



Original article

Role of survivor bias in pancreatic cancer case-control studies

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ABSTRACT

Purpose: The purpose of this study was 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 (ORs) 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 cutpoint of 3 months was significant ($P < .01$) as was the interaction between waist circumference and survival time ($P < .01$).

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

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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 was 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 (ORs) 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

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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 Health Registry of Iowa, which is part of the National Cancer Institute Surveillance, Epidemiology, and End Results 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, one endocrine cancer; and four 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 ($n = 1480$).

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).

Table 1

Odds ratios for risk factor of pancreatic cancer incidence with respect to case-control constructs, based on the IWHS cohort, 1986–2010

Variables	Base group (296 cases)	Survival ≥ 1.5 mo (222 cases, 25% case loss)	Survival ≥ 3 mo (166 cases, 43.9% case loss)	Survival ≥ 4.5 mo (138 cases, 53.4% case loss)	Survival ≥ 6 mo (114 cases, 61.5% case loss)
Smoking status[†]					
Never	Reference				
Current	1.80** (1.24–2.61)	1.82** (1.18–2.81)	1.98** (1.21–3.23)	1.86* (1.08–3.2)	1.94* (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)
<i>P</i> [‡]	.007	.01	.02	.08	.10
Number of pack years[†]					
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)
<i>P</i> [‡]	.18	.59	.26	.34	.52
BMI (per 5 kg/m²)[§]					
BMI	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)
<i>P</i>	.71	.71	.13	.37	.55
BMI[§]					
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)
<i>P</i> [‡]	.82	.94	.21	.52	.66
Waist circumference (per 5 cm)[§]					
Waist circumference	0.99 (0.88–1.11)	0.92 (0.81–1.05)	0.82* (0.70–0.96)	0.85* (0.72–1.00)	0.87 (0.72–1.04)
<i>P</i>	.86	.21	.01	.05	.13
Diabetes					
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)
<i>P</i>	.12	.48	.26	.36	.30
Alcohol consumption (per 10 grams/day)					
Alcohol consumption	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)
<i>P</i>	.98	.40	.87	.58	.98
Alcohol consumption					
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)
<i>P</i> [‡]	.67	.36	.39	.33	.88

IWHS, Iowa Women's Health Study; BMI, body mass index.

* $P \leq .05$; ** $P \leq .01$.

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

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

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

^{||} Diabetes and alcohol consumption were adjusted for baseline age, smoking status, number of pack years, and BMI.

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