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Ann Epidemiol. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Ann Epidemiol. 2016 January ; 26(1): 50–56. doi:10.1016/j.annepidem.2015.11.001.

Role of Survivor Bias in Pancreatic Cancer Case-Control Studies

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Abstract

Purpose—The purpose of this study is to evaluate the impact of survivor bias on pancreatic cancer case-control studies.

Methods—The authors constructed five case-loss scenarios based on the Iowa Women's Health Study cohort to reflect how case recruitment in population-based studies varies by case survival time. Risk factors for disease incidence included smoking, body mass index (BMI), waist circumference, diabetes, and alcohol consumption. Odds ratios (OR) were estimated by conditional logistic regression; and quantitatively compared by the interactions between risk factors and 3-month survival time. Additionally, Kaplan-Meier estimates for overall survival were compared within the subset cohort of pancreatic cancer cases.

Results—BMI and waist circumference showed a significant inverse relationship with survival time. Decreasing trends in ORs for BMI and waist circumference were observed with increasing case survival time. The interaction between BMI and survival time based on a cut-point of 3 months was significant ($P < 0.01$) as was the interaction between waist circumference and survival time ($P < 0.01$).

Conclusions—The findings suggested that case losses could result in survivor bias causing underestimated odds ratios for both BMI and waist circumference, while other risk factors were not significantly affected by case losses.

Keywords

pancreatic neoplasm; survivor bias; case control study; body mass index; waist circumference

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Conflicts of Interest

There is no conflict of interest in this study.

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INTRODUCTION

Retrospective case-control studies are widely used in epidemiologic research on pancreatic cancer[1–4], because they require considerably less time and expense to achieve adequate statistical power than a longitudinal cohort study. A critical assumption to ensure the validity of results in case-control studies is that cases and controls must be randomly selected from the same underlying cohort[5]. However, because the disease is so often rapidly fatal[6–8], many pancreatic cancer patients die before they can be interviewed regarding exposure factors, or become physically unable to participate in a study[9,10].

Selection bias – specifically, survivor bias – is a serious threat in case-control studies and it can occur when the exposure (or a cause of the exposure) and the outcome (or a cause of the outcome) are conditionally associated within survival time[11]. Case losses in pancreatic cancer case-control studies could therefore introduce survivor bias, especially for those risk factors of pancreatic cancer incidence that are also conditionally associated with survival time. The common effect of such selection bias is that the observed conditional associations between the risk factors and the disease incidence deviate from the true associations in the underlying cohort[11].

Despite the fact that case-control studies are more sensitive to survivor bias than other study designs[5], few researchers have tried to quantify its effects[3]; those that have, have focused on diseases other than pancreatic cancer[5,12,13]. Only a few recent studies have investigated the association between overweight and overall survival of pancreatic cancer, and none of these were based on prospective cohort studies and hence lack an identified source cohort that would allow for the estimation of survivor bias[1,14].

The purpose of this study is to evaluate the potential impact of survivor bias on pancreatic cancer case-control studies. We hypothesized that survivor bias would have an impact on the estimation of odds ratios (OR) for risk factors of pancreatic cancer incidence such as obesity, waist circumference, and diabetes[1,4,15–17]. The Iowa Women's Health Study (IWHS) cohort with 24 years of follow-up was used for the analyses. Being a complete cohort with data collected in advance of the disease, the IWHS cohort itself has no impact from survivor bias. Using this ideal cohort as a base to address the hypothesis, we constructed a series of nested case-loss scenarios to simulate what would happen in case-control studies if eligible cases were not enrolled due to case losses.

MATERIAL AND METHODS

Data Source

The IWHS is a prospective cohort that started in 1986. Detailed descriptions of the IWHS cohort have been previously published[18,19]. In short, a total of 41,837 randomly selected postmenopausal Iowa women completed a self-administrated questionnaire in 1986 and enrolled in the follow-up. Later, five subsequent questionnaires were sent in 1987, 1989, 1992, 1997 and 2004 respectively. Demographic and health-related information was collected in both the baseline and the five follow-up questionnaires. Information on deaths and cancer incidences was ascertained by annual linkage (from 1986 to 2010) with the State

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Health Registry of Iowa, which is part of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program[20] and the National Death Index. The IWHS and this study were conducted under a protocol approved for human subjects research by the University of Minnesota Institutional Review Board.

Study Design

Of the 41,837 individuals in the IWHS cohort, 38,006 were identified as cancer free at baseline. 338 individuals developed pancreatic cancer by the end of the follow-up. Among them, the following patients were excluded: 37 second primary cancers, 1 endocrine cancer; and 4 rare subtypes, leaving 296 individuals selected as cases, comprising 2.5% of the total cancer population (n = 10,441).

Individuals without primary pancreatic cancer were eligible to be included in the control pool, including those free of cancer and those diagnosed with other types of primary cancers (1.75% upper gastrointestinal tract cancers, 1.54% biliary cancers, 16.6% colorectal cancers, and 80.1% other types of cancers). For each of these 296 cases, five controls with the same baseline age who submitted questionnaires during the same follow-up survey period and were alive at the date of diagnosis of the case were randomly selected from the control pool (n = 1,480).

A total of five case-loss scenarios were constructed with respect to different minimum case survival times after diagnosis:

1. All cases (n = 296, base group).
2. Cases who lived ≥ 1.5 months after diagnosis (n = 222, 75.0% alive, 25% case loss).
3. Cases who lived ≥ 3 months after diagnosis (n = 166, 56.1% alive, 43.9% case loss).
4. Cases who lived ≥ 4.5 months after diagnosis (n = 138, 46.6% alive, 53.4% case loss).
5. Cases who lived ≥ 6 months after diagnosis (n = 114, 38.5% alive, 61.5% case loss).

Statistical Analysis

A conditional logistic regression model was used to estimate the odds ratios of pancreatic cancer incidence for the constructed case-control pairs. Risk factors under investigation included smoking status, pack-years of smoking, body mass index (BMI in kg/m^2), waist circumference, diabetes (age at diagnosis ≥ 30 years), and alcohol consumption. Information for smoking status, BMI and waist circumference was obtained from the latest questionnaire prior to the date of diagnosis for each case, or to the assigned starting dates for the controls. Number of pack-years, diabetes, and alcohol consumption were retrieved from the baseline questionnaire. All odds ratios were adjusted for smoking status and pack-years of smoking as these are well-established risk factors for pancreatic cancer incidence[21]. BMI was also adjusted except for models with waist circumference as the main effect due to their close

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correlations. Continuous variables were standardized. The Wald chi-square statistic was computed to indicate the overall significance of each categorical variable with more than 2 categories.

In order to quantitatively evaluate the differences among the odds ratios, a dichotomous delay category related to the survival time was created with a cut-point at 3 months (Cases who died within 3 months were given a value of 0 along with their controls, while cases who survived longer than 3 months were given a value of 1, as were their controls). The interaction between the delay category and each risk factor was evaluated via the conditional logistic regression. Where the interaction term is statistically significant, the corresponding risk factor would be deemed subject to survivor bias. The odds ratios from the five scenarios for each risk factor, along with their 95% confidence intervals (CI), were also plotted together to provide a visual display of the survivor bias.

Additionally, since survivor bias in case-control studies is induced when the variable of etiological interest is associated with a common effect, here the survival time[5,11], Kaplan-Meier estimates and point-wise *p*-values at 3 months were computed within the subset cohort of pancreatic cancer cases to further demonstrate the differences of survival times across different categories of the risk factors.

All analyses were performed with SAS 9.3 (SAS Institute Inc.). Figures were generated in R 2.10.1[22]. All tests were two-tailed and a *p*-value of less than 0.05 was considered statistically significant. Adjustments for multiple comparisons were not applied.

RESULTS

Case-Control Constructs based on the Entire Cohort

The odds ratios for current smokers versus never-smokers stayed statistically significant across all groups with the overall *p*-values gradually increased from 0.007 to 0.10 (Table 1). By contrast, after limiting minimum survival time to 3 months, the *p*-values of odds ratios for waist circumference showed a significant drop from 0.86 to 0.01, resulting in statistically significant odds ratios even though the sample sizes were smaller than those in the base group. The odds ratios for both waist circumference and BMI decreased when more participants were excluded (1.02 to 0.94 for continuous BMI, 0.99 to 0.87 for waist circumference). The odds ratios for diabetes and alcohol consumption, either continuous or categorized, remained statistically non-significant.

Figure 1 provides a visual display of the effects of survivor biases. Only the odds ratios for continuous and dichotomous categorical predictors are presented. Since the odds ratios between former and never-smokers were not statistically significantly different from each other (Table 1), the two categories were shown combined together in the figure. The 95% CI became wider as more participants were excluded from left to right in each plot. The odds ratios for BMI in different case-control scenarios showed a decreasing trend with increasing case survival times (Figure 1.B), whereas the odds ratios for other risk factors did not change in any obvious pattern.

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The effects of survivor bias were then quantitatively evaluated by the delay category with a cut-point at 3 months (Table 2; Figure 2). Both BMI and waist circumference showed a statistically significant interaction with the delay category ($P = 0.006$ for continuous BMI, 0.004 for categorized BMI, respectively; $P < 0.001$ for waist circumference). There was no significant interaction between the delay category and either smoking or pack year of smoking (overall $P = 0.80$ and 0.67, respectively). Similarly, the interaction between diabetes and the delay category was not significant ($P = 0.91$). There was also no statistically significant interaction between the delay category and alcohol consumption, either continuous or categorized ($P = 0.75$ and 0.51, respectively).

Survival Analysis on the Subset Cohort of Pancreatic Cancer Cases

3 months survival rates for pancreatic cancer patients who had been overweight or obese prior to diagnosis were 52% (95% CI: 43–62%) and 46% (95% CI: 35–58%) respectively, versus their normal weight counterparts being 67% (95% CI: 58–75) ($P = 0.01$). The Kaplan-Meier curves for overweight and obese categories also deviated from the baseline curve (Figure 3.B). The other risk factors such as smoking status, diabetes, and alcohol consumption did not demonstrate significant differences in overall survival at 3 months across the categories (Table 3; Figure 3.A, 3.C, 3.D). We also tested the hazard ratios using the Cox proportional hazards model with adjustment for the effect of cancer stage. There was no interaction found between cancer stage and either BMI or waist circumference ($P =$ 0.91 and 0.81 respectively). The hazard ratios for both BMI and waist circumference had lower p-values than those of other risk factors. However, due to limited sample size, they were not shown as statistically significant.

DISCUSSION

The findings of this study suggest that the effect of survivor bias in pancreatic cancer case-control studies could result in a significant deviation in odds ratio estimations for BMI and waist circumference than would be estimated if all cases in the source population were recruited. The associations between pancreatic cancer and these two risk factors could be underestimated in case-control studies that do not include cases who survive less than 3 months after diagnosis. Significant survivor bias was not found in relation to cigarette smoking, diabetes or alcohol consumption.

According to Hernán, et al.[11], to introduce selection bias, including survivor bias, the selection must be correlated with both the outcome (case versus control) and another risk factor, which he defined as a “common effect”. The significant interactions with the 3-month delay category indicate that incidence of pancreatic cancer is conditionally associated with BMI and waist circumference. The inverse associations (exponentiated coefficients = 0.72 for continuous BMI, 0.65 for waist circumference) indicate that cases with relatively low BMI and/or small waist circumference were more likely to have longer survival times than those with high BMI and/or large waist circumference, which makes survival time a “common effect” of the incidence of pancreatic cancer and these two risk factors. The odds ratio plots comparing different case-control scenarios are also consistent with this interpretation.

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Since it is reasonable to assume that risk factors for controls would remain almost constant within one or two years from self-report, the potential survivor bias in case-control studies can also be highlighted in the survival analysis. The significant associations of both overweight and large waist circumference with reduced survival time further support the potential for survivor biases.

Obesity has been reported to be associated with lower survival rates of pancreatic cancer, especially for older individuals[1,14]. Li and coworkers demonstrated a significant association between obesity and reduced overall survival in patients with pancreatic cancer based on a case-control study[1,14]. Subsequently, Olson and coworkers also reported reduced survival for obese individuals, but the association was non-significant[14]. However, to our knowledge, no such investigations have been done on a prospective cohort.

In 2007, the World Cancer Research Fund and American Institute for Cancer Research reported a significant association between BMI and pancreatic cancer risk with a summary effect estimate of 1.14 per 5 kg/m^2 (95% CI: 1.07–1.22) based on a meta-analyses of 17 cohort studies. But they did not find such an association from the meta-analyses of 15 case-control studies. The summary effect estimate for the case-control studies was 1.00 per 5 kg/m^2 (95% CI: 0.87–1.15)[23]. Difference in results from these study types could be explained, in part, by survivor bias in case-control studies.

Of note, a common presenting symptom for pancreatic cancer is sudden unexplained weight loss. To avoid underestimating the risk of weight on incident disease, many researchers routinely ask case-control subjects to report their “usual adult weight” or weight one year prior to diagnosis. If they fail to do this, it could also underestimate the association between BMI and cancer.

The exact biological mechanism for the associations between higher pre-diagnosis BMI or waist circumference and reduced overall survival of pancreatic cancer is unclear but may be related to increased cancer recurrence, lymph node metastasis and/or cachexia. Cachexia, accompanied with anorexia and malabsorption, is a predictor for more advanced tumor stages, poor prognoses, and reduced survivals[24]. A study from England reported that local secretion of pro-inflammatory cytokines by macrophages, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), may increase the degree of cachexia[25,26]. Since chronic inflammations such as IL-6 overexpression and TNF-α upregulation are commonly associated with obesity[25,27–29], those who are overweight and/or with large waist circumferences could be more likely to suffer from cachexia. Fleming and coworkers also reported that after pancreatectomy as a treatment for pancreatic cancer, patients with higher weight were more likely to have metastasis around regional lymph nodes along with increased risks of cancer recurrence, which consequentially leads to reduced overall survivals[30]. Since the overall survival of pancreatic cancer is generally short[7], other causes of death related to obesity, such as cardiovascular diseases, are unlikely to explain such inverse conditional associations.

In this study, we found no evidence of potential survivor bias for the other risk factors examined. The interactions between the 3-month delay category and these risk factors were

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non-significant; while the odds ratio plots also did not show any regular increasing or decreasing pattern. Consistently, the Kaplan-Meier survival curves for these risk factors also did not differ from each other between different categories.

Several limitations of this study must be considered. Information for diabetes was based on self-report, (although several studies, including a recent study in elderly women, have found that self-reported diabetes is fairly accurate[31–33]). A validation study within the IWHS, of 44 self-reported diabetes cases at baseline suggested some over-reporting of diabetes since only 28 (64%) cases were confirmed by a physician[34]. There is also the possibility of under-diagnosis of diabetes since it is estimated that there are 7 million people in the United States who have diabetes but have not been diagnosed[35]. The results of the study could be different if either over-reporting or under-reporting of diabetes diagnosis occurred, with under-reporting generally leading to attenuation of odds ratio estimations.

An additional limitation is the range of alcohol consumption in this particular population; no subjects selected as cases reported an alcohol consumption ≥ 30 grams/day and only baseline information was available for the analyses; therefore the measure may not represent the true exposure of alcohol across follow-ups.

The BMI and waist circumference information was obtained from the questionnaires closest in time prior to diagnosis. A small proportion could potentially be impacted by cachexia near the time of diagnosis, although among cases, the median interval between the time the questionnaire was collected and the date of diagnosis was 39 months, and less than 5% of the cases reported their weight within 4.5 months before diagnosis.

Another issue to consider is that even though the date of death was ascertained through the cancer registry, SEER reports provide only the month and year of diagnosis. Therefore we assigned the 15th date of each month as the diagnosis date for each patient. This may add little in the way of misclassification since a precise diagnosis date for most cases may be uncertain or inaccurate since symptoms often occur only with advanced stages of the disease.

The study population was retrieved from the Midwestern state of Iowa with 98% white women aged 55–69 years at baseline. The results, therefore, might not be fully generalizable to men or to individuals with other demographic backgrounds or of other ages.

In conclusion, the findings of the study suggest that survivor bias in case-control studies could result in underestimations of odds ratios for BMI and waist circumference associated with pancreatic cancer, while other risk factors, such as smoking status, diabetes and alcohol consumption, would not be significantly affected by case losses. Future studies could focus on the associations between BMI, waist circumference, and overall survival for pancreatic cancer among middle-aged populations, to determine whether or not age is an effect modifier for survivor bias. Given that the underlying biological mechanism needs further clarification and the number of studies on survivor bias of this kind is limited, further studies are warranted.

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Acknowledgments

Source of Funding

Grant support for the IWHS was from the National Cancer Institute, grant RO1 CA39742.

The authors would like to acknowledge the helpful suggestions from Dr. Claire Weinberg in revising this manuscript.

LIST OF ABBREVIATIONS

BMI	body mass index
CI	confidence interval
IL-6	interleukin-6
IWHS	Iowa Women's Health Study
OR	odds ratio
SEER	Surveillance, Epidemiology, and End Results
TNF-α	tumor necrosis factor-α

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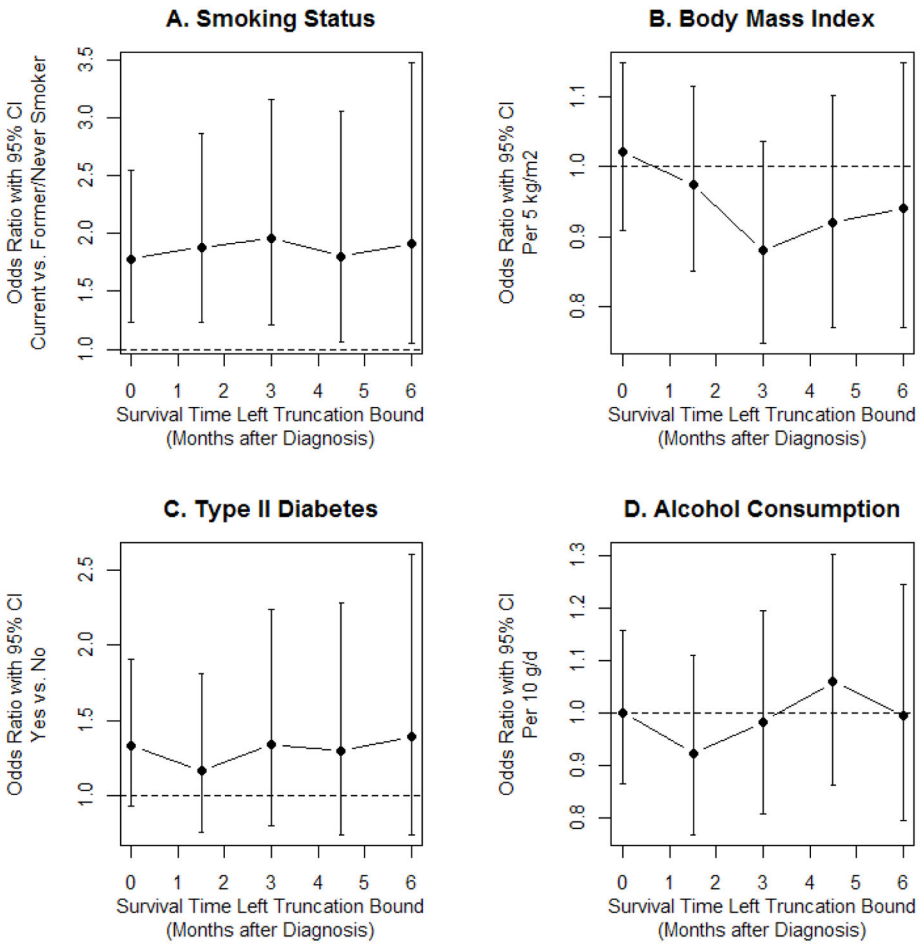

Figure 1.

Odds Ratios for Pancreatic Cancer with 95% Confidence Intervals for Case-Control Constructs, Based on the IWHS Cohort, 1986–2010

5 odds ratios were computed for each risk factor with respect to the case-control constructs. Smoking status and diabetes were dichotomous variables. BMI and alcohol consumption were continuous variables. The conditional logistic regression was used to adjust the effects of other covariates.

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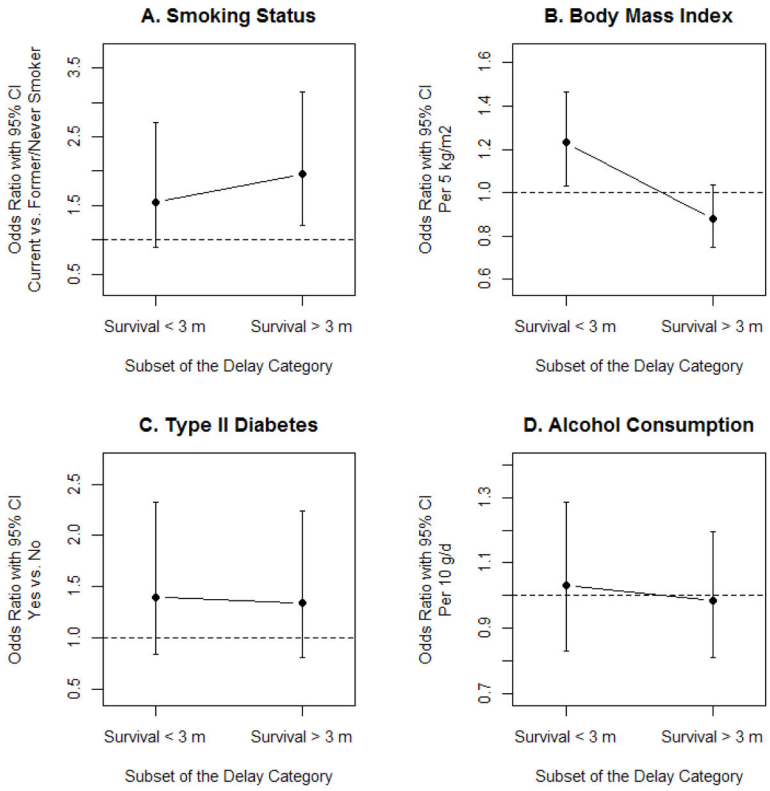

Figure 2.

Comparisons of Odds Ratios between Individuals with Case Survival Time Less than 3 Months and Those with Case Survival Time Longer than 3 Months, IWHS Cohort, 1986–2010.

The delay category separated the study population into two subsets (case survival time < 3 months vs. case survival time > 3 months). Odds ratios for each risk factor with respect to the subsets were generated for comparison. Smoking status and diabetes were dichotomous variables. BMI and alcohol consumption were continuous variables. The conditional logistic regression was used to adjust the effects of other covariates.

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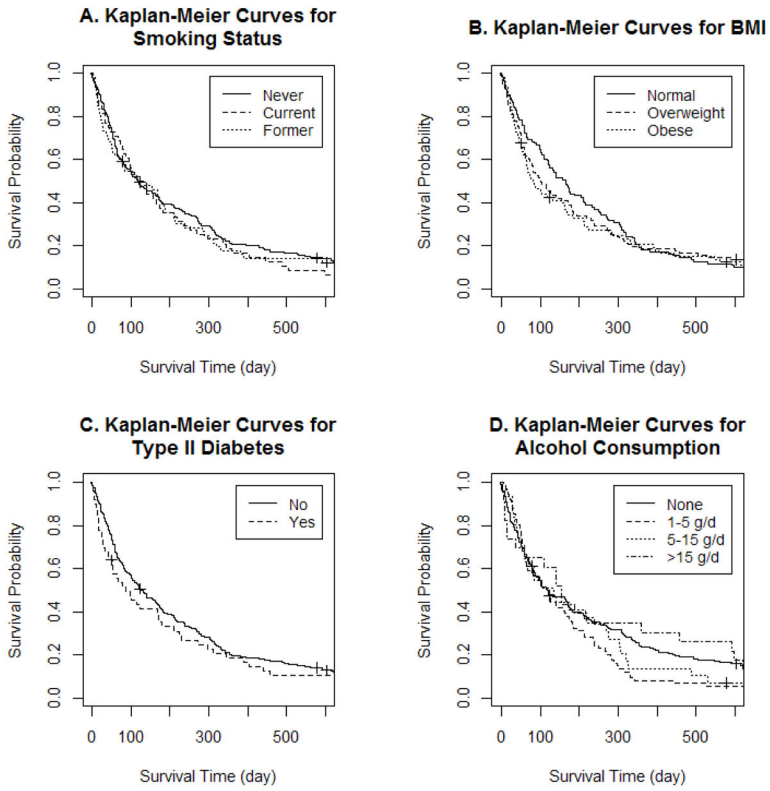

Figure 3.

Kaplan-Meier Curves for Overall Survival among Patients with Pancreatic Cancer, Based on the IWHS Cohort, 1986–2010.

Kaplan-Meier estimates for overall survival have been generated among patients with pancreatic cancer, grouped by risk factors of disease incidence. Loss of follow-up has been treated as right censoring.

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Table 1

Odds Ratios for Risk Factor of Pancreatic Cancer Incidence with Respect to Case-Control Constructs, Based on the IWHS[a] Cohort, 1986–2010.

Variables	Base Group (296 cases)	Survival ≥ 1.5 Months (222 cases, 25% case loss)	Survival ≥ 3 Months (166 cases, 43.9% case loss)	Survival ≥ 4.5 Months (138 cases, 53.4% case loss)	Survival ≥ 6 Months (114 cases, 61.5% case loss)
Smoking status[d]					
Never	Reference				
Current	1.80**[b] (1.24–2.61)	1.82**[b] (1.18–2.81)	1.98**[b] (1.21–3.23)	1.86*[b] (1.08–3.2)	1.94*[b] (1.05–3.58)
Former	1.06 (0.77–1.46)	0.89 (0.61–1.3)	1.04 (0.67–1.61)	1.13 (0.71–1.81)	1.06 (0.63–1.80)
P-value[c]	0.007	0.01	0.02	0.08	0.10
Number of pack-years[d]					
None	Reference				
< 40 pack-years	1.32 (0.98–1.78)	1.18 (0.84–1.67)	1.31 (0.87–1.95)	1.36 (0.88–2.1)	1.26 (0.78–2.05)
≥ 40 pack-years	1.19 (0.76–1.87)	1.17 (0.69–2.00)	1.47 (0.81–2.69)	1.32 (0.67–2.6)	1.40 (0.64–3.06)
P-value[c]	0.18	0.59	0.26	0.34	0.52
BMI[a] (per 5 kg/m^2)[e]	1.02 (0.91–1.15)	0.97 (0.85–1.12)	0.88 (0.75–1.04)	0.92 (0.77–1.10)	0.94 (0.77–1.15)
P-value	0.71	0.71	0.13	0.37	0.55
BMI[e]					
Normal	Reference				
Overweight	1.07 (0.79–1.45)	0.94 (0.67–1.33)	0.73 (0.49–1.10)	0.79 (0.51–1.23)	0.83 (0.51–1.34)
Obese	1.11 (0.80–1.54)	0.95 (0.65–1.39)	0.72 (0.46–1.12)	0.81 (0.49–1.32)	0.81 (0.47–1.40)
P-value[c]	0.82	0.94	0.21	0.52	0.66
Waist circumference (per 5 cm)[e]	0.99 (0.88–1.11)	0.92 (0.81–1.05)	0.82*[b] (0.70–0.96)	0.85*[b] (0.72–1.00)	0.87 (0.72–1.04)
P-value	0.86	0.21	0.01	0.05	0.13
Diabetes[f]					
No	Reference				
Yes	1.33 (0.93–1.91)	1.17 (0.76–1.81)	1.34 (0.8–2.24)	1.3 (0.74–2.28)	1.39 (0.74–2.6)
P-value	0.12	0.48	0.26	0.36	0.30
Alcohol consumption (per 10 grams/day)[f]	1.00 (0.87–1.16)	0.92 (0.77–1.11)	0.98 (0.81–1.2)	1.06 (0.86–1.3)	1.00 (0.8–1.25)
P-value	0.98	0.40	0.87	0.58	0.98

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Variables	Base Group (296 cases)	Survival ≥ 1.5 Months (222 cases, 25% case loss)	Survival ≥ 3 Months (166 cases, 43.9% case loss)	Survival ≥ 4.5 Months (138 cases, 53.4% case loss)	Survival ≥ 6 Months (114 cases, 61.5% case loss)
Alcohol consumption[f]					
None	Reference				
1–5	1.17 (0.86–1.60)	1.32 (0.92–1.89)	1.20 (0.78–1.84)	1.04 (0.64–1.69)	0.94 (0.55–1.61)
5–15	0.93 (0.60–1.44)	0.86 (0.52–1.44)	0.74 (0.40–1.38)	0.76 (0.39–1.47)	0.79 (0.39–1.62)
≥ 15	1.18 (0.68–2.05)	1.11 (0.57–2.16)	1.42 (0.70–2.92)	1.73 (0.82–3.67)	1.16 (0.49–2.75)
P-value[c]	0.67	0.36	0.39	0.33	0.88

[a] Abbreviation: IWHS, Iowa Women's Health Study; BMI, body mass index.

[b] * *P*-value ≤ 0.05, ** *P*-value ≤ 0.01.

[c] *P*-values for variables with more than 2 categories are based on the Wald chi-square statistic.

[d] Smoking status and number of pack-years were adjusted for baseline age, and BMI.

[e] BMI and waist circumference were adjusted for baseline age, smoking status and number of pack-years.

[f] Diabetes and alcohol consumption were adjusted for baseline age, smoking status, number of pack-years and BMI.

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Table 2

Interactions between Risk Factors of Pancreatic Cancer Incidence and the Delay Category with a Cut-Point of 3 Months, Based on the IWHS[a] Cohort, 1986–2010.

Variables	Exponentiated Coefficient	*P*-value
Smoking status[d]		0.80[c]
Never	Reference	
Current	1.24	0.58
Former	0.92	0.80
Number of pack-years[d]		0.67[c]
None	Reference	
< 40 pack-years	0.97	0.93
≥ 40 pack-years	1.49	0.40
BMI[a] (per 5 kg/m^2)[e]	0.72**[b]	0.006
BMI[e]		0.004[c]
Normal	Reference	
Overweight	0.42**[b]	0.006
Obese	0.37**[b]	0.004
Waist circumference (per 5 cm) [e]	0.65**[b]	< 0.001
Diabetes[f]		
No	Reference	
Yes	0.96	0.91
Alcohol consumption (per 10 grams/day)[f]	0.95	0.75
Alcohol consumption[f]		0.51[c]
None	Reference	
1–5	1.07	0.83
5–15	0.61	0.27
≥ 15	1.58	0.43

[a] Abbreviation: IWHS, Iowa Women's Health Study; BMI, body mass index

[b] ** *P*-value ≤ 0.01.

[c] *P*-values for variables with more than two categories are based on the Wald chi-square statistic.

[d] Smoking status and number of pack-years were adjusted for baseline age, and BMI.

[e] BMI and waist circumference were adjusted for baseline age, smoking status and number of pack-years.

[f] Diabetes and alcohol consumption were adjusted for baseline age, smoking status, number of pack-years and BMI.

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Table 3

Kaplan-Meier Estimates of Overall Survival for Patients with Pancreatic Cancer, IWHS[a], 1986–2010.

Risk Factors for Pancreatic Cancer	N	Median Survival Time (IQR[a]), Days	N at Risk (3 Months)	Overall Survival (3 Months)
Smoking status				
Non-smoker	183	120 (81–170)	101	56 (48–63)%
Current	48	127 (79–183)	29	60 (46–74)%
Past	60	119 (53–185)	32	55 (42–67)%
				p-value: 0.81
Number of pack-years				
None	183	120 (81–170)	101	56 (48–63)%
< 40 pack-years	76	139 (79–185)	43	58 (46–69)%
≥ 40 pack-years	27	123 (33–183)	16	59 (41–77)%
				p-value: 0.92
BMI[a]				
Normal	111	165 (119–211)	74	67 (58–75)%
Overweight	105	100 (70–155)	54	52 (43–62)%
Obese	77	82 (59–162)	35	46 (35–58)%
				p-value: 0.01
Diabetes				
No	246	127 (100–166)	142	58 (52–64)%
Yes	50	86 (43–172)	24	50 (36–63)%
				p-value: 0.27
Alcohol consumption, g/day				
None	166	119 (86–172)	92	56 (48–63)%
1–5	76	118 (64–168)	43	57 (45–67)%
5–15	31	134 (58–270)	16	54 (37–71)%
≥ 15	23	154 (37–360)	15	65 (45–83)%
				p-value: 0.84

[a]Abbreviation: IWHS, Iowa Women's Health Study; IOR, interquartile range; BMI, body mass index.