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**Original Research Article**

# Risk of pancreatic cancer in Minia district, Egypt

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## ABSTRACT

**Background:** Pancreatic cancer is considered one of the most lethal malignant neoplasms. Therefore, a better understanding of the etiology and identifying the risk factors are essential for the development of preventive strategies.
**Methods:** This case-control study included pancreatic cancer patients attending Minia Cancer Center during the period from June 2014 to December 2015 and controls from the general population. Several suspected risk factors were evaluated during personal interviews with the study participants. Statistical analysis included crude odds ratio (OR) and multivariable logistic regression with an adjusted OR and 95% confidence interval (CI).
**Results:** The study included 224 subjects, 75 pancreatic cancer cases, and 149 controls. Cases had higher age and male gender than controls. Bivariate analyses showed that age, sex, smoking, family history of pancreatic cancer, physical activity, mental stress, age at first birth, hormonal contraception, diabetes, hepatitis C virus (HCV) infection, pancreatitis, and cholecystitis were associated with pancreatic cancer. In the final multivariable analysis, smoking, physical activity, diabetes, HCV infection, and cholecystitis were significantly associated with pancreatic cancer risk.
**Conclusions:** Pancreatic cancer risk is associated with some potentially modifiable factors like tobacco smoking and low physical activity and related health problems as diabetes, HCV infection, and cholecystitis. Control of known risk factors for pancreatic cancer should be considered to help in risk reduction and prevention.

**Keywords:** Pancreatic cancer, Risk factors, Minia Cancer Center, Egypt

## INTRODUCTION

Pancreatic cancer was the seventh most prevalent cause of cancer death globally in 2012.[1] The majority of cases and deaths (55%) occur in the more developed regions, and part of the variation in the incidence of pancreatic cancer worldwide may relate to under diagnosis, under-reporting and imperfect mortality data in the less developed countries.[1] The estimated number of pancreatic cancer cases in Egypt in 2013 was 2226, and it is projected to be 2836 and 6883 in 2020 and 2050 respectively.[2] The overall age-adjusted pancreatic cancer mortality rate in Egypt was 1.47/100,000 population and analysis of the regional distribution showed significant variations in rates among provinces with Northern provinces having higher rates than Southern regions.[3] And the incidence rates of pancreatic cancer in Middle Egypt in 2009 were 2.1 and 0.9 in 100,000 population among males and females, respectively.[3]

Pancreatic cancer is still representing a scary malignancy especially in developing countries where all the limitations are gathered such as unequipped health centers, patients' unawareness, delayed diagnosis, lack of

appropriate medical treatments, and insufficient funds for research. Moreover, there are no current cost-effective screening recommendations for pancreatic cancer, so primary prevention is of utmost importance. Therefore, a better understanding of the epidemiology and identifying the risk factors for pancreatic cancer is essential for the development of preventive strategies. The causes of pancreatic cancer are insufficiently known. Several risk factors have been reported; however, only a few of them have been confirmed more consistently.[4] To our knowledge, no previous studies had explored the risk factors for pancreatic cancer in Egypt so, we investigated the association between pancreatic cancer risk and sociodemographic, lifestyle, reproductive factors, and medical disorders.

## METHODS

### *Study population*

This case-control study was conducted during the period from June 2014 to December 2015. Cases with a primary pancreatic cancer confirmed by the treating physicians were considered eligible for the study. Pancreatic cancer cases were identified and enrolled in the study within 30 days of their diagnosis. The participation rate was 95% for cases. Our experience suggests that severe deterioration of health and rapid demise due to the cancer were the major reasons for nonparticipation among cases. Controls were selected randomly from urban and rural areas of Minia district during the same period of the study to represent the source population. They were selected and interviewed during field visits that were conducted for health education purposes from the public health department of Faculty of Medicine. Eligible controls were men and women ≥40 years, residing in Minia, and had no personal history of cancer.

### *Data collection*

All participants were interviewed in person by a trained interviewer to complete the same questionnaire including information on socio-demographic characteristics, tobacco smoking, alcohol drinking, physical activity, reproductive history, family history of pancreatic cancer and personal medical history. Anthropometric measures including weight and height were measured for all participants. No proxy interviews were conducted. Approvals to conduct the study were obtained from Scientific and Ethical Committee of the Central Directorate of Research and Health Development of Ministry of Health and Population and IRB of Minia University.

### *Statistical analysis*

Statistical analyses were conducted using SAS software V9.4 (SAS Institute, Inc., Cary, NC). Several variables were created. Age was grouped into three groups (<60, 60-69 and ≥70 years). Body Mass Index (BMI) was calculated in kg/m2 then grouped according to WHO standard classification. We estimated each participant's lifetime cumulative quantity of tobacco smoking (dose) in pack-years by multiplying total smoking duration by the intensity. The smoking variable was categorized into four groups; non-smokers, moderate smokers (pack-years <25), heavy smokers (with pack-years ≥25) and unknown smoking intensity or duration. Diabetes was grouped according to the onset of the disease into three categories which are nondiabetic or diabetic <1years (to avoid the problem of reverse causality), diabetic for1-4 years, and diabetic ≥5 years. Physical activity index (PAI) was calculated through The General Practice Physical Activity Questionnaire (GPPAQ) which calculated the 4-level PAI. Patients were classified into four categories; Inactive, moderately inactive, moderately active and active.[5]

Unconditional logistic regression models were used to estimate the OR and 95% CI for the association between the potential risk factors and pancreatic cancer risk. Significant factors with $p<0.05$ at the bivariate analysis were entered into a multivariable model. Subsequently, a full predictive multivariable model was constructed including all of the suspected risk factors. Working backward from the full model, variables were manually removed to create the most parsimonious final model.

## RESULTS

Data for this study were available from 75 cases and 149 controls. The mean age of cases and controls was 60.7 (SD= 9.9), and 59.5 (SD= 6.7) years, respectively. Cases represented 40.4% of the male participants and 27% of the females. Regarding education, cases were more educated than controls with 26% of the illiterate having pancreatic cancer while 74% were from controls. Distribution of socio-demographics of pancreatic cancer cases and controls and the bivariate associations were shown in Table 1. Age, sex, smoking and family history of pancreatic cancer were associated with the risk of pancreatic cancer.

Pancreatic cancer risk was higher in old age (≥70 years) versus younger age (<60 years) (OR 3.3; 95% CI, 1.31-8.56, P 0.018); in males versus females (OR 1.8; 95% CI, 1.05-3.22, P 0.034); in heavy smoker (≥ 25 pack-years) than nonsmokers (OR 7.6; 95% CI, 3.51-16.72, P <0.0001); and in subjects with family history of pancreatic cancer than those without (OR 7.5; 95% CI 1.53-37.35, P 0.013) as shown in Table 1.

Associations of occupational factors and medical history with pancreatic cancer risk were presented in Table 2. Although occupation, nightshifts, exposure to pesticides, hypertension, and bilharziasis were not associated with pancreatic cancer risk, we found that physical activity, mental stress, diabetes, HCV infection, cholecystitis, and pancreatitis were significantly associated with pancreatic cancer (Table 2).

**Table 1: Sociodemographic characteristics of pancreatic cancer patients and controls.**

| Sociodemographic Characteristics | Cases No (%) | Controls No (%) | OR* (95% CI) P value |
|---|---|---|---|
| **Age** | | | |
| <60 years | 32 (31.7) | 69 (68.3) | 1 |
| 60-69 years | 29 (29) | 71 (71) | 0.88 (0.48-1.61) |
| ≥70 years | 14 (60.9) | 9 (39.1) | 3.35 (1.31-8.56) |
| | | | 0.018 |
| **Sex** | | | |
| Female | 31 (27) | 84 (73) | 1 |
| Male | 44 (40.4) | 65 (59.6) | 1.83 (1.05-3.22) |
| | | | 0.034 |
| **Residence** | | | |
| Urban | 25 (37.9) | 41 (62.1) | 1 |
| Rural | 50 (31.6) | 108 (68.4) | 0.76 (0.42-1.38) |
| | | | 0.368 |
| **Marital status** | | | |
| Single, widow | 12 (37.5) | 20 (62.5) | 1 |
| Married | 63 (32.8) | 129 (67.2) | 0.81 (0.37-1.77) |
| | | | 0.603 |
| **Education** | | | |
| Illiterate | 32 (26) | 91 (74) | 1 |
| Read and write | 14 (38.9) | 22 (61.1) | 1.81 (0.83-3.95) |
| Secondary | 16 (41) | 23 (59) | 1.98 (0.93-4.21) |
| University and above | 13 (50) | 13 (50) | 2.84 (1.19-6.77) |
| | | | 0.056 |
| **BMI[a]** | | | |
| < 25 | 40 (38.8) | 63 (61.2) | 1 |
| 25-29.9 | 19 (23.7) | 61 (76.3) | 0.49 (0.26-0.94) |
| ≥ 30 | 16 (39) | 25 (61) | 1.01 (0.48-2.12) |
| | | | 0.074 |
| **Smoking** | | | |
| Non smoker | 21 (17.5) | 99 (82.5) | 1 |
| Current | 29 (42) | 40 (58) | 3.42 (1.75-6.69) |
| Former | 10 (76.9) | 3 (23.1) | 15.71 (3.98-62.05) |
| Goza | 15 (68.2) | 7 (31.8) | 10.10 (3.67-27.82) |
| | | | <0.0001 |
| **Smoking intensity** | | | |
| Non smoker | 21 (17.5) | 99 (82.5) | 1 |
| Moderate smokers [b] | 12 (31.6) | 26 (68.4) | 2.18 ( 0.95-4.99) |
| Heavy smokers [c] | 26 (61.9) | 16 (38.1) | 7.66 (3.51-16.72) |
| Unknown intensity | 16 (66.7) | 8 (33.3) | 9.43 (3.57-24.89) |
| | | | <0.0001 |
| **Family history of pancreatic cancer** | | | |
| No | 68 (31.6) | 147 (68.4) | 1 |
| Yes | 7 (77.8) | 2 (22.2) | 7.56 (1.53-37.35) |
| | | | 0.013 |

***Odds ratio of bivariate logistic regression; [a]BMI: body mass index; [b]Moderate smokers: <25 pack-years; [c] Heavy smokers: ≥25 pack-years.

Figure 1 showed the distribution of reproductive factors among the women participants. We found that pancreatic cancer patients constituted 63.6% of the unmarried females, 40.3% of the postmenopausal and 37% of women who had used hormonal contraception. The bivariate analysis showed that marital state, age at first birth, and hormonal contraception were associated with risk of pancreatic cancer but in the multivariable analysis, none of the reproductive factors were significantly associated with pancreatic cancer risk.

**Table 2: Occupational and medical factors affecting pancreatic cancer risk.**

| Characteristics | Cases No (%) | Controls No (%) | OR* (95% CI) P value |
|---|---|---|---|
| **Occupation** | | | |
| Non-worker | 29 (39.7) | 44 (60.3) | 1 |
| Farmer | 26 (26.5) | 72 (73.5) | 0.55 (0.29-1.05) |
| Manual | 5 (26.3) | 14 (73.7) | 0.54 (0.18-1.67) |
| Clerk | 11 (47.8) | 12 (52.2) | 1.39 (0.54-3.57) |
| Professional | 4 (36.4) | 7 (63.6) | 0.87 (0.23-3.23) |
| | | | 0.207 |
| **Exposure to pesticides** | | | |
| No | 9 (22.5) | 31 (77.5) | 1 |
| Yes | 25 (36.8) | 43 (63.2) | 2.00 (0.82-4.88) |
| | | | 0.127 |
| **Nightshifts** | | | |
| No | 70 (32.9) | 143(67.1) | 1 |
| Yes | 5 (45.4) | 6 (54.6) | 1.70 (0.50-5.77) |
| | | | 0.393 |
| **Physical activity** | | | |
| Inactive | 9 (42.9) | 12 (57.1) | 1 |
| Moderate inactive | 42 (50) | 42 (50) | 1.33 (0.51-3.50) |
| Moderate active | 18 (24.7) | 55 (75.3) | 0.44 (0.16-1.20) |
| Active | 6 (13) | 40 (87) | 0.20 (0.06-0.68) |
| | | | 0.0001 |
| **Diabetes** | | | |
| Non-diabetic | 51 (27.7) | 133 (72.3) | 1 |
| Diabetic 1-4 years | 10 (43.5) | 13 (56.5) | 2 (0.83-4.86) |
| Diabetic ≥5 years | 14 (82.3) | 3 (17.7) | 12.16 (3.36-44.10) |
| | | | 0.0004 |
| **Hypertension** | | | |
| Not hypertensive | 61 (31.8) | 131 (68.2) | 1 |
| Hypertensive | 14 (43.7) | 18 (56.3) | 1.67 (0.78-3.58) |
| | | | 0.187 |
| **Bilharziasis** | | | |
| No history bilharziasis | 68 (32.2) | 143 (67.8) | 1 |
| History of bilharziasis | 7 (53.8) | 6 (46.2) | 2.45 (0.79-7.58) |
| | | | 0.119 |
| **HCV[a]** | | | |
| -ve HCV | 62 (30.4) | 142 (69.6) | 1 |
| +ve HCV | 13 (65) | 7 (35) | 4.25 (1.62-11.18) |
| | | | 0.003 |
| **Cholecystitis** | | | |
| No history cholecystitis | 55 (28.1) | 141(71.9) | 1 |
| History of cholecystitis | 20 (71.4) | 8 (28.6) | 6.41 (2.66-15.41) |
| | | | <0.0001 |
| **Pancreatitis** | | | |
| No history pancreatitis | 64 (30.3) | 147 (69.7) | 1 |
| History of pancreatitis | 11 (84.6) | 2 (15.4) | 12.63 (2.72-58.63) |
| | | | 0.001 |
| **Mental stress** | | | |
| No | 51 (28.7) | 127 (71.3) | 1 |
| Yes | 24 (52.2) | 22 (47.8) | 2.72 (1.40-5.27) |
| | | | 0.003 |

*****Odds ratio of bivariate logistic regression; [a]HCV: hepatitis C virus.

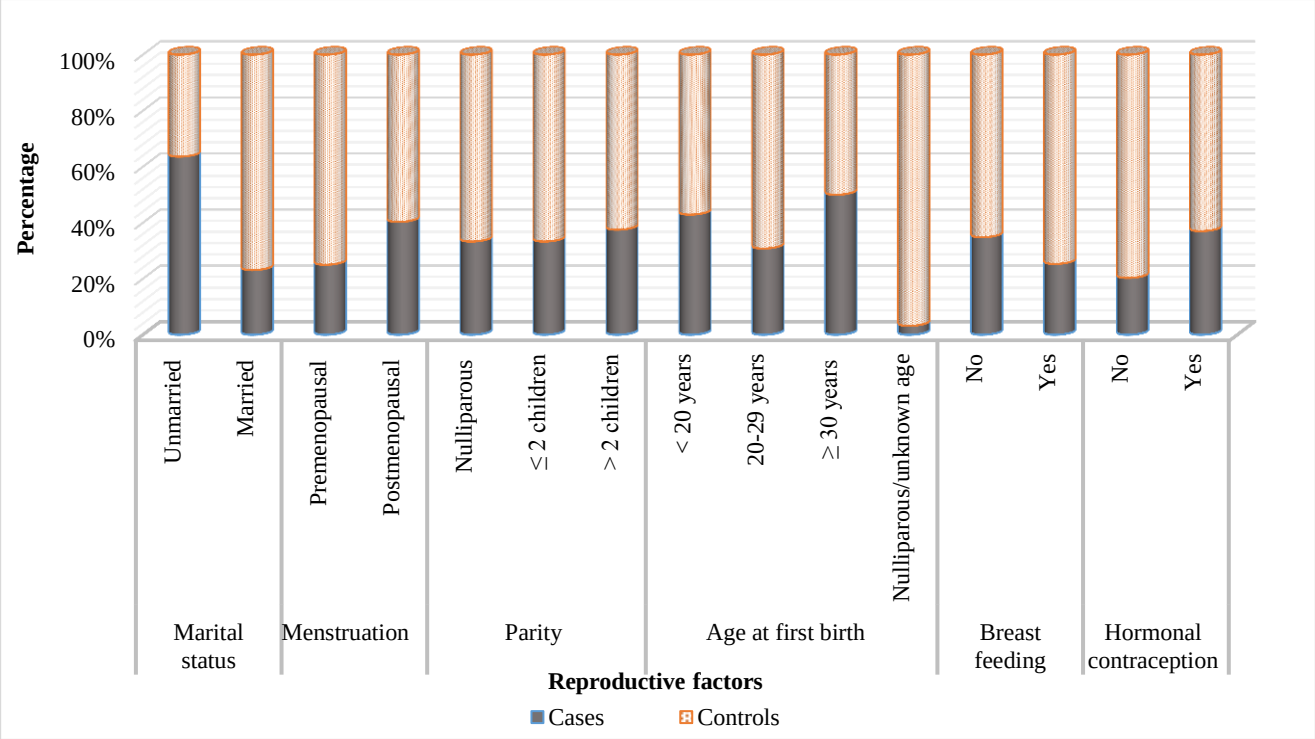


**Figure 1: Reproductive factors affecting pancreatic cancer risk in Minia Cancer Center.**

**Table 3: Factor affecting pancreatic cancer risk in Minia Cancer Center.**

| Variable | OR *(95% CI) | P value |
|---|---|---|
| **Smoking** | | |
| Non smoker | 1 | <0.0001 |
| Moderate smokers[a] | 2.60 (0.92-7.36) | |
| Heavy smokers[b] | 12.71 (4.61-35.07) | |
| Unknown intensity | 10.93 (3.12-38.32) | |
| **Physical activity** | | 0.0005 |
| Inactive | 1 | |
| Moderate inactive | 1.44(0.40-5.18) | |
| Moderate active | 0.29 (0.08-1.14) | |
| Active | 0.19 (0.04-0.87) | |
| **Diabetes** | | |
| Non-diabetic | 1 | 0.013 |
| Diabetic 1-4 years | 1.08 (0.35-3.37) | |
| Diabetic ≥5 years | 12.02 (2.31-62.40) | |
| **HCV [c]** | | |
| -ve HCV | 1 | 0.031 |
| +ve HCV | 3.90 (1.13-13.40) | |
| **Cholecystitis** | | |
| No history cholecystitis | 1 | <0.0001 |
| History of cholecystitis | 12.41 (4.08-37.75) | |

*Final multivariable model including significant risk factors for pancreatic cancer at p<0.05; [a]Moderate smokers: <25 pack-years; [b]Heavy smokers: ≥25 pack-years; [c]HCV: hepatitis C virus.

In the multivariable analyses, smoking (adjusted OR for heavy smoker versus non-smoker 12.7; 95% CI, 4.61–35.07), physical activity (adjusted OR for active versus inactive 0.19; 95% CI, 0.04–0.87), diabetes (adjusted OR for long-term diabetic versus non-diabetic 12.02; 95% CI, 2.31–62.40), HCV infection (adjusted OR 3.9; 95% CI, 1.13–13.40) and cholecystitis (adjusted OR 12.4; 95% CI, 4.08–37.75) were significantly associated with pancreatic cancer risk (Table 3).

## DISCUSSION

Identification of high-risk individuals for pancreatic cancer and targeted screening may be valuable methods for early diagnosis and preventive strategies. Among all factors investigated, the study found that smoking, physical activity, diabetes, HCV infection, and cholecystitis were independently associated with the risk of pancreatic cancer.

According to the literature, advancing age is one of the most significant demographic factors affecting pancreatic cancer risk, as 80% of all tumors are diagnosed in the age range of 60-80 years.[4] Moreover, males have a higher risk to develop pancreatic cancer than females.[4] Our results were inconsistent with the previous studies. Although we found an increased risk of pancreatic cancer in old age (≥70 years) and also in male gender in the bivariate analysis, age and sex were not significantly associated with pancreatic cancer risk in the final multivariable model.[5] This finding was supported by a previous study by Kriegel et al, who found that East Nile Delta region in Egypt exhibited a high rate of young-onset pancreatic cancer (<65 years) which was associated with elevated serum cadmium and farming occupations.[6] They concluded that pancreatic cancer could occur at a younger age (<65 years) due to environmental exposure and also hereditary causes.[6] Regarding sex, the GLOBOCAN estimates for 2012 reported that the sex ratio of pancreatic cancer is close to one.[1] So, it seems that the gap between age groups and sexes can be explained by differences in exposures such as smoking, hereditary causes and sex-specific risk factors that could be important in pancreatic carcinogenesis.

Cigarette smoking has been definitively identified as the most important environmental risk factor for pancreatic cancer, as many studies concluded higher risk of pancreatic cancer in current smokers versus non-smokers and the risk increased with greater intensity and pack-years.[7-11] Our results are broadly consistent with the published literature, although our estimate for current smoking of 3.4 versus non-smoker is similar to that of a recent study, it is somewhat higher than those previously reported, which range from approximately 1.7 to 2.2.[7,9,10] It is possible that control selection bias contributed to this apparently higher risk. Similarly, the high estimate for heavy smoking (OR 12.7; 95% CI 4.61-35.07) that may be affected by small subgroup size.

Diabetes may be a risk factor or a manifestation of pancreatic cancer. We added diabetic patients for <1years to the nondiabetics to avoid the problem of reverse causality. Consistent with previous studies, we found that long-term diabetes (≥5 years) was associated with increased risk of pancreatic cancer compared to non-diabetics.[8,12] While short-term diabetes (1-4 years) was associated with nonsignificant higher risk. Unlike other studies that found that patients with short-term (1-4 years) diabetes had a higher pancreatic cancer risk than non-diabetics.[13] A recent prospective cohort study reported a risk of pancreatic cancer as low as 0.11% in patients with new onset diabetes (within 3 years) without other risk factors, and the risk increased progressively as one, two, or three of other potential risk factors were present reaching 0.72% in patients with three risk factors.[14] They concluded that newly onset diabetic patients were at higher risk of pancreatic cancer only if it was associated with other potential risk factors 14 which can support our results. Several studies tried to explain the role of diabetes in predisposing pancreatic cancer. This role is likely related to increased insulin-like growth factor 1 (IGF-1) levels, hyperglycemia, insulin resistance and compensatory hyperinsulinemia.[12] Moreover, pancreatic cancer patients with diabetes had a higher frequency of blood type B, male gender, age older than 70 years and family history of diabetes than non-diabetic patients suggesting that these underlying factors which are associated with longstanding type 2 diabetes might play a role in predisposing diabetic patients to pancreatic cancer.[15]

Several studies including our study have suggested that HCV infection represents a risk factor for pancreatic cancer, whereas others have not confirmed this association.[16,17] The biological reason for an association between HCV and pancreatic cancer is unclear. A previous study in Egypt found evidence for an association between diabetes and active HCV infection.[18] Therefore, HCV infection promoting diabetes might act in cooperation with hyperinsulinemia, hyperglycemia in the promotion of pancreatic cancer.[19] The prevalence of HCV antibody in Egypt in 2015 was found to be 10% and that of HCV RNA to be 7% in the age groups 15-59 year.[20] Although, the high prevalence of HCV infection, pancreatic cancer is not common in Egypt. This can be explained by low accuracy of diagnostic methods and deficiency of the available data used to assess the rates of incidence of pancreatic cancer leading to underdiagnosis and under-reporting. Planning of well-designed studies and enrolling a larger number of patients, are essential to further investigate the association between HCV infection and pancreatic cancer.

The study found that active subjects had a reduced risk of pancreatic cancer, compared to non-active persons (OR=0.19, 95% CI=0.04-0.87). On the contrary, previous literature does not provide strong evidence for an association between physical activity and risk for pancreatic cancer.[21] Some studies suggested potential pancreatic cancer risk reduction with consistent physical activity over time or for light and moderate types of activity only.[22,23] Inconsistent results may be due to differences and inaccuracy of methods used to assess physical activity level so using more objective tools to assess the type, intensity, and duration of physical activity is recommended in future studies.

Several studies have demonstrated a significant association between high BMI and risk of pancreatic

cancer.[24,25] On the other hand, other investigations including our study have not been able to demonstrate this significant relationship.[11] Moreover, a recent study found that higher waist-hip ratio, but not high BMI, was significantly associated with an increased risk of pancreatic cancer.[26] Indeed, BMI being measured at the time of diagnosis provides an inaccurate measure of long-term exposure to obesity and insulin resistance. Obesity can be a leading cause of type 2 diabetes mellitus, and these both diagnoses commonly coexist. It is thus difficult to fully identify their independent effects on pancreatic cancer. As with diabetes, obesity-related insulin resistance and hyperinsulinemia are thought to play major roles in the development of pancreatic cancer.[27]

Unlike the previous findings, we could not confirm the higher risk of pancreatic cancer among individuals with a history of pancreatitis and those with a family history of pancreatic cancer in the multivariable analysis which can be attributed to small sample size and insufficient statistical power.[24,28] A family history of pancreatic cancer can likely increase pancreatic cancer risk due to genetic and/or other risk factors that are shared by family members. It is also estimated that 8-10% of pancreatic cancer are familial pancreatic cancer.[28] A previous study reported that the association between pancreatitis and pancreatic cancer was much stronger at intervals of ≤2 years from cancer diagnosis probably reflecting a combination of reverse causation and antecedent misdiagnosis of pancreatic cancer as pancreatitis. Moreover, despite the strong association between pancreatitis (diagnosed before >2 years) and pancreatic cancer risk, the population attributable fraction was 1.34% (95% CI: 0.612–2.07%).[24] So, a relatively small proportion of pancreatic cancer might be avoided if pancreatitis could be prevented.[24] And it is important to note that alcohol intake was very rare in our dataset, so we could not evaluate the association between alcohol consumption and pancreatic cancer risk. Larger studies are needed to investigate pancreatic cancer risk in relation to familial factors and chronic pancreatitis.

Concerning reproductive factors among women, the multivariable analysis found no association between any of the reproductive factors and pancreatic cancer risk. A few studies but not all found significant associations of pancreatic cancer risk with age at first birth.[29-31] Similarly, there is little evidence of an association between pancreatic cancer and hormonal contraception use.[29] Given the conflicting results in the literature, further large studies are needed to clarify the associations of reproductive factors and female hormones use with pancreatic cancer risk.

There are some potential limitations of this study. Pancreatic cancer is not common in Egypt and has a poor prognosis; thus, the study sample may be relatively small. So, we increased the number of control subjects to be double the number of cases trying to increase the statistical efficiency and power. Recall bias is another potential with case-control studies. Despite these limitations, the study does have several strengths. Firstly, it is one of the first studies that have been conducted in Egypt evaluating pancreatic cancer risk factors. Secondly, we used different measures to reduce the possibility of bias. We used face-to-face interviews and asked comprehensive questions about covariates known to influence the risk of pancreatic cancer, so we were able to control for many variables simultaneously. The similar interview setting of cases and controls has reduced the scope for information bias. Also, we used controls from the same catchment areas to have similar prevalence of exposures as the general population. Moreover, the almost complete participation of cases and controls reassuring against any major role of selection bias.

In summary, our results support a growing literature that suggests that there are some potentially modifiable risk factors for pancreatic cancer as tobacco smoking and low physical activity and possible related health issues as diabetes mellitus and HCV infection that should be controlled to help in risk reduction and prevention of pancreatic cancer. Further large multicenter studies are needed to provide a strong evidence and better understanding of etiological factors of pancreatic cancer in developing countries which have different exposures, limited health care resources, and insufficient funds for research.

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