.92, $P = 1.32 \times 10–8$)
Smoking	Zheng Z. et al., China, 2016	323 case-control pairs	Case-control	Pancreatic cancer is associated with smoking (OR = 1.78, 95% CI 1.02–3.10) but frequency and quantities were not statistically significant
	Wang Y. et al., China, 2014	307 cases and 1228 controls	Case-control	Current smokers vs. never smokers (OR = 1.71; 95% CI 1.25–2.35) Pancreatic cancer is associated with smoking intensity (≥ 20 cigarettes/day) (OR = 2.18; 95% CI 1.66–3.69)
	Bosetti C. et al., 2012	6507 cases and 12,890 controls from 12 case-control studies within the International Pancreatic Cancer Case-Control Consortium (PanC4)	Pooled Analysis	Current smokers vs. never smokers (OR = 2.2; 95% CI 1.7–2.8) Pancreatic cancer is associated with smoking intensity (≥ 35 cigarettes/day) (OR = 3.4; P for trend < 0.0001)
	Zou L. et al., 2014	9044 cases and 32,039 controls from 30 retrospective studies 8962 cases and 2,075,947 participants in 12 prospective studies	Meta-analysis	Compared to non-smokers: 10 cigarettes/day (OR = 1.5; 95% CI 1.4–1.6) 20 cigarettes/day (OR = 1.9; 95% CI 1.8–2.0) 30 cigarettes/day (OR = 2.0; 95% CI 1.9–2.1) 40 cigarettes/day (OR = 2.1; 95% CI 1.9–2.3)
Obesity	Jiao L. et al., 2010	2454 cases and 943,759 participants from 7 cohort studies	Pooled analysis	Overweight vs. normal weight (RR = 1.13; 95% CI 1.03–1.23) Obese vs. normal weight (RR = 1.19 95% CI: 1.05–1.35)
	Arslan AA et al., 2010	2170 cases and 2209 controls from PanScan consortium	Pooled analysis	BMI: highest vs lowest BMI quartile (OR = 1.33; 95% CI 1.12–1.58) (OR = 1.33; 95% CI 1.04–1.69) among men (OR = 1.34; 95% CI 1.05–1.70) among womenWaist-to-hip ratio (WHR): highest vs. lowest WHR quartile among women (OR = 1.87; 95% CI 1.31–2.69); but not significant among men
	Genkinger JM et al., 2011	2135 cases and 846,340 participants from 14 cohort studies	Pooled analysis	BMI: Early adulthood BMI ≥ 25 kg/m(2) vs. BMI 21–22.9 kg/m(2) (RR = 1.30, 95% CI 1.09–1.56)WHR: highest vs lowest WHR quartile(RR = 1.35; 95% CI 1.03–1.78)
	Genkinger JM et al., 2015	1947 cases and 647,478 participants from 20 prospective in the National Cancer Institute BMI and Mortality Cohort Consortium	Pooled analysis	WHR (HR = 1.09; 95% CI 1.02–1.17 per 0.1 increase, pancreatic cancer mortality). Waist circumference (HR = 1.07; 95% CI 1.00–1.14 per 10 cm increase, pancreatic cancer mortality) BMI in early adulthood (HR = 1.18; 95% CI 1.11–1.25 per 5 kg/m2 increase, pancreatic cancer mortality)
Alcohol	Genkinger JM et al., 2009	2187 cases and 862,664 participants from 14 cohort studies	Pooled analysis	Pancreatic cancer is associated with alcohol (RR = 1.22; 95% CI 1.03–1.45, > or = 30 vs. 0 g/day)

Table 1 (continued)

Risk factor	Study, country, year	Study population	Study design	Main findings
	Lucenteforte et al., 2012	5585 cases and 11,827 controls from PanC4	Pooled analysis	No association between light-to-moderate alcohol consumption (≤ 4 drinks per day) and pancreatic cancer risk. Pancreatic cancer is associated with higher consumption level (drinking ≥ 9 drinks per day) (OR = 1.6; 95% CI 1.2–2.2)
	Michaud et al.,2010	1530 cases and 1530 controls from PanScan	Pooled analysis	No association between total alcohol intake (≥ 60 g/day vs. 0–5 g/day) and pancreatic cancer risk (OR = 1.38; 95% CI 0.86–2.23)
Diet	Inoue-Choi M. et al., USA, 2011	256 cases and 34,642 participants from Iowa Women's Health Study	Cohort	No association between dietary intake of any nutrients or food groups and pancreatic cancer
	Nöthlings U. et al., 2008	610 cases and 183,513 participants from Multiethnic Cohort (MEC) study 517 cases and 424,978 participants from EPIC study	Cohort	No significant association between food group or food item pattern and pancreatic cancer risk in the overall cohort
	Bosetti et al., 2013	326 cases and 652 controls	Case-control	Pancreatic cancer is associated with "animal products" pattern (OR = 2.03; 95% CI 1.29–3.19) and "starch-rich" pattern (OR = 1.69; 95% CI: 1.02–2.79). Pancreatic cancer is inversely associated with "vitamins and fiber" pattern (OR = 0.55; 95% CI 0.35–0.86). No association between "unsaturated fats" pattern (OR = 1.13; 95% CI 0.71–1.78) and pancreatic cancer
	Chan et al., 2013	532 cases and 1701 controls	Case-control	Pancreatic cancer is inversely associated with the prudent dietary pattern (greater intake of vegetables, fruit, fish, poultry, whole grains, and low-fat dairy) (OR = 0.51; 95% CI 0.31–0.84, p-trend = 0.001 among men); (OR = 0.51; 95% CI: 0.29–0.90, p-trend = 0.04 among women). Pancreatic cancer is associated with the western dietary pattern (higher intake of red and processed meats, potato chips, sugary beverages, sweets, high-fat dairy, eggs, and refined grains) (OR = 2.4; 95% CI 1.3–4.2, *p* trend = 0.008 among men) but was not associated with risk among women.
	Michaud et al.,2005	366 cases and 124,672 participants from 2 cohorts	Pooled analysis	No associations between the prudent pattern (RR = 1.32; 95% CI 0.66–2.63) or the western pattern (RR = 0.91; 95% CI 0.57–1.47) and pancreatic cancer.
Physical activity	Behrens et al., 2015	10,501 cases	Meta-analysis	High vs. low levels of physical activity (RR = 0.93; 95% CI: 0.88–0.98) among 22 cohort studies and (RR = 0.78; 95% CI 0.66–0.94) among 8 case-control studies.
	Brenner et al., 2014	826 cases and 930 controls	Case-control	Pancreatic cancer is associated with regular leisure-time physical activity (OR = 0.65; 95% CI: 0.52–0.87)
	Calton et al., 2008	70 cases and 33,530 participants	Cohort	The RRs for increasing quartiles of total physical activity were 1.0, 0.80, 0.66, 0.52 (95%CI 0.26–1.05, *p* trend = 0.05)
	Hanley et al., 2001	312 cases and 2919 controls	Case-control	Pancreatic cancer is inversely associated with composite moderate and strenuous physical activity among men (OR = 0.53; 95% CI 0.31–0.90). No association between physical activity and pancreatic cancer among women, though a tendency for reduced risk with increasing levels of strenuous activity was suggested (*p* for trend = 0.06)
	Berrington de Gonzalez et al., 2006	324 cases and 438,405 participants	Cohort	No significant decreased risk with total physical activity (RR = 0.82; 95% CI 0.50–1.35)
	Nothlings et al., 2007	472 cases and 167,430 participants	Cohort	No association between physical activity and pancreatic cancer
	Patel et al., 2005	242 cases and 145,627 participants	Cohort	

Table 1 (continued)

Risk factor	Study, country, year	Study population	Study design	Main findings
				No association between physical activity and pancreatic cancer (RR = 1.20; 95% CI 0.63–2.27)
	Stolzenberg-Solomon et al., 2008	654 cases and 495,035 participants	Cohort	No association between physical activity and pancreatic cancer
Reproductive factors	Andersson et al., 2018	110 cases and 17,035 participants	Cohort	No association between age at menopause or first childbirth, parity and breastfeeding history and pancreatic cancer
	Prizment et al., 2007	228 cases and 37,459 participants	Cohort	Pancreatic cancer is inversely associated with age at menopause (HR = 0.61, 95% CI 0.40–0.94 for menopause at 45–49 years; HR = 0.75, 95% CI 0.51–1.09 for 50–54 years; and HR = 0.35, 95% CI 0.18–0.68 for menopause at 55 years or more; *P* trend = 0.005) No associations between age at first birth, number of births, age at menarche, or use of hormones and pancreatic cancer
	Skinner et al., 2003	243 cases and 115,474 participants	Cohort	Pancreatic cancer is inversely associated with ≥ 5 births vs. nulliparous (RR = 0.58, 95% CI 0.34–0.98)
	Navarro Silvera et al.,	187 cases and 89,835 participants	Cohort	Pancreatic cancer is associated with postmenopausal (OR = 2.44, 95% CI 1.45–4.09)No associations between age at first live birth, parity, age at menarche, use of oral contraceptive, and use of hormone replacement therapy (HRT) and pancreatic cancer. However, among parous women, risk increased with increasing parity.
	Luo et al., 2016	2535 cases from 5 case-control studies and 6 cohort studies	Meta-analysis	Pancreatic cancer is associated with age at first birth (RR = 1.21, 95% CI 1.01–1.45, highest versus lowest categories)
	Stevens et al., 2009	1182 cases and 995,192 participants	Cohort	No significant association between age at menarche, number of children, age at first birth, breast-feeding, type of menopause, age at menopause, or time since menopause and pancreatic cancer
	Lujan-Barroso et al., 2016	2838 cases and 4748 controls from Panc4	Pooled analysis	Pancreatic cancer is inversely associated with hysterectomy (OR = 0.78, 95% CI 0.67–0.91)
Medical history	Kirkegard et al., 2018	41,669 acute pancreatitis and 208,340 comparison. 937 pancreatic cases through follow up period	Cohort	Pancreatic cancer is associated with acute pancreatitis (HR = 2.02, 95% CI 1.57–2.61)
	Raimondi et al., 2010	12 case-control studies and 10 cohort studies	Meta-analysis	Pancreatic cancer is associated with all types of pancreatitis (RR = 5.1, 95% CI: 3.5–7.3 for unspecified pancreatitis; RR = 13.3, 95% CI: 6.1–28.9 for chronic pancreatitis; RR = 69.0, 95% CI 56.4–84.4 for hereditary pancreatitis.
	Pang et al., 2017	595 cases and 512,000 participants for cohort study	Cohort and meta-analysis	Pancreatic cancer is associated with diabetes (HR = 1.87, 95% CI 1.48–2.37 for cohort study; HR = 1.52, 95% CI 1.43–1.63 for meta-analysis)
	Bosetti et al., 2014	8305 cases and 13,987 controls	Pooled analysis	Pancreatic cancer is associated with diabetes 20 or more years after diabetes diagnosis (OR = 1.30, 95% CI 1.03–1.63)
	Haugvik et al., 2015	827 cases and 2407 controls	Meta-analysis	Pancreatic cancer is associated with diabetes (OR = 2.74, 95% CI 1.63–4.62)
	Walker et al., 2015	536 cases and 869 controls	Case-control	No association between metformin and pancreatic cancer
	Lu et al., 2015	529 cases and 5000 controls	Nested case-control	No association between metformin and pancreatic cancer
	Wang et al., 2014	10 cohort studies and 3 case–control studies	Meta-analysis	Pancreatic cancer is inversely associated with metformin use (RR = 0.63, 95% CI 0.46–0.86)
	Hamada et al., 2018	583 cases and 113,059 participants	Cohort	

Table 1 (continued)

Risk factor	Study, country, year	Study population	Study design	Main findings
				No association between statin use and pancreatic cancer (HR = 0.98, 95% CI 0.82–1.16)
	Chiu et al., 2011	190 cases and 760 control	Case-control	No association between statin use and pancreatic cancer (OR = 0.87, 95% CI 0.56–1.36)
	Walker et al., 2015	536 cases and 869 controls	Case-control	Pancreatic cancer is inversely associated with statin use among men (OR = 0.50, 95% CI 0.32–0.79); no association between statin use and pancreatic cancer among women (OR = 0.86, 95% CI 0.52–1.43)
	Cui et al., 2012	7807 cases and 1,692,863 participants from 16 studies	Meta-analysis	No significant association between statin use and pancreatic cancer (RR = 0.89, 95% CI 0.74–1.07)
	Archibugi et al., 2018	11,975 cases and 3,433,175 controls from 27 studies	Meta-analysis	Pancreatic cancer is inversely associated with statin use (OR = 0.70, 95% CI 0.60–0.82)
	Ben et al., 2012	943 cases and 1128 controls	Case-control	Pancreatic cancer is associated with hepatitis B (OR = 1.60, 95% CI 1.15–2.24)
	Xu et al., 2013	3758 cases and 744,120 controls	Meta-analysis	Pancreatic cancer is associated with hepatitis B (OR = 1.20, 95%CI 1.01–1.39). Pancreatic cancer is associated with hepatitis C (OR = 1.26, 95%CI 1.03–1.50)
	Krull et al., 2016	116 cases and 20,360 participants	Cohort	No significant association between hepatitis B (OR = 1.22, 95%CI: 0.81–1.84) or hepatitis C (OR = 0.69, 95%CI: 0.28–1.69) and pancreatic cancer
	Risch et al., 2014	761 case and 794 controls		Pancreatic cancer is inversely associated with CagA seropositive individuals (OR = 0.68, 95% CI 0.54–0.84)
	Huang et al., 2017	448 cases and 448 controls	Nested case-control	No association between *H. pylori* seropositivity (OR = 0.96, 95% CI: 0.70–1.31) or CagA seropositivity (OR = 1.07, 95% CI: 0.77–1.48)
	Liu et al., 2017	65,155 participants	Meta-analysis	No association between *H. pylori* infection (OR = 1.09, 95% CI 0.81–1.47) or CagA seropositivity (OR = 1.18, 95% CI 0.80–1.72) and pancreatic cancer
	Schulte et al., 2015	580 cases and 626 controls		No association between H. pylori seropositivity (OR 1.00, 95% CI: 0.74–1.35) or CagA seropositivity (OR 0.74, 95% CI 0.48–1.15) and pancreatic cancer
	Fan et al., 2018	361 cases and 371 controls	Nested case-control	Pancreatic cancer is associated with *Porphyromonas gingivalis* (OR = 1.60, 95% CI 1.15–2.22), *Aggregatibacter actinomycetemcomitans* (OR = 2.20, 95% CI 1.16–4.18) and pancreatic cancer
	Huang et al., 2016	126 cases and 19,924 participants	Cohort	Pancreatic cancer is associated with unacceptable dental plaque (HR = 2.1, 95% CI: 1.0–4.7)
	Michaud et al., 2013	405 cases and 416 controls	Nested case-control	Pancreatic cancer is associated with Porphyromonas gingivalis ATTC 53978 (OR = 2.14, 95% CI 1.05–4.36; > 200 ng/ml vs ≤ 200 ng/ml)
	Michaud et al., 2007	216 cases and 51,529 participants	Cohort	Pancreatic cancer is associated with history of periodontal disease (RR = 1.64, 95% CI 1.19–2.26)

Risk Factors for Pancreatic Cancer

Familial and Genetic Risk

Genetic variation, both familial and sporadic, plays an important role in pancreatic cancer. Family history of any cancer has been associated with a 15–30% higher pancreatic cancer risk [6, 7]; risk is stronger when considering only a family history of pancreatic cancer, with risk ratios of 1.68 for any relative, 3.88 for at least two first-degree relatives, and up to fivefold for when an individual has an affected sibling [6, 8]. A meta-analysis consisting of seven case-control studies and two cohort studies reported an association between having a family history of pancreatic cancer and pancreatic cancer risk (summary RR = 1.80, 95% CI 1.48–2.12). Increased risks were observed when considering the number of first degree relatives affected (summary RR = 4.6, 95% CI 0.5, 16.4; summary RR = 6.4, 95% CI 1.8–16.4; summary RR = 32.0, 95% CI 10.2–74.7, for one relative, two relatives, or three relatives affected, respectively) [9].

The associations between family history and pancreatic cancer risk suggest that there are genes of varying penetrance that influence the pancreatic carcinogenesis. Several genes have been implicated in pancreatic cancer risk (e.g., BRCA1, BRCA2, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1, and STK11), as well as the ABO genotype [10•]. A recent meta-analysis conducted with the largest pancreatic cancer GWAS that included up to 11,537 cases and 17,107 controls observed several new genome-wide significant loci. Specifically, SNPs located on the *NOC2L* gene were statistically significantly associated with pancreatic cancer risk (OR = 1.26, 95% CI 1.19–1.35, $P = 8.36 \times 10^{-14}$) [11•]. Additionally, genetic syndromes have been shown to be associated with a 4–40% increased pancreatic cancer risk such as familial atypical multiple mole melanoma, Peutz-Jeghers syndrome, hereditary pancreatitis, hereditary nonpolyposis colon cancer, and multiple endocrine neoplasia type 1 syndrome [12]. However, family history and/or genetic predisposition is reported to account for only 5–10% of all pancreatic cancer cases in the US; estimates have remained stable over the last few decades [10•, 13, 14].

Lifestyle Factors

Smoking Tobacco use is one of the strongest and most consistent lifestyle risk factors for pancreatic cancer with an estimated population attributable fraction of 11–32% [15•]. Nicotine derivatives in cigarette smoke can promote carcinogenesis of the pancreas by inducing cellular damage, formation of DNA adducts, or interfering with physiological pathways [16]. Two recent case-control studies [17, 18], a pooled analysis of 12 case-control studies from Panc4 consortium [19], as well as a large meta-analysis of 30 case-control and 12 cohort studies [20], reported a twofold higher pancreatic cancer risk for current compared with never smokers, and the risk increased up to threefold with ≥ 35 cigarettes per day.

Overall and Central Obesity The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) estimate that healthy weight is the second most important factor, besides not smoking, for cancer prevention; excess weight is estimated to be attributable for up to 15% of all pancreatic cancer cases [21]. Excess body fat has been implicated in pancreatic cancer risk due to modification of insulin, hormonal, and inflammation pathways [22–25]. Prior research has shown that overall obesity, as measured by BMI, and central obesity, as measured by waist circumference or waist-to-hip ratio, are positively associated with pancreatic cancer incidence [26, 27, 28•]. In four pooled analyses [26, 27, 28•, 29], a significant 8–14% higher pancreatic cancer risk and mortality were observed for a 5 kg/m^2 increase in BMI at baseline (usually measured in mid to late adulthood) and a 55% higher risk when examining > 35 compared with 18.5–24.9 kg/m^2). A slightly stronger 18–20% higher pancreatic cancer risk was observed for a 5 kg/m^2 increment in BMI at younger ages (usually retrospectively assessed for ages 18–21) [28•, 29]. In only one [28•] of three pooled analyses [26, 28•, 29] was waist circumference positively associated with pancreatic cancer; however, all three pooled analyses reported statistically significant positive associations for waist-to-hip ratio [26, 28•, 29]. In 2018, the expert panel of the WCRF/AICR report stated that there was convincing evidence that greater body fatness is associated with higher pancreatic cancer risk [30•].

Alcohol Heavy alcohol drinking has been hypothesized to be associated with higher pancreatic cancer risk. Alcohol may promote carcinogenesis through several mechanisms, such as the creation of acetaldehyde, an alcohol metabolism byproduct; upregulation of immunosuppressive and inflammatory pathways; activation of phase I cytochrome P450 biotransformation enzymes; and folate depletion that can interfere with DNA processes [31–34]. Most case-control studies have observed no association with alcohol intake [35–54], while a number of case-control studies found positive [55–60] and inverse [61–63] associations. Additionally, inconsistent associations have been reported with pancreatic cancer risk from 12 prospective studies [64–70, 71•, 72•, 73•, 74, 75]. In a pooled analysis of 14 prospective cohort studies, a 22% (95% CI 3–45%) higher pancreatic cancer risk was observed for alcohol intake ≥ 30 g(g) (equivalent to ≥ two drinks per day) compared with 0 g/day [71•]; whereas no statistically significant association was noted in PanScan or PanC4 case-control consortia for that contrast [72•, 73•]. Yet, a 60% increased risk was noted for those consuming more than

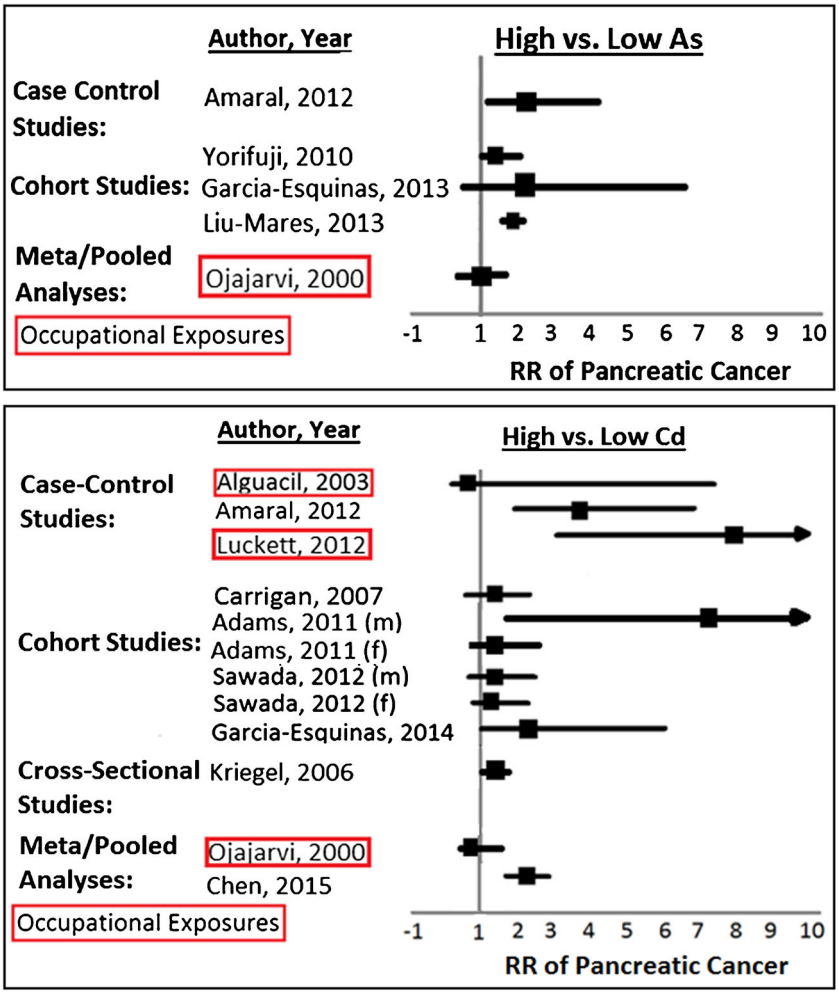

Fig. 1 Risk estimates for studies examining arsenic and cadmium exposure with pancreatic cancer risk. The meta-analyses included are Ojajarvi, 2000 (92 occupational studies); Chen, 2015: (five published studies and one de novo study). The black squares and horizontal lines correspond to the study-specific relative risks and 95% confidence intervals. The area of the black squares is proportional to the inverse of the sum of the between-studies variance and the study-specific variance. The red boxes represent studies in which the exposure was occupational exposure to arsenic or cadmium

nine drinks compared with < one drink/day in PanC4 [72•]. Based on this evidence, the WCRF/AICR expert panel concluded that the current data on alcohol intake were too inconsistent to reach a judgment [30•].

Diet Dietary factors have long been hypothesized to be associated with pancreatic cancer risk due to the large geographic variation in incidence rates worldwide [76]. To date, most research, including consortia studies, has focused on individual foods and nutrients including fruits and vegetables [77], dairy products [78], sugar-sweetened beverages [79], fats, meats, and protein (all individual studies cited in WCRF/AICR 2018 report) [80]. In 2018, an expert panel for the WCRF/AICR stated the evidence was suggestive for a positive association between consumption of red meat, processed meat, foods containing saturated fatty acids, and foods containing fructose and pancreatic cancer risk [30•]. However, as pancreatic cancer is believed to be a disease of multifactorial origins, it is also critical to understand risk in the context of multiple, simultaneous dietary, and lifestyle factors. Few studies have examined associations between dietary and lifestyle patterns and indices, which capture multiple exposures simultaneously, and pancreatic cancer risk. In studies examining data-driven dietary patterns (e.g., prudent pattern) identified within their own cohorts; results have been inconsistent [48, 81–85], whereas indices that are a priori (e.g., Alternative Healthy Eating Index) have been associated with lower pancreatic cancer risk for those who adhered to a healthier dietary and lifestyle [86–89]. Yet, case-control studies pose the potential for information and selection biases, or and cohort studies had limited case numbers and statistical power [81, 82, 85, 86].

Physical Activity Physical activity, through reducing insulin resistance, adiposity, DNA damage, and inflammation, has been posited to lower pancreatic cancer risk [90]. Prior case-control [91, 92] and a cohort study [93], as well as two large meta-analyses [90, 94], have suggested that physical activity is inversely associated with pancreatic cancer risk with risk estimates ranging from 7 to 35% lower risk when comparing high to low levels of physical activity, while several

prospective cohort studies have found nonsignificant or no association [95–98]. Some studies have suggested that risk may be limited to leisure-time physical activity only [91, 94•]. The WCRF in 2018 stated that the evidence of a protective effect of physical activity on pancreatic cancer risk is too limited and inconsistent to draw a conclusion [30•].

Reproductive Factors

Due to suggested hormonal effects on pancreatic carcinogenesis in rat and human tissue models [99–102], reproductive and hormonal factors have been hypothesized to play a role in pancreatic cancer risk. Results have been inconsistent when examining age at menarche, oral contraceptive use, parity, age at first birth, menopausal status, and hormone replacement therapy (HRT) use as possible risk factors of pancreatic cancer. Although individual studies have reported null [103, 104], inverse [105], and positive associations with increasing parity [106], a meta-analysis of six cohorts and five case-control studies reported a 21% higher pancreatic cancer risk for highest vs. lowest categories of age at first birth [107]. Overall, there was no association with hormone use [104–106] and age at menopause [103, 108]. However, one cohort study observed a protective effect of older age of menopause on pancreatic cancer risk (HR = 0.35 (95% CI 0.18–0.68) comparing menopause at $\geq$ 55 to < 45 years) [104], and for women who have had a hysterectomy (OR=0.78; 95% CI 0.67–0.91) in the Panc4 case-control consortium [109]. Overall, there is conflicting evidence of reproductive factors and pancreatic cancer risk in women that warrants further research.

Medical History

Pancreatitis Pancreatitis, the acute or chronic inflammation of the pancreas [110], has been implicated in pancreatic cancer incidence. Specifically, a twofold higher risk has been observed in patients diagnosed with acute pancreatitis [110, 111], while a meta-analysis of six cohort studies and one case-control reported a 13-fold higher pancreatic cancer risk in those diagnosed with chronic pancreatitis [112].

Diabetes and Metformin Type 2 diabetes mellitus, a disease that can occur when the body develops insulin resistance or not enough is produced, has been associated with an excess pancreatic cancer risk; however, it has also been posited that diabetes may be a consequence or early manifestation of pancreatic cancer. Two meta-analyses and one pooled analysis observed a 50–90% higher pancreatic cancer risk in patients who have a history of diabetes [113–115]; risk was similar even for individuals who had diabetes for up to 20 years prior to diagnosis [114]. Medications, like metformin, used to treat type II diabetes, has been hypothesized to have been protective due to its hypoglycemic and hypoinsulinemic effects [116], but results have been heterogeneous. A case-control and nested case-control study have observed a non-significant positive association between metformin use and pancreatic cancer risk [116, 117] while a meta-analysis of 10 cohort studies and three case-control studies observed an inverse association for metformin use in individuals with type 2 diabetes (summary RR = 0.63, 95% CI 0.46, 0.86) [118].

Statins Statins are traditionally used for the treatment and prevention of cardiovascular disease and have been studied in relation to cancer due to their possible anti-neoplastic properties [119]. One case-control and one cohort studies observed no association with statin use and pancreatic cancer risk [119, 120], while a 34% (95% CI 8–53%) lower risk was observed in a case-control study; the statistically significant inverse association was limited to men (OR_{men} = 0.50; 95% CI 0.32–0.79; OR_{women} = 0.86; 95% CI 0.52–1.43) [121]. Two meta-analyses observed a suggestive (summary RR = 0.89, 95% CI 0.74, 1.07) [122] and statistically significant protective effect of statin use on pancreatic cancer risk (pooled OR = 0.70; 95% CI 0.60–0.82) [123].

Hepatitis B, Hepatitis C, and *Helicobacter pylori* (*H. pylori*) Infection Hepatitis B, hepatitis C, and *H. pylori* infections have been investigated due to their ability to be detected and replicated within the pancreas [124, 125], their association with pancreatitis [126, 127], and their ability to enhance inflammatory responses which may promote pancreatic carcinogenesis [128], respectively. A meta-analysis of five case-control and three cohort studies [129] observed a 20–60% higher pancreatic cancer risk with a previous hepatitis B infection, while a large Japanese cohort observed a null association [130]. For hepatitis C, a 26% higher risk was observed in the meta-analysis [129], while subsequent to the meta-analysis, a suggestive inverse association (OR = 0.69, 95% CI-0.28-1.69) was observed in the large Japanese cohort [130]. For *H. pylori*, a nested case-control study [128] and two meta-analyses [131, 132] observed no statistically significant association with *H. pylori* infection. In contrast, a case-control study examining CagA genes, found in some *H. pylori* strains, found a lower pancreatic cancer risk in CagA seropositive individuals (OR = 0.68; 95% CI 0.54–0.84) and a non-significant increased risk for CagA negative, *H. pylori*-positive individuals when compared with those who were seronegative for both *H. pylori* and CagA [133].

Periodontal Disease The oral microbiome has recently been hypothesized to be involved in immune response and carcinogen metabolism [134]. Poor oral health has been associated with up to a twofold higher pancreatic cancer risk in multiple prospective studies [134, 135, 136•, 137]. *Porphyromonas gingivalis*, has specifically been implicated with reported

significant odds ratios of 1.60 (presence vs. absence) [134] and 2.14 (presence vs. absence of antibodies) [136•].

Environmental (Other "Environmental" Exposures Are Discussed under the Lifestyle Section) and Occupational Exposures

Metals and Metalloids Although the International Agency for Research on Cancer (IARC) concluded there are sufficient evidence to classify inorganic arsenic (As) and cadmium (Cd) as class I human carcinogens [138, 139•], these statements refer to other cancers. Few studies have examined these metals and metalloids with pancreatic cancer risk; the associations have been inconsistent with studies reporting null [140–144] and positive associations [145–154]. Furthermore, a recent study by Antwi et al. reported significant associations between exposure to asbestos, benzene, and chlorinated hydrocarbons and an increased pancreatic cancer risk with ORs ranging from 1.21 to 1.70 [155]. Given that most studies were small, had limited power, were retrospective or restricted to populations exposed to high occupational levels, future high-quality prospective studies with direct measurements of metal exposure are needed.

Summary of Risk Factors

As many of the suspected risk factors for pancreatic cancer may be modifiable, primary prevention by reducing harmful exposures and increasing preventative exposures over time may help to reduce incidence and mortality rates of this highly fatal cancer. Throughout the last 30 years, smoking rates have decreased in the USA [156] and worldwide [157], while obesity and diabetes rates have increased globally [158–160]. Changes in these key risk factors for pancreatic cancer, accounting for latency, may have a strong impact on future incidence and mortality of pancreatic cancer.

Screening

Primary Prevention of Pancreatic Cancer: Existing Pancreatic Cancer Risk Models Have Modest Discrimination

Given the high fatality rate and no current effective chemopreventive agents or screening tools for pancreatic cancer, prevention through identification of novel risk factors and behavioral modification of these factors offers the most promising approach to reducing incidence and mortality. As described above, these established or suspected risk factors [79, 161–164], the majority of which confirm risks < 1.5–2-fold [163], are insufficient, even jointly, for early detection or risk stratification. Currently, a few validated risk assessment models integrating established risk factors were developed for primary prevention [165•, 166•, 167, 168]. The PancPro model includes the number of family members affected, their relationship and age at diagnosis; the AUC was 0.61 (95% CI 0.51 to 0.71) for any family history, which increased to 0.75 (95% CI 0.68 to 0.81) when the relationship and age at onset were included [166•]. The Klein model includes smoking, diabetes, alcohol use, family history of pancreatic cancer, body mass index, ABO genotype, and three risk alleles; the AUC range from 0.57 for genetic factors, 0.58 for non-genetic factors to 0.61 for genetic and non-genetic factors [165•]. A third model included five SNPs, smoking, and family history of cancer (AUC = 0.63,95% CI 0.60–0.66) [167]. The last model included age, height, BMI, fasting glucose, urine glucose, smoking, and age at smoking initiation, and drinking habits showed similar c-statistics for men and women, 0.81 (95% CI:0.80–0.83) and 0.80 (95% CI:0.79–0.82), respectively [168]. The use of current risk assessment models has limited utility in the general population due to the low incidence of the disease [165•] and the modest discriminatory power for all models evaluated [169].

No Effective Screening Modality for Pancreatic Cancer Exists

Currently, the US Preventive Services Task Force does not recommend screening for pancreatic cancer in asymptomatic individuals [170]. Further, due to the low prevalence of the disease, no effective screening tool, and lack of effective treatments after diagnosis, population-level screening has the potential to cause significant harm that may outweigh the benefits [170]. However, screening recommendations for higher risk individuals have been proposed. The International Consortium for Pancreatic Cancer Screening (CAPs) recommends that individuals who are first-degree relatives (FDRs) of patients with pancreatic cancer from a familial pancreatic cancer kindred with at least two affected FDRs or patients with Peutz-Jeghers syndrome and p16, BRCA2, and hereditary non-polyposis colorectal cancer (HNPCC) mutation carriers with ≥ 1 affected FDR should undergo initial screening using endoscopic ultrasonography (EUS) and/or magnetic resonance cholangiopancreatography (MRI) [171•]. No consensus was reached for the age to initiate screening or stop surveillance, the optimal screening modalities, and intervals for follow-up imaging, and which screening abnormalities were of sufficient concern for surgery to be recommended. In contrast to CAPs, The American College of Gastroenterology (ACG) [172•] recommended endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) of the pancreas annually starting at age 50 years or 10 years younger than the earliest age of pancreatic cancer in the family. Further, they conditionally recommended, that patients with Peutz-Jeghers syndrome should start surveillance at age 35 years [172•].

Given the rareness of the disease, the lack of consensus regarding screening recommendations, a two-tiered approach in which risk assessment models are employed to identify high-risk individuals for screening using additional biomarkers in pathways known to affect pancreatic cancer risk may reduce false positives and mortality compared with just risk assessment or screening alone. Recent modeling has supported this approach for other diseases [173–175]; thus research into less invasive biomarkers may provide an opportunity to improve primary and secondary prevention approaches.

Early Detection Using Blood Markers

As most people are diagnosed at the late stage, surgical resection is only possible for approximately 15–20% of patients [176]. A major focus of pancreatic cancer research is to develop effective early detection methods through biomarkers (which includes genetic markers discussed in the familial and genetic risk section) with sufficient sensitivity and specificity to accurately detect asymptomatic pancreatic adenocarcinoma at the early stage when treatment might be more effective and thereby increase the 5-year survival. Several novel candidate biomarkers have been proposed for earlier diagnosis, though none have been adopted into routine clinical use. Prior studies, conducted for other cancers, suggest that the inclusion of biomarker and genetic data may improve the performance of existing risk models; the inclusion of biomarkers into existing risk models depends on easily being able to obtain these measures. As such, tissue does not lend itself to a screening or risk assessment as tissue sampling of the pancreas is not trivial. A promising alternative is measurement in blood, a less invasive and more easily collected biospecimen. Below, we summarize the latest research on blood biomarkers for early detection.

CA19-9

To date, CA19-9, a type of carbohydrate secreted by exocrine epithelial cells and, more specifically, an isolated form of Lewis antigen, is currently the best serological pancreatic cancer biomarker that is approved by the FDA for pancreatic cancer management (e.g., prognostic marker). Yet it lacks the sensitivity and specificity to be utilized as a screening tool. Prior retrospective, cross-sectional or nested case-control studies have suggested that CA19-9 has a sensitivity and specificity of 68–74% when examining pancreatic cancer cases with healthy or non-cancer controls [177, 178]. Further complicating the use of CA19-9 as a screening tool, CA19-9 may also be elevated in non-malignant conditions, such as pancreatitis and biliary obstruction or other malignancies (e.g., colorectal cancer), and it can only be expressed in individuals with Lewis a+/b− or Lewis a+/b+ genotypes (5–10% of population are Lewis a−/b− genotype and cannot express CA19-9) [179]. Therefore, many efforts have been taken to improve the performance of the CA19-9 test. Like most complex diseases, the etiology of pancreatic cancers involves a number and combination of risk factors. Thus, a panel of multiple biomarkers may be necessary for use as a screening tool [180–183, 184•]; the combined effect of a panel may increase sensitivity and reduce false positives. To this end, one large prospective study, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO, examined 67 biomarkers including CA 19-9, carcinoembryonic antigen (CEA), neuron-specific enolase, beta human chorionic gonadotropin, carcinoembryonic antigen-related cell adhesion molecule 1, and prolactin (which are significantly altered in sera) in combination. CA19-9 plus CEA had the highest diagnostic power of 0.66 in all possible two biomarker panels; no biomarkers were identified that performed significantly better than CA19-9 alone (AUC = 0.66) [185]. Given the low diagnostic power, CA19-9 alone or in combination is not effective as a screening tool.

Proteins and Proteomics

Aberrant glycosylation of glycoproteins has been correlated to several diseases including cancer; a number of studies have examined select proteins or glycoproteins with pancreatic cancer risk. In one cross-sectional study, the combination of α-1-antichymotrypsin (AACT), thrombospondin-1 (THBS-1), and haptoglobin (HPT) (AUC = 0.95, AUC = 0.85) outperformed CA 19–9 (AUC = 0.89) in distinguishing 37 pancreatic cancer cases from 30 healthy control and 112 non-cancer controls, respectively [186]. Other studies have observed strong AUCs for MUC5AC, a member of the mucin family, a heterogeneous group of 21 abundant, high molecular weight O-glycoproteins that can be either secreted or membrane bound; the AUC for the combination of MUC5AC with CA19-9 to differentiate pancreatic cancer cases from benign and chronic pancreatitis controls was statistically significantly greater (0.91, 0.86–0.95) compared with the AUC for the CA19-9 model alone (0.61, CI 0.86–0.95). Inclusion of MUC5AC with CA19-9 improved its specificity (from 43 to 83%) and sensitivity (from 79 to 83%) for differentiating pancreatic cancer cases from controls (e.g., healthy, benign gastrointestinal conditions, chronic pancreatitis) [187]. Whereas, a large prospective study, United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS, which profiled 225 serum proteins, found the combination of THBS-1 and CA19–9 achieved a significantly higher AUC of 0.85 ($P < 0.01$) than both markers alone [188]. In addition, plasma thrombospondin-2 (THBS-2) concentrations discriminated among all stages of pancreatic adenocarcinoma with a receiver operating characteristic (ROC) c-statistic of 0.76–0.88 [189]; the c-statistic improved to 0.96–0.97 with CA19-9. Further, the sensitivity was 87% and specificity was 98% for the combination of THBS-2 and CA19-9. A recent study identified CA19-9 and melanoma

inhibitory activity (MIA) or CA19-9 and macrophage inhibitory cytokine-1 (MIC-1) as best biomarkers to separate early stage pancreatic adenocarcinoma cases from chronic pancreatitis (AUC CA19-9 + MIA = 0.86 vs. AUC CA19-9 = 0.81) or IPMN (AUC CA19-9 + MIC-1 = 0.81 vs. AUC CA19-9 = 0.75) in 188 pancreatic adenocarcinoma cases and 220 non-cancer controls [190]. Future research should confirm these findings in larger prospective studies.

ctDNA

Nucleic acids are released due to apoptosis and necrosis of cells and circulate in the peripheral blood [191]. Circulating nucleic acids (DNA, mRNA, and microRNA (miRNA)) have been positively associated with tumor burden and malignant progression [191]. Thus, many attempts have been made to exploit ctDNA as a cancer biomarker for many tumor types including the pancreas. The major ctDNA biomarker of interest for pancreatic cancer is mutated KRAS, given it is the earliest genetic alteration, an important component in the pathogenesis of pancreatic cancer [192], and is mutated in > 90% of pancreas cancer patients [193]. Circulating mutated KRAS DNA was identified in 48% of individuals with localized pancreatic cancer and in 85% of patients with advanced disease in a cross-sectional study that included 155 pancreas cancer patients [194]. When KRAS mutations in ctDNA were combined with four protein markers (CA19-9, CEA, HGF, OPN), the sensitivity increased from 30% for detectable KRAS mutation alone to 64% with 99.5% specificity [195]. In a subsequent cross-sectional study, they tested CancerSEEK, a combined assay for genetic alterations and a panel of eight protein biomarkers, which detects 95% of pancreas cancer at 99% specificity [196•]. However, it should be noted that these studies were cross-sectional and not prospective, and mutations in KRAS are not specific to pancreatic cancer but arise in many other cancers.

Circulating Cancer Cells

The presence of circulating tumor cells (CTCs) that have disseminated into peripheral blood is the first step during the formation of metastasis [197]. Therefore, the detection of pancreatic tumor cells in the peripheral circulation may be a useful tool for screening. The greatest challenge in the detection of CTCs is their rarity in the blood (~ 1 CTC per billion blood cells). In a cross-sectional study ($N = 25$ cases, 15 benign controls) [198], the positive expression rates of C-MET, h-TERT, CK20, and CEA in the pancreatic cancer group were 80% (20/25), 100% (25/25), 84% (21/25), and 80% (20/25), respectively, while in the benign disease control group the rates were 0% (0/15), 0% (0/15), 6.77% (1/15), and 0% (0/15), respectively. Several other studies also reported the presence of CTCs in peripheral blood from pancreatic cancer patients, but using different platforms make it challenging to reach a consensus for clinical application [199, 200]. Although promising, given the small clinical sample and cross-sectional nature, future prospective research is warranted.

Circulating Exosomal DNA

Exosomes are 40–150 nm extracellular vesicles that contain DNA, RNA, and proteins [201]. All living cells, including cancer cells, generate exosomes, and cancer cells generate higher levels of exosomes than normal cells [202]. Exosomes arise from viable cancer cells and may reflect different biology than circulating cell-free DNA (cfDNA) shed from dying tissues [203]. Emerging research has focused on exosomes and their molecular contents as a potential cancer biomarker [204]. Allenson et al. [203] compared exosome-derived DNA to cfDNA to validate KRAS detection rates in liquid biopsies of patients with pancreatic adenocarcinoma using a discovery cohort of 88 pancreatic adenocarcinoma patients, 54 age-matched healthy controls, and a validation cohort of 39 cancer patients and 82 healthy controls. KRAS mutations in exoDNA, were identified in 7.4%, 66.7%, 80%, and 85% of age-matched controls, localized, locally advanced, and metastatic pancreatic adenocarcinoma patients, respectively. Comparatively, mutant KRAS cfDNA was detected in 14.8%, 45.5%, 30.8%, and 57.9% of these individuals. Similarly, KRAS mutations (39.6%) was observed in 48 pancreatic adenocarcinoma patients but only 2.6% in healthy subject [205]. Other studies have also observed higher glypican-1–positive (GPC1) exosome levels [206•] in patients with pancreatic cancer than in controls; GPC1+ crExos (from pancreatic adenocarcinoma, chronic pancreatitis patients and healthy individuals) revealed a near perfect classifier with an AUC of 1.0 (95% CI 0.956–1.0). However, the sample size was small, and all studies were cross-sectional.

Antibody Arrays

Given antibodies are generated against certain tumor-associated antigens (e.g., mesothelin, TNP1) [207], antibody arrays may be useful as potential cancer biomarkers [208]. A three-protein (ERBB2, TNC, and ESR1) panel of plasma biomarkers was identified from 130 test set [209] and demonstrated an AUC of 0.68 and 0.86 when using prediagnostic and diagnostic specimens of pancreatic adenocarcinoma, respectively. When CA 19-9 was added to the panel, the AUC increased to 0.71 and 0.97 for prediagnostic and diagnostic specimens, respectively, suggesting the possibility for use as a diagnostic biomarker panel. Additional studies [210] suggest that IGFBP2 and IGFBP3 are statistically more effective (AUC = 0.94) than CA19-9 alone (AUC = 0.89) at discriminating pancreas cancer patients($n = 101$) at an early stage from healthy controls($n = 38$). Gerdtsson et al. [211] evaluated an

antibody array on human recombinant antibody targeting cytokines and estimated AUC values in the test sets ranged from 0.77 to 0.87 to distinguish pancreatic adenocarcinoma vs. individuals not known to have pancreatic cancer as controls.

Metabolites

Interested in whether altered metabolism may indicate subclinical pancreatic cancer, Mayers et al. [212•] collected prediagnostic plasma from pancreatic cancer cases ($N = 453$) and matched controls ($N = 900$) in a pooled analysis of individual-level data from four prospective cohort studies (median time between blood collected and diagnosis was 8.7 years). They discovered three metabolites (out of 133 studied), the branched chain amino acids (BCAAs) isoleucine, leucine, and valine were significantly associated with a future diagnosis of pancreatic adenocarcinoma. The result also confirmed that plasma BCAAs were elevated in mice with early-stage pancreatic cancers driven by mutant Kras expression. Although not the focus of this review, select urinary metabolites have also been identified as potential early detection markers, including Acetone, O-Acetylcarnitine, Dimethylamine, and Choline. [213]

miRNA

MicroRNAs (miRNAs) are small RNAs (22–25 nt) that negatively regulate gene expression by binding to complementary mRNA resulting in gene silencing, translational repression, or target degradation. The deregulation of some miRNAs has been identified as a mechanism responsible for cell transformation including pancreatic cancer development [214]. Previous studies have reported miR-21, miR-375, miR-196, miR-210, and miR-200 as potential miRNA candidates [214–217]. One small cross-sectional study ($n = 48$ cases) conducted profiling of 45 miRNAs and suggested that MicroRNA-375 improves diagnosis of pancreatic adenocarcinoma in this study (70% accuracy) but did not outperform CA19-9 [218]. Lai et al. [219] found that exosomal glypican-1 (GPC1) is not diagnostic for pancreatic adenocarcinoma whereas the AUC for exosomal miR-10b, miR-21, miR-30c, miR-181a, and miR-let7a had 100% sensitivity and specificity with respect to their accuracy in distinguishing pancreatic adenocarcinoma from normal controls; only miR-106b and miR-483 failed to have an excellent AUC. However, their sample size is small, and the findings should be prospectively confirmed.

Conclusions

Given the late stage of diagnosis and the lack of effective treatment of pancreatic cancer, primary (reduction in exposure to risk factors) and secondary prevention efforts (effective screening modalities) are the best approaches to reduce the morbidity and mortality from this disease. Currently, pancreatic cancer has few known and suspected risk factors, and risk assessment tools have limited utility given their modest discriminatory power range of 0.57–0.81 [220]. Although emerging evidence suggests blood-based biomarkers may be useful as early detection markers, findings need to be confirmed in prospective studies. Due to the rarity of disease, future studies should consider a two-tiered approach in which risk assessment is used to identify high-risk individuals for screening, and then effective imaging and biomarkers in pathways known to affect pancreatic cancer risk are employed; these combination approaches may reduce false positives and mortality compared with just risk assessment or screening alone.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Globocan 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon: International Agency for Research on Cancer; 2016. http://globocan.iarc.fr/. Accessed 06 May 2019.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10–29. https://doi.org/10.3322/caac.20138.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30. https://doi.org/10.3322/caac.21387.
4. American Cancer Society. Survival rates for exocrine pancreatic cancer. 2018. https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html. Accessed 17 May 2019.
5. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER cancer statistics review, 1975–2015. National Cancer Institute Bethesda, MD, https://www.seercancergov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
6. Molina-Montes E, Gomez-Rubio P, Marquez M, Rava M, Lohr M, Michalski CW, et al. Risk of pancreatic cancer associated with family history of cancer and other medical conditions by accounting for smoking among relatives. Int J Epidemiol. 2018;47(2):473–83. https://doi.org/10.1093/ije/dyx269.
7. Ghadirian P, Liu G, Gallinger S, Schmocker B, Paradis AJ, Lal G, et al. Risk of pancreatic cancer among individuals with a

family history of cancer of the pancreas. Int J Cancer. 2002;97(6):807–10.
8. Fehringer G, Gallinger S, Borgida A, Zhang LR, Adams L, Liu G, et al. The association of family history of cancer and medical history with pancreatic cancer risk. Pancreas. 2014;43(5):812–4. https://doi.org/10.1097/mpa.0000000000000126.
9. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Familial Cancer. 2009;8(2):109–17. https://doi.org/10.1007/s10689-008-9214-8.
10.• Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog. 2012;51(1):14–24. https://doi.org/10.1002/mc.20855 **A comprehensive review article on genetic susceptibility and pancreatic cancer.**
11.• Klein AP, Wolpin BM, Risch HA, Stolzenberg-Solomon RZ, Mocci E, Zhang M, et al. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. Nat Commun. 2018;9(1):556. https://doi.org/10.1038/s41467-018-02942-5 **This article identified five new susceptibility loci for pancreatic cancer.**
12. Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP. Update on familial pancreatic cancer. Adv Surg. 2010;44:293–311.
13. Petersen GM. Familial pancreatic cancer. Semin Oncol. 2016;43(5):548–53. https://doi.org/10.1053/j.seminoncol.2016.09.002.
14. McWilliams RR, Rabe KG, Olswold C, De Andrade M, Petersen GM. Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. Cancer. 2005;104(2):388–94. https://doi.org/10.1002/cncr.21166.
15.• Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015;44(1):186–98. https://doi.org/10.1093/ije/dyu240 **A comprehensive review article on the epidemiology of pancreatic cancer.**
16. Wittel UA, Momi N, Seifert G, Wiech T, Hopt UT, Batra SK. The pathobiological impact of cigarette smoke on pancreatic cancer development (review). Int J Oncol. 2012;41(1):5–14. https://doi.org/10.3892/ijo.2012.1414.
17. Zheng Z, Zheng R, He Y, Sun X, Wang N, Chen T, et al. Risk factors for pancreatic cancer in China: a multicenter case-control study. J Epidemiol. 2016;26(2):64–70. https://doi.org/10.2188/jea.JE20140148.
18. Wang Y, Duan H, Yang X, Guo J. Cigarette smoking and the risk of pancreatic cancer: a case-control study. Med Oncol. 2014;31(10):184. https://doi.org/10.1007/s12032-014-0184-4.
19. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the international pancreatic cancer case-control consortium (Panc4). Ann Oncol. 2012;23(7):1880–8. https://doi.org/10.1093/annonc/mdr541.
20. Zou L, Zhong R, Shen N, Chen W, Zhu B, Ke J, et al. Non-linear dose-response relationship between cigarette smoking and pancreatic cancer risk: evidence from a meta-analysis of 42 observational studies. Eur J Cancer. 2014;50(1):193–203. https://doi.org/10.1016/j.ejca.2013.08.014.
21. Gapstur SM, Gann P. Is pancreatic cancer a preventable disease? JAMA. 2001;286(8):967–8.
22. Elena JW, Steplowski E, Yu K, Hartge P, Tobias GS, Brotzman MJ, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Cancer Causes Control. 2013;24(1):13–25. https://doi.org/10.1007/s10552-012-0078-8.
23. Meinhold CL, Berrington de Gonzalez A, Albanes D, Weinstein SJ, Taylor PR, Virtamo J, et al. Predictors of fasting serum insulin and glucose and the risk of pancreatic cancer in smokers. Cancer Causes Control. 2009;20(5):681–90. https://doi.org/10.1007/s10552-008-9281-z.
24. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir. 2004;59(2):99–111.
25. Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1199–209 e4. https://doi.org/10.1053/j.gastro.2013.02.007.
26. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, 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. https://doi.org/10.1001/archinternmed.2010.63.
27. Jiao L, Berrington de Gonzalez A, Hartge P, Pfeiffer RM, Park Y, Freedman DM, 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):1305–14. https://doi.org/10.1007/s10552-010-9558-x.
28.• Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol. 2015;26(11):2257–66. https://doi.org/10.1093/annonc/mdv355 **This pooled analysis, representing one of the largest studies to date, observed an association between central obesity and pancreatic cancer mortality.**
29. Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer. 2011;129(7):1708–17. https://doi.org/10.1002/ijc.25794.
30.• Diet, nutrition, physical activity and cancer: a global perspective. Washington, DC: World Cancer Research Fund and the American Institute for Cancer Research; 2018. **This report is a systematic review of the associations between diet, nutrition, obesity and physical activity and risk of site-specific cancers (e.g., pancreatic).**
31. Foster JR, Idle JR, Hardwick JP, Bars R, Scott P, Braganza JM. Induction of drug-metabolizing enzymes in human pancreatic cancer and chronic pancreatitis. J Pathol. 1993;169(4):457–63.
32. Go VL, Gukovskaya A, Pandol SJ. Alcohol and pancreatic cancer. Alcohol. 2005;35(3):205–11.
33. Poschl G, Seitz HK. Alcohol and cancer. Alcohol Alcohol. 2004;39(3):155–65.
34. Ulrich CM, Bigler J, Bostick R, Fosdick L, Potter JD. Thymidylate synthase promoter polymorphism, interaction with folate intake, and risk of colorectal adenomas. Cancer Res. 2002;62(12):3361–4.
35. Bouchardy C, Clavel F, La Vecchia C, Raymond L, Boyle P. Alcohol, beer and cancer of the pancreas. Int J Cancer. 1990;45(5):842–6.
36. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P. Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in the Netherlands. Int J Cancer. 1992;50(4):514–22.
37. Clavel F, Benhamou E, Auquier A, Tarayre M, Flamant R. Coffee, alcohol, smoking and cancer of the pancreas: a case-control study. Int J Cancer. 1989;43(1):17–21.
38. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr. Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol. 1988;128(2):324–36.
39. Ferraroni M, Negri E, La Vecchia C, D'Avanzo B, Franceschi S. Socioeconomic indicators, tobacco and alcohol in the aetiology of digestive tract neoplasms. Int J Epidemiol. 1989;18(3):556–62.

40. Haines AP, Moss AR, Whittemore A, Quivey J. A case-control study of pancreatic carcinoma. J Cancer Res Clin Oncol. 1982;103(1):93–7.
41. Ji BT, Chow WH, Dai Q, McLaughlin JK, Benichou J, Hatch MC, et al. Cigarette smoking and alcohol consumption and the risk of pancreatic cancer: a case-control study in Shanghai, China. Cancer Causes Control. 1995;6(4):369–76.
42. Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A, Trichopoulos D. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. Cancer Causes Control. 1993;4(4):375–82.
43. Lyon JL, Mahoney AW, French TK, Moser R Jr. Coffee consumption and the risk of cancer of the exocrine pancreas: a case-control study in a low-risk population. Epidemiology. 1992;3(2):164–70.
44. Lyon JL, Slattery ML, Mahoney AW, Robison LM. Dietary intake as a risk factor for cancer of the exocrine pancreas. Cancer Epidemiol Biomarkers Prev. 1993;2(6):513–8.
45. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. J Natl Cancer Inst. 1986;76(1):49–60.
46. MacMahon B. Risk factors for cancer of the pancreas. Cancer. 1982;50(11 Suppl):2676–80.
47. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, et al. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol. 1992;22(4):286–91.
48. Nkondjock A, Krewski D, Johnson KC, Ghadirian P. Dietary patterns and risk of pancreatic cancer. Int J Cancer. 2005;114(5):817–23.
49. Silverman DT. Risk factors for pancreatic cancer: a case-control study based on direct interviews. Teratog Carcinog Mutagen. 2001;21(1):7–25.
50. Silverman DT, Brown LM, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, et al. Alcohol and pancreatic cancer in blacks and whites in the United States. Cancer Res. 1995;55(21):4899–905.
51. Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E. Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. Eur J Cancer Prev. 1998;7(6):455–60.
52. Tavani A, Pregnolato A, Negri E, La Vecchia C. Alcohol consumption and risk of pancreatic cancer. Nutr Cancer. 1997;27(2):157–61.
53. Villeneuve PJ, Johnson KC, Hanley AJ, Mao Y. Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian enhanced surveillance system case-control project. Canadian Cancer registries epidemiology research group. Eur J Cancer Prev. 2000;9(1):49–58.
54. Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. Int J Cancer. 1993;53(4):601–7.
55. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int J Cancer. 1989;43(3):415–21.
56. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol. 2007;102(12):2696–707.
57. Lu XH, Wang L, Li H, Qian JM, Deng RX, Zhou L. Establishment of risk model for pancreatic cancer in Chinese Han population. World J Gastroenterol. 2006;12(14):2229–34.
58. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. Am J Public Health. 1989;79(8):1016–9.
59. Partanen TJ, Vainio HU, Ojajarvi IA, Kauppinen TP. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. Cancer Lett. 1997;116(1):27–32.
60. Pfeffer F, Avilas Rosas H, Vargas F, Villalobos JJ. Smoking, consumption of alcoholic beverages and coffee as factors associated with the development of cancer of the pancreas. Rev Investig Clin. 1989;41(3):205–8.
61. Ghadirian P, Simard A, Baillargeon J. Tobacco, alcohol, and coffee and cancer of the pancreas. A population-based, case-control study in Quebec, Canada. Cancer. 1991;67(10):2664–70.
62. Inoue M, Tajima K, Takezaki T, Hamajima N, Hirose K, Ito H, et al. Epidemiology of pancreatic cancer in Japan: a nested case-control study from the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC). Int J Epidemiol. 2003;32(2):257–62.
63. Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, et al. Diet and other risk factors for cancer of the pancreas. Cancer. 1985;55(2):460–7.
64. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's health study. Cancer Epidemiol Biomarkers Prev. 1997;6(12):1081–6.
65. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish twin registry. Int J Cancer. 2002;98(3):480–2.
66. Kato I, Nomura AM, Stemmermann GN, Chyou PH. Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. Cancer Causes Control. 1992;3(2):145–51.
67. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. Int J Cancer. 2002;99(5):742–6.
68. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. Cancer Epidemiol Biomarkers Prev. 2001;10(5):429–37.
69. Ye W, Lagergren J, Weiderpass E, Nyren O, Adami HO, Ekbom A. Alcohol abuse and the risk of pancreatic cancer. Gut. 2002;51(2):236–9.
70. Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control. 1993;4(5):477–82.
71.• Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomark Prev. 2009;18(3):765–76. https://doi.org/10.1158/1055-9965.EPI-08-0880. **One of the largest analyses of prospective data on the association between alcohol intake and pancreatic cancer.**
72.• Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the international pancreatic cancer case-control consortium (PanC4). Ann Oncol. 2012;23(2):374–82. https://doi.org/10.1093/annonc/mdr120. **One of the largest analyses of retrospective data on the association between alcohol consumption and pancreatic cancer.**
73.• Michaud DS, Vrieling A, Jiao L, Mendelsohn JB, Steplowski E, Lynch SM, et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). Cancer Causes Control. 2010;21(8):1213–25. https://doi.org/10.1007/s10552-010-9548-z. **One of the largest analyses of**

prospective data on the association between alcohol and pancreatic cancer risk.

74. 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):915–23.
75. Larsson SC, Hakansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. J Natl Cancer Inst. 2006;98(6):407–13.
76. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
77. Koushik A, Spiegelman D, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, et al. Intake of fruits and vegetables and risk of pancreatic cancer in a pooled analysis of 14 cohort studies. Am J Epidemiol. 2012;176(5):373–86. https://doi.org/10.1093/aje/kws027.
78. Genkinger JM, Wang M, Li R, Albanes D, Anderson KE, Bernstein L, et al. Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. Ann Oncol. 2014. https://doi.org/10.1093/annonc/mdu019.
79. Genkinger J, Li R, Spiegelman D, Anderson KE, Albanes D, Bergkvist L, et al. Coffee, tea and sugar-sweetened carbonated soft drink intake and pancreatic cancer risk: a pooled analysis of 14 cohort studies. Cancer Epidemiol Biomarkers Prev. 2012;21(2):305–18. https://doi.org/10.1158/1055-9965.EPI-11-0945-T.
80. Bray GA, Benfield JR. Intestinal bypass for obesity a summary and perspective. Am J Clin Nutr. 1977;30(1):121–7.
81. Inoue-Choi M, Flood A, Robien K, Anderson K. Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2011;20(4):711–4. https://doi.org/10.1158/1055-9965.EPI-11-0026.
82. Nothlings U, Murphy SP, Wilkens LR, Boeing H, Schulze MB, Bueno-de-Mesquita HB, et al. A food pattern that is predictive of flavonol intake and risk of pancreatic cancer. Am J Clin Nutr. 2008;88(6):1653–62. https://doi.org/10.3945/ajcn.2008.26398.
83. Bosetti C, Bravi F, Turati F, Edefonti V, Polesel J, Decarli A, et al. Nutrient-based dietary patterns and pancreatic cancer risk. Ann Epidemiol. 2013;23(3):124–8. https://doi.org/10.1016/j.annepidem.2012.12.005.
84. Chan JM, Gong Z, Holly EA, Bracci PM. Dietary patterns and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Nutr Cancer. 2013;65(1):157–64. https://doi.org/10.1080/01635581.2012.725502.
85. Michaud DS, Skinner HG, Wu K, Hu F, Giovannucci E, Willett WC, et al. Dietary patterns and pancreatic cancer risk in men and women. J Natl Cancer Inst. 2005;97(7):518–24.
86. Arem H, Reedy J, Sampson J, Jiao L, Hollenbeck AR, Risch H, et al. The healthy eating index 2005 and risk for pancreatic cancer in the NIH-AARP study. J Natl Cancer Inst. 2013;105(17):1298–305. https://doi.org/10.1093/jnci/djt185.
87. Bosetti C, Turati F, Dal Pont A, Ferraroni M, Polesel J, Negri E, et al. The role of Mediterranean diet on the risk of pancreatic cancer. Br J Cancer. 2013;109(5):1360–6. https://doi.org/10.1038/bjc.2013.345.
88. Lu PY, Shu L, Shen SS, Chen XJ, Zhang XY. Dietary patterns and pancreatic cancer risk: a meta-analysis. Nutrients. 2017;9(1). https://doi.org/10.3390/nu9010038.
89.• Zheng J, Guinter MA, Merchant AT, Wirth MD, Zhang J, Stolzenberg-Solomon RZ, et al. Dietary patterns and risk of pancreatic cancer: a systematic review. Nutr Rev. 2017;75(11):883–908. https://doi.org/10.1093/nutrit/nux038. **A comprehensive review on dietary patterns and pancreatic cancer.**
90. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. Eur J Epidemiol. 2015;30(4):279–98. https://doi.org/10.1007/s10654-015-0014-9.
91. Brenner DR, Wozniak MB, Feyt C, Holcatova I, Janout V, Foretova L, et al. Physical activity and risk of pancreatic cancer in a central European multicenter case-control study. Cancer Causes Control. 2014;25(6):669–81. https://doi.org/10.1007/s10552-014-0370-x.
92. 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):140–7. https://doi.org/10.1002/ijc.1446.
93. Calton BA, Stolzenberg-Solomon RZ, Moore SC, Schatzkin A, Schairer C, Albanes D, et al. A prospective study of physical activity and the risk of pancreatic cancer among women (United States). BMC Cancer. 2008;8:63. https://doi.org/10.1186/1471-2407-8-63.
94.• Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1462–73. https://doi.org/10.1158/1055-9965.Epi-15-0301. **A comprehensive review on leisure-time physical activity and pancreatic cancer.**
95. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, 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):879–85.
96. 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):165–75.
97. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. cohort. Cancer Epidemiol Biomarkers Prev. 2005;14(2):459–66.
98. Stolzenberg-Solomon RZ, Adams K, Leitzmann M, Schairer C, Michaud DS, Hollenbeck A, et al. Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP diet and health cohort. Am J Epidemiol. 2008;167(5):586–97. https://doi.org/10.1093/aje/kwm361.
99. Andren-Sandberg A, Hoem D, Backman PL. Other risk factors for pancreatic cancer: hormonal aspects. Ann Oncol. 1999;10(Suppl 4):131–5.
100. Robles-Diaz G, Duarte-Rojo A. Pancreas: a sex steroid-dependent tissue. Isr Med Assoc J. 2001;3(5):364–8.
101. Sumi C, Brinck-Johnsen T, Longnecker DS. Inhibition of a transplantable pancreatic carcinoma by castration and estradiol administration in rats. Cancer Res. 1989;49(23):6687–92.
102. Sumi C, Longnecker DS, Roebuck BD, Brinck-Johnsen T. Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in Fischer rats treated with azaserine. Cancer Res. 1989;49(9):2332–6.
103. Andersson G, Borgquist S, Jirstrom K. Hormonal factors and pancreatic cancer risk in women: the Malmo diet and Cancer study. Int J Cancer. 2018;143(1):52–62. https://doi.org/10.1002/ijc.31302.
104. Prizment AE, Anderson KE, Hong CP, Folsom AR. Pancreatic cancer incidence in relation to female reproductive factors: Iowa Women's health study. JOP. 2007;8(1):16–27.
105. Skinner HG, Michaud DS, Colditz GA, Giovannucci EL, Stampfer MJ, Willett WC, et al. Parity, reproductive factors, and the risk of pancreatic cancer in women. Cancer Epidemiol Biomarkers Prev. 2003;12(5):433–8.

106. Navarro Silvera SA, Miller AB, Rohan TE. Hormonal and reproductive factors and pancreatic cancer risk: a prospective cohort study. Pancreas. 2005;30(4):369–74.
107. Luo AJ, Feng RH, Wang XW, Wang FZ. Older age at first birth is a risk factor for pancreatic cancer: a meta-analysis. Hepatobiliary Pancreat Dis Int. 2016;15(2):125–30.
108. Stevens RJ, Roddam AW, Green J, Pirie K, Bull D, Reeves GK, et al. Reproductive history and pancreatic cancer incidence and mortality in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1457–60. https://doi.org/10.1158/1055-9965.Epi-08-1134.
109. Lujan-Barroso L, Zhang W, Olson SH, Gao YT, Yu H, Baghurst PA, et al. Menstrual and reproductive factors, hormone use, and risk of pancreatic Cancer: analysis from the international pancreatic cancer case-control consortium (PanC4). Pancreas. 2016;45(10):1401–10. https://doi.org/10.1097/mpa.0000000000000635.
110. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, Mortensen FV. Acute pancreatitis and pancreatic cancer risk: a Nationwide matched-cohort study in Denmark. Gastroenterology. 2018;154(6):1729–36. https://doi.org/10.1053/j.gastro.2018.02.011.
111. Ekbom A, McLaughlin JK, Karlsson BM, Nyren O, Gridley G, Adami HO, et al. Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst. 1994;86(8):625–7.
112. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24(3):349–58. https://doi.org/10.1016/j.bpg.2010.02.007.
113. Pang Y, Kartsonaki C, Guo Y, Bragg F, Yang L, Bian Z, et al. Diabetes, plasma glucose and incidence of pancreatic cancer: a prospective study of 0.5 million Chinese adults and a meta-analysis of 22 cohort studies. Int J Cancer. 2017;140(8):1781–8. https://doi.org/10.1002/ijc.30599.
114. Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the international pancreatic cancer case-control consortium. Ann Oncol. 2014;25(10):2065–72. https://doi.org/10.1093/annonc/mdu276.
115. Haugvik SP, Hedenstrom P, Korsaeth E, Valente R, Hayes A, Siuka D, et al. Diabetes, smoking, alcohol use, and family history of cancer as risk factors for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Neuroendocrinology. 2015;101(2):133–42. https://doi.org/10.1159/000375164.
116. Walker EJ, Ko AH, Holly EA, Bracci PM. Metformin use among type 2 diabetics and risk of pancreatic cancer in a clinic-based case-control study. Int J Cancer. 2015;136(6):E646–53. https://doi.org/10.1002/ijc.29120.
117. Lu Y, Garcia Rodriguez LA, Malgerud L, Gonzalez-Perez A, Martin-Perez M, Lagergren J, et al. New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. Br J Cancer. 2015;113(11):1607–14. https://doi.org/10.1038/bjc.2015.353.
118. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, Zhu J, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2014;106(1):19–26. https://doi.org/10.1016/j.diabres.2014.04.007.
119. Hamada T, Khalaf N, Yuan C, Babic A, Morales-Oyarvide V, Qian ZR, et al. Statin use and pancreatic cancer risk in two prospective cohort studies. J Gastroenterol. 2018;53(8):959–66. https://doi.org/10.1007/s00535-018-1430-x.
120. Chiu HF, Chang CC, Ho SC, Wu TN, Yang CY. Statin use and the risk of pancreatic cancer: a population-based case-control study. Pancreas. 2011;40(5):669–72. https://doi.org/10.1097/MPA.0b013e31821fd5cd.
121. Walker EJ, Ko AH, Holly EA, Bracci PM. Statin use and risk of pancreatic cancer: results from a large, clinic-based case-control study. Cancer. 2015;121(8):1287–94. https://doi.org/10.1002/cncr.29256.
122. Cui X, Xie Y, Chen M, Li J, Liao X, Shen J, et al. Statin use and risk of pancreatic cancer: a meta-analysis. Cancer Causes Control. 2012;23(7):1099–111. https://doi.org/10.1007/s10552-012-9979-9.
123. Archibugi L, Arcidiacono PG, Capurso G. Statin use is associated to a reduced risk of pancreatic cancer: a meta-analysis. Dig Liver Dis. 2018. https://doi.org/10.1016/j.dld.2018.09.007.
124. Shimoda T, Shikata T, Karasawa T, Tsukagoshi S, Yoshimura M, Sakurai I. Light microscopic localization of hepatitis B virus antigens in the human pancreas. Possibility of multiplication of hepatitis B virus in the human pancreas. Gastroenterology. 1981;81(6):998–1005.
125. Yoshimura M, Sakurai I, Shimoda T, Abe K, Okano T, Shikata T. Detection of HBsAg in the pancreas. Acta Pathol Jpn. 1981;31(4):711–7.
126. Alvares-Da-Silva MR, Francisconi CF, Waechter FL. Acute hepatitis C complicated by pancreatitis: another extrahepatic manifestation of hepatitis C virus? J Viral Hepat. 2000;7(1):84–6.
127. Torbenson M, Yeh MM, Abraham SC. Bile duct dysplasia in the setting of chronic hepatitis C and alcohol cirrhosis. Am J Surg Pathol. 2007;31(9):1410–3. https://doi.org/10.1097/PAS.0b013e318053d122.
128. Huang J, Zagai U, Hallmans G, Nyren O, Engstrand L, Stolzenberg-Solomon R, et al. Helicobacter pylori infection, chronic corpus atrophic gastritis and pancreatic cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort: a nested case-control study. Int J Cancer. 2017;140(8):1727–35. https://doi.org/10.1002/ijc.30590.
129. Xu JH, Fu JJ, Wang XL, Zhu JY, Ye XH, Chen SD. Hepatitis B or C viral infection and risk of pancreatic cancer: a meta-analysis of observational studies. World J Gastroenterol. 2013;19(26):4234–41. https://doi.org/10.3748/wjg.v19.i26.4234.
130. Krull Abe S, Inoue M, Sawada N, Iwasaki M, Shimazu T, Yamaji T, et al. Hepatitis B and C virus infection and risk of pancreatic cancer: a population-based cohort study (JPHC study cohort II). Cancer Epidemiol Biomarkers Prev. 2016;25(3):555–7. https://doi.org/10.1158/1055-9965.Epi-15-1115.
131. Liu H, Chen YT, Wang R, Chen XZ. Helicobacter pylori infection, atrophic gastritis, and pancreatic cancer risk: a meta-analysis of prospective epidemiologic studies. Medicine. 2017;96(33):e7811. https://doi.org/10.1097/md.0000000000007811.
132. Schulte A, Pandeya N, Fawcett J, Fritschi L, Risch HA, Webb PM, et al. Association between helicobacter pylori and pancreatic cancer risk: a meta-analysis. Cancer Causes Control. 2015;26(7):1027–35. https://doi.org/10.1007/s10552-015-0595-3.
133. Risch HA, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, et al. Helicobacter pylori seropositivities and risk of pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev. 2014;23(1):172–8. https://doi.org/10.1158/1055-9965.Epi-13-0447.
134. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut. 2018;67(1):120–7. https://doi.org/10.1136/gutjnl-2016-312580.
135. Huang J, Roosaar A, Axell T, Ye W. A prospective cohort study on poor oral hygiene and pancreatic cancer risk. Int J Cancer. 2016;138(2):340–7. https://doi.org/10.1002/ijc.29710.
136.• Michaud DS, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjonneland A, et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut, 2013;62(12):1764–70. https://doi.org/10.1136/gutjnl-2012-303006. **This study found that periodontal disease may increase the risk of pancreatic cancer.**

137. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst. 2007;99(2):171–5. https://doi.org/10.1093/jnci/djk021.
138. Humans IWGotEoCRt. Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum. 2012;100(PT C):11.
139.• IARC. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC Monogr Eval Carcinog Risks Hum. 1993;58:1–415 **This article identified compounds in occupational settings as carcinogens.**
140. Ojajarvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2000;57(5):316–24.
141. Alguacil J, Porta M, Kauppinen T, Malats N, Kogevinas M, Carrato A. Occupational exposure to dyes, metals, polycyclic aromatic hydrocarbons and other agents and K-ras activation in human exocrine pancreatic cancer. Int J Cancer. 2003;107(4):635–41. https://doi.org/10.1002/ijc.11431.
142. Carrigan PE, Hentz JG, Gordon G, Morgan JL, Raimondo M, Anbar AD, et al. Distinctive heavy metal composition of pancreatic juice in patients with pancreatic carcinoma. Cancer Epidemiol Biomarkers Prev. 2007;16(12):2656–63. https://doi.org/10.1158/1055-9965.Epi-07-0332.
143. Adams SV, Passarelli MN, Newcomb PA. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. Occup Environ Med. 69(2):153–6.
144. Sawada N, Iwasaki M, Inoue M, Takachi R, Sasazuki S, Yamaji T, et al. Long-term dietary cadmium intake and cancer incidence. Epidemiology. 2012;23(3):368–76. https://doi.org/10.1097/EDE.0b013e31824d063c.
145. Amaral AF, Porta M, Silverman DT, Milne RL, Kogevinas M, Rothman N, et al. Pancreatic cancer risk and levels of trace elements. Gut. 2012;61(11):1583–8. https://doi.org/10.1136/gutjnl-2011-301086.
146. Elinder CG, Kjellstrom T, Hogstedt C, Andersson K, Spang G. Cancer mortality of cadmium workers. Br J Ind Med. 1985;42(10):651–5.
147. Garcia-Esquinas E, Pollan M, Tellez-Plaza M, Francesconi KA, Goessler W, Guallar E, et al. Cadmium exposure and cancer mortality in a prospective cohort: the strong heart study. Environ Health Perspect. 2014;122(4):363–70. https://doi.org/10.1289/ehp.1306587.
148. Garcia-Esquinas E, Pollan M, Umans JG, Francesconi KA, Goessler W, Guallar E, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1944–53. https://doi.org/10.1158/1055-9965.EPI-13-0234-T.
149. Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occup Environ Med. 1998;55(11):755–9.
150. Kriegel AM, Soliman AS, Zhang Q, El-Ghawalby N, Ezzat F, Soultan A, et al. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta region of Egypt. Environ Health Perspect. 2006;114(1):113.
151. Liu-Mares W, Mackinnon JA, Sherman R, Fleming LE, Rocha-Lima C, Hu JJ, et al. Pancreatic cancer clusters and arsenic-contaminated drinking water wells in Florida. BMC Cancer. 2013;13:111. https://doi.org/10.1186/1471-2407-13-111.
152. Luckett BG, Su LJ, Rood JC, Fontham ET. Cadmium exposure and pancreatic cancer in South Louisiana. J Environ Public Health. 2012;2012:180186. https://doi.org/10.1155/2012/180186.
153. Yorifuji T, Tsuda T, Grandjean P. Unusual cancer excess after neonatal arsenic exposure from contaminated milk powder. J Natl Cancer Inst. 2010;102(5):360–1. https://doi.org/10.1093/jnci/djp536.
154. Chen C, Xun P, Nishijo M, Sekikawa A, He K. Cadmium exposure and risk of pancreatic cancer: a meta-analysis of prospective cohort studies and case-control studies among individuals without occupational exposure history. Environ Sci Pollut Res Int. 2015;22(22):17465–74. https://doi.org/10.1007/s11356-015-5464-9.
155. Antwi SO, Eckert EC, Sabaque CV, Leof ER, Hawthorne KM, Bamlet WR, et al. Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. Cancer Causes Control. 2015;26(11):1583–91. https://doi.org/10.1007/s10552-015-0652-y.
156. Current cigarette smoking among adults - United States, 2011. MMWR Morbid Mortal Wkly Rep. 2012;61(44):889–94.
157. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 2014;311(2):183–92. https://doi.org/10.1001/jama.2013.284692.
158. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006;295(13):1549–55. https://doi.org/10.1001/jama.295.13.1549.
159. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81. https://doi.org/10.1016/s0140-6736(14)60460-8.
160. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414–31.
161. Ghadirian P, Lynch HT, Krewski D. Epidemiology of pancreatic cancer: an overview. Cancer Detect Prev. 2003;27(2):87–93.
162. Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. J Cell Biochem. 2005;95(4):649–56.
163. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20(2):197–209.
164. Food, Nutrition, Physical activity and the prevention of cancer: a global perspective. Washington, DC: World Cancer Research Fund and the American Institute for Cancer Research; 2007.
165.• Klein AP, Lindstrom S, Mendelsohn JB, Steplowski E, Arslan AA, Bueno-de-Mesquita HB, et al. An absolute risk model to identify individuals at elevated risk for pancreatic cancer in the general population. PloS one. 2013;8(9):e72311. https://doi.org/10.1371/journal.pone.0072311 **This study developed an absolute risk model for men and women of European descent using non-genetic and genetic factors to identify individuals at high-risk of pancreatic cancer.**
166.• Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol. 2007;25(11):1417–22. https://doi.org/10.1200/jco.2006.09.2452. **PancPRO, a mendelian risk prediction model for pancreatic cancer in individuals with familial pancreatic cancer, was developed and validated within this study.**
167. Nakatochi M, Lin Y, Ito H, Hara K, Kinoshita F, Kobayashi Y, et al. Prediction model for pancreatic cancer risk in the general Japanese population. PLoS One. 2018;13(9):e0203386. https://doi.org/10.1371/journal.pone.0203386.
168. Yu A, Woo SM, Joo J, Yang HR, Lee WJ, Park SJ, et al. Development and validation of a prediction model to estimate individual risk of pancreatic cancer. PLoS One. 2016;11(1):e0146473. https://doi.org/10.1371/journal.pone.0146473.
169. Pfeiffer RM, Park Y, Kreimer AR, Lacey JV Jr, Pee D, Greenlee RT, et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and

validation from population-based cohort studies. PLoS Med. 2013;10(7):e1001492. https://doi.org/10.1371/journal.pmed.1001492.

170. Wenten M, Gilliland FD, Baumgartner K, Samet JM. Associations of weight, weight change, and body mass with breast cancer risk in Hispanic and non-Hispanic white women. Ann Epidemiol. 2002;12(6):435–4.

171.• Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International cancer of the pancreas screening (CAPS) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013;62(3):339–47. https://doi.org/10.1136/gutjnl-2012-303108 **A consortium on screening for pancreatic cancer of high-risk individuals.**

172.• Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-62; quiz 63. https://doi.org/10.1038/ajg.2014.435. **Guidelines on screening of patients with genetic risk of gastrointestinal cancers.**

173. Munoz D, Near AM, van Ravesteyn NT, Lee SJ, Schechter CB, Alagoz O et al. Effects of screening and systemic adjuvant therapy on ER-Specific US breast cancer mortality. J Natl Cancer Instit. 2014;106(11). https://doi.org/10.1093/jnci/dju289.

174. Usher-Smith JA, Emery J, Kassianos AP, Walter FM. Risk prediction models for melanoma: a systematic review. Cancer Epidemiol Biomarkers Prev. 2014;23(8):1450–63. https://doi.org/10.1158/1055-9965.EPI-14-0295.

175. Wang X, Oldani MJ, Zhao X, Huang X, Qian D. A review of cancer risk prediction models with genetic variants. Cancer Informat. 2014;13(Suppl 2):19–28. https://doi.org/10.4137/CIN.S13788.

176. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015;27(4):332–48. https://doi.org/10.3978/j.issn.1000-9604.2015.06.07.

177. Haab BB, Huang Y, Balasenthil S, Partyka K, Tang HY, Anderson M et al. Definitive characterization of CA 19–9 in resectable pancreatic cancer using a reference set of serum and plasma specimens. Plos One. 2015;10(10). https://doi.org/10.1371/journal.pone.0139049.

178. O'Brien DP, Sandanayake NS, Jenkinson C, Gentry-Maharaj A, Apostolidou S, Fourkala EO, et al. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. Clin Cancer Res. 2015;21(3):622–31. https://doi.org/10.1158/1078-0432.ccr-14-0365.

179. Ballehaninna UK, Chamberlain RS. Serum CA 19-9 as a biomarker for pancreatic cancer-a comprehensive review. Indian J Surg Oncol. 2011;2(2):88–100. https://doi.org/10.1007/s13193-011-0042-1.

180. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? BMJ. 1999;319(7224):1562–5.

181. Barrow TM, Michels KB. Epigenetic epidemiology of cancer. Biochem Biophys Res Commun. 2014;455(1–2):70–83. https://doi.org/10.1016/j.bbrc.2014.08.002.

182. Cho YH, Shen J, Gammon MD, Zhang YJ, Wang Q, Gonzalez K, et al. Prognostic significance of gene-specific promoter hypermethylation in breast cancer patients. Breast Cancer Res Treat. 2012;131(1):197–205. https://doi.org/10.1007/s10549-011-1712-y.

183. Zhang P, Zou M, Wen X, Gu F, Li J, Liu G, et al. Development of serum parameters panels for the early detection of pancreatic cancer. Int J Cancer. 2014;134(11):2646–55. https://doi.org/10.1002/ijc.28584.

184.• Zhou B, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L, et al. Early detection of pancreatic cancer: where are we now and where are we going? Int J Cancer. 2017;141(2):231–41. https://doi.org/10.1002/ijc.30670 **A comprehensive review article on the early detection of pancreatic cancer.**

185. Nolen BM, Brand RE, Prosser D, Velikokhatnaya L, Allen PJ, Zeh HJ, et al. Prediagnostic serum biomarkers as early detection tools for pancreatic cancer in a large prospective cohort study. PLoS One. 2014;9(4):e94928. https://doi.org/10.1371/journal.pone.0094928.

186. Nie S, Lo A, Wu J, Zhu J, Tan Z, Simeone DM, et al. Glycoprotein biomarker panel for pancreatic cancer discovered by quantitative proteomics analysis. J Proteome Res. 2014;13(4):1873–84. https://doi.org/10.1021/pr400967x.

187. Kaur S, Smith LM, Patel A, Menning M, Watley DC, Malik SS, et al. A combination of MUC5AC and CA19-9 improves the diagnosis of pancreatic cancer: a multicenter study. Am J Gastroenterol. 2017;112(1):172–83. https://doi.org/10.1038/ajg.2016.482.

188. Jenkinson C, Elliott VL, Evans A, Oldfield L, Jenkins RE, O'Brien DP, et al. Decreased serum thrombospondin-1 levels in pancreatic cancer patients up to 24 months prior to clinical diagnosis: association with diabetes mellitus. Clinical Cancer Res. 2016;22(7):1734–43. https://doi.org/10.1158/1078-0432.CCR-15-0879.

189. Kim J, Bamlet WR, Oberg AL, Chaffee KG, Donahue G, Cao XJ et al. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. Sci Transl Med. 2017;9(398). https://doi.org/10.1126/scitranslmed.aah5583.

190. Song J, Sokoll LJ, Pasay JJ, Rubin AL, Li H, Bach DM, et al. Identification of serum biomarker panels for the early detection of pancreatic cancer. Cancer Epidemiol Biomark Prev. 2018. https://doi.org/10.1158/1055-9965.EPI-18-0483.

191. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer. 2011;11(6):426–37. https://doi.org/10.1038/nrc3066.

192. di Magliano MP, Logsdon CD. Roles for KRAS in pancreatic tumor development and progression. Gastroenterology. 2013;144(6):1220–9. https://doi.org/10.1053/j.gastro.2013.01.071.

193. Eser S, Schnieke A, Schneider G, Saur D. Oncogenic KRAS signalling in pancreatic cancer. Br J Cancer. 2014;111(5):817–22. https://doi.org/10.1038/bjc.2014.215.

194. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med. 2014;6(224):224ra24. https://doi.org/10.1126/scitranslmed.3007094.

195. Cohen JD, Javed AA, Thoburn C, Wong F, Tie J, Gibbs P, et al. Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. Proc Natl Acad Sci U S A. 2017;114(38):10202–7. https://doi.org/10.1073/pnas.1704961114.

196.• Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018;359(6378):926–30. https://doi.org/10.1126/science.aar3247 **A cross-sectional study using CancerSEEK assay for detection of pancreatic cancer.**

197. Zippelius A, Pantel K. RT-PCR-based detection of occult disseminated tumor cells in peripheral blood and bone marrow of patients with solid tumors. An overview. Ann N Y Acad Sci. 2000;906:110–23.

198. Zhou J, Hu L, Yu Z, Zheng J, Yang D, Bouvet M, et al. Marker expression in circulating cancer cells of pancreatic cancer patients. J Surg Res. 2011;171(2):631–6. https://doi.org/10.1016/j.jss.2010.05.007.

199. Pimienta M, Edderkaoui M, Wang R, Pandol S. The potential for circulating tumor cells in pancreatic cancer management. Front Physiol. 2017;8:381. https://doi.org/10.3389/fphys.2017.00381.

200. Kulemann B, Pitman MB, Liss AS, Valsangkar N, Fernandez-Del Castillo C, Lillemoe KD, et al. Circulating tumor cells found in patients with localized and advanced pancreatic cancer. Pancreas. 2015;44(4):547–50. https://doi.org/10.1097/mpa.0000000000000324.
201. Kalluri R. The biology and function of exosomes in cancer. J Clin Invest. 2016;126(4):1208–15. https://doi.org/10.1172/JCI81135.
202. Whiteside TL. Tumor-derived exosomes and their role in cancer progression. Adv Clin Chem. 2016;74:103–41. https://doi.org/10.1016/bs.acc.2015.12.005.
203. Allenson K, Castillo J, San Lucas FA, Scelo G, Kim DU, Bernard V, et al. High prevalence of mutant KRAS in circulating exosome-derived DNA from early-stage pancreatic cancer patients. Ann Oncol. 2017;28(4):741–7. https://doi.org/10.1093/annonc/mdx004.
204. Kahlert C, Kalluri R. Exosomes in tumor microenvironment influence cancer progression and metastasis. J Mol Med. 2013;91(4):431–7. https://doi.org/10.1007/s00109-013-1020-6.
205. Yang S, Che SP, Kurywchak P, Tavormina JL, Gansmo LB, Correa de Sampaio P, et al. Detection of mutant KRAS and TP53 DNA in circulating exosomes from healthy individuals and patients with pancreatic cancer. Cancer Biol Ther. 2017;18(3):158–65. https://doi.org/10.1080/15384047.2017.1281499.
206.• Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature. 2015;523(7559):177–82. https://doi.org/10.1038/nature14581 **This study identified Glypican-1 on cancer exosomes as a possible biomarker to detect pancreatic cancer.**
207. Dumstrei K, Chen H, Brenner H. A systematic review of serum autoantibodies as biomarkers for pancreatic cancer detection. Oncotarget. 2016;7(10):11151–64. https://doi.org/10.18632/oncotarget.7098.
208. Young MR, Wagner PD, Ghosh S, Rinaudo JA, Baker SG, Zaret KS, et al. Validation of biomarkers for early detection of pancreatic cancer: summary of the alliance of pancreatic cancer consortia for biomarkers for early detection workshop. Pancreas. 2018;47(2):135–41. https://doi.org/10.1097/mpa.0000000000000973.
209. Mirus JE, Zhang Y, Li CI, Lokshin AE, Prentice RL, Hingorani SR, et al. Cross-species antibody microarray interrogation identifies a 3-protein panel of plasma biomarkers for early diagnosis of pancreas cancer. Clin Cancer Res. 2015;21(7):1764–71. https://doi.org/10.1158/1078-0432.CCR-13-3474.
210. Yoneyama T, Ohtsuki S, Honda K, Kobayashi M, Iwasaki M, Uchida Y et al. Identification of IGFBP2 and IGFBP3 as compensatory biomarkers for CA19-9 in early-stage pancreatic cancer using a combination of antibody-based and LC-MS/MS-based proteomics. Plos One. 2016;11(8). https://doi.org/10.1371/journal.pone.0161009.
211. Gerdtsson AS, Wingren C, Persson H, Delfani P, Nordstrom M, Ren H, et al. Plasma protein profiling in a stage defined pancreatic cancer cohort - implications for early diagnosis. Mol Oncol. 2016;10(8):1305–16. https://doi.org/10.1016/j.molonc.2016.07.001.
212.• Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 2014;20(10):1193–8. https://doi.org/10.1038/nm.3686 **This study found elevated levels of BCAAs is associated with pancreatic cancer risk, suggesting that whole-body protein breakdown is an early event in the development of PDAC.**
213. Davis VW, Schiller DE, Eurich D, Bathe OF, Sawyer MB. Pancreatic ductal adenocarcinoma is associated with a distinct urinary metabolomic signature. Ann Surg Oncol. 2013;20(Suppl 3):S415–23. https://doi.org/10.1245/s10434-012-2686-7.
214. Jenkinson C, Earl J, Ghaneh P, Halloran C, Carrato A, Greenhalf W, et al. Biomarkers for early diagnosis of pancreatic cancer. Exp Rev Gastroenterol Hepatol. 2015;9(3):305–15. https://doi.org/10.1586/17474124.2015.965145.
215. Giovannetti E, Funel N, Peters GJ, Del Chiaro M, Erozenci LA, Vasile E, et al. MicroRNA-21 in pancreatic cancer: correlation with clinical outcome and pharmacologic aspects underlying its role in the modulation of gemcitabine activity. Cancer Res. 2010;70(11):4528–38. https://doi.org/10.1158/0008-5472.can-09-4467.
216. Yu J, Li A, Hong SM, Hruban RH, Goggins M. MicroRNA alterations of pancreatic intraepithelial neoplasias. Clin Cancer Res. 2012;18(4):981–92. https://doi.org/10.1158/1078-0432.ccr-11-2347.
217. Munding JB, Adai AT, Maghnouj A, Urbanik A, Zollner H, Liffers ST, et al. Global microRNA expression profiling of microdissected tissues identifies miR-135b as a novel biomarker for pancreatic ductal adenocarcinoma. Int J Cancer. 2012;131(2):E86–95. https://doi.org/10.1002/ijc.26466.
218. Carlsen AL, Joergensen MT, Knudsen S, de Muckadell OB, Heegaard NH. Cell-free plasma microRNA in pancreatic ductal adenocarcinoma and disease controls. Pancreas. 2013;42(7):1107–13. https://doi.org/10.1097/MPA.0b013e318296bb34.
219. Lai XY, Wang M, McElyea SD, Sherman S, House M, Korc M. A microRNA signature in circulating exosomes is superior to exosomal glypican-1 levels for diagnosing pancreatic cancer. Cancer Lett. 2017;393:86–93. https://doi.org/10.1016/j.canlet.2017.02.019.
220. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med. 2013;13(3):340–51.