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Evaluating The Association Between Severe Acne And Pancreatic Cancer Risk

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Abstract

Objective: Inflammation is a suggested mediator in pancreatic carcinogenesis. Severe acne may be a proxy of inflammation; however, the association between severe acne with pancreatic cancer is unstudied. Here, we explored the association between self-reported severe acne and pancreatic cancer risk for the purpose of hypothesis generation.

Methods: In a hospital-based case-control study, we used information from personal interviews with 939 confirmed cases of pancreatic adenocarcinoma and 440 controls to assess history of teenage and adult acne. We evaluated the association between severe acne and pancreatic cancer risk by estimating adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable logistic regression.

Results: After adjusting for age, race, sex, recent body mass index, education, and diabetes, any history of severe acne was not significantly associated with pancreatic cancer risk (adjusted OR ever vs. never=1.42, 95% CI: 0.65, 3.09). Similarly, there were no statistically significant associations with pancreatic cancer risk when specifically examining teenage severe acne (OR=1.60, 95% CI: 0.67, 3.80), adult severe acne (OR=1.23, 95% CI: 0.32, 4.76), or cystic acne (OR=1.37, 95% CI: 0.71, 2.67).

Conclusion: We did not observe statistically significant associations between severe acne and risk of pancreatic cancer. The low prevalence of severe acne in this population limited our ability to detect modest associations. Observed magnitudes of association suggest a possible positive association that warrants follow-up in larger studies.

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Table of Contents

Introduction

Pancreatic cancer is a deadly disease that currently has poor prognosis. There were 56,770 estimated new cases in 2019 (3.2% of all new cancer cases) and resulted in 45,750 estimated deaths in 2019 (7.5% of all cancer deaths).[1] In fact, a study published in 2011 reported a 5-year survival rate of 1.3%.[2] The pancreas is an organ that aids digestion and produces hormones that help manage and regulate blood sugar. Both cancerous and noncancerous tumors can occur in the pancreas but the most common type of cancer that forms starts in the cells that line the ducts that carry the digestive enzymes and ductular fluid and bicarbonate out of the pancreas, known as pancreatic ductal adenocarcinoma (PDAC).[3] Unfortunately, pancreatic cancer is hard to detect at its early stages when it is most treatable. This is partially a result of there being close to no symptoms until the cancer has spread to the other organs.[4] Since pancreatic cancer often presents at an advanced stage, it is ranked among cancers as last in terms of prognostic outcomes for patients (with 5-year survival rates between 2-9%).[5]

Research fueled by curiosity around the disease and its low survival rate has highlighted inflammation as a hypothesized mediator of pancreatic cancer development.[6] Other risk factors include smoking, diabetes, family history, obesity, and old age. Although further research is needed to determine the exact mechanisms through which inflammation contributes to tumor initiation and development, pancreatitis is a strong risk factor.[7] A growing body of evidence also supports inflammation playing a role at all stages of acne development (contrary to the conventional perspective that *Propionibacterium acnes* colonizes a sebaceous follicle duct, causing an inflammatory immune response).[8] Instead of focusing on inflammation's secondary role in the development of acne, more research has emphasized its primary role (the idea that inflammation triggers the process). New research shows that systemic inflammation, which can

be caused by stress, poor diet, and other environmental factors, can cause normal levels of sebum in follicles to "oxidize."[9] Therefore, inflammation can contribute to lowering the oxygen content of the sebum which provides an optimal environment for *Propionibacterium acnes* to grow. Given this, we hypothesize that severe acne may serve as a proxy of underlying inflammatory processes and could thus be associated with increased pancreatic cancer risk. Additionally, studies have found that androgens can affect acne severity; these androgens may generate inflammatory processes as well.[10] [11] Schooling's study argued that androgens in men, for example, may be a factor in generating rather than protecting against inflammation by suppressing the immune system.[12]

Prior epidemiologic studies suggest acne may play a role in cancer risk. In the Nurses' Health Study II, for instance, women who reported a history of severe acne as a teenager were 44% more likely to develop melanoma and 17% more likely to develop breast cancer than those with mild or no acne.[13] In addition, a meta-analysis of eight studies evaluating the association between acne and prostate cancer risk reported a 1.5-fold increased risk for acne in cohort studies (OR=1.51, 95% CI 1.19-1.93), but no association in case-control studies.[14]

There currently have been no studies evaluating the potential association between severe acne (diagnosed in teenage years and in adulthood) and pancreatic cancer risk specifically. The objective of this thesis is to explore if self-reported severe acne is associated with increased pancreatic cancer risk for the purpose of hypothesis generation. This association is of particular interest since it has not been looked at before and acne may be an indicator of inflammation.

Methods

Study Population

This hospital-based case-control study was conducted at Memorial Sloan Kettering Cancer Center (MSKCC) within the Pancreatic Tumor Registry, established in 2002. As detailed previously, eligible cases were defined as those with pathologically or cytologically confirmed pancreatic adenocarcinoma and who spoke English.[1516] Cases were identified upon initial consultation and diagnosis, follow-up after surgery, or receipt of chemotherapy. Of approached potential cases, 13% were ineligible (primarily because they did not speak English); of eligible cases, 79% consented to participate. Eligible controls had no personal history of cancer other than non-melanoma skin cancer and who also spoke English. Controls were identified from individuals who accompanied patients to clinics at Memorial Sloan Kettering Cancer Center, other than clinics where patients with pancreatic cancer or intraductal papillary mucinous neoplasms were seen (N=265), or from spouses of patients with pancreatic cancer (N=175). Of approached potential controls, 15% were ineligible (primarily because of history of cancer); of eligible controls, 59% consented to participate. Eligible individuals filled out questionnaires and provided biospecimens. Epidemiologic (family history, sociodemographics, lifestyle), clinical (tumor characteristics, treatment), and biological (blood and saliva) components were collected. This study was also reviewed by the institutional review board at MSKCC.

For this analysis, we excluded 6 controls who had personal histories of cancer other than non-melanoma skin cancer. We also excluded 11 individuals who did not fill out any of the variables regarding whether or not they had had acne as a teenager or as an adult (categorized as individuals in their twenties) and the severity of said acne. This resulted in a final study sample of 939 cases and 440 controls.

Variables of Interest

Data on self-reported occurrence of acne and subsequent severity in teenage and adult years were of interest as well as the occurrence of cystic acne. An "ever acne" variable was also created by positive history of acne either in teenage or adult years. Other baseline characteristics and variables of interest such as age, gender, recent body mass index (BMI), smoking status, histories of pancreatitis, alcohol use and diabetes diagnosis, race/ethnicity, and attained education level were assessed. Whether or not the patient had undergone a hysterectomy, oophorectomy, and whether or not the patient was taking birth control or menopausal hormonal medication was also recorded.

For determining history of acne, the questionnaire contained the following questions: "When you were a teenager, did you have acne?" and "If yes, was your acne mild, moderate, or severe?" Other questions included "When you were in your twenties and thirties, did you have acne?" and "If yes, would you say your acne in your twenties was mild, moderate, or severe?" and "Sometimes people who have acne in their twenties or thirties have cystic acne, which has large painful solid lumps under the skin. Did you have this kind of acne?"

Statistical Analysis

We computed baseline characteristics for the 939 cases and 440 controls. BMI was evaluated in both continuous and categorical form (<18.5, 18.5-24.9, 25-29.9, 30-34.9, >35 kg/m^2). Analyses were run in SAS and logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association of pancreatic cancer with the a priori variables history of severe acne, severe teenage acne, severe adult acne, and cystic acne. We used a minimally adjusted model including age, race, and sex. We also defined a "fully" adjusted model using a backwards variable elimination technique to evaluate the

inclusion of variables in Table 1. The final fully adjusted model included age (continuous), race (white, other), sex, BMI (continuous), education (<12 years, 12 years, 12-16 years, or >16 years), and diabetes status (yes, no). To address missing covariate data, we used the missing indicator approach to address missing BMI information. Missing birth control data were assigned a single separate category to represent missingness. Because the frequency of missing data for remaining variables was low, missing race was assigned to white, and missing hysterectomy, oophorectomy, menopausal hormone, and pancreatitis data were assigned to the "No" category. We also calculated p for trend for severity of teenage acne and severity of adult acne by modeling the categories (mild/none, moderate, severe) as an ordinal variable. We used α=0.05 to determine nominal statistical significance.

We explored interactions by stratifying associations by age (<=50, >50 years) and sex. We examined heterogeneity using likelihood ratio statistics comparing nested models with and without multiplicative interaction terms between sex and acne variables and age and acne variables. We conducted additional sensitivity analyses to assess the influence of excluding spouse controls (N=175), those with alcoholism (N=22), those with pancreatitis (N=117), and cases who had another cancer in addition to pancreatic (besides basal cell non-melanoma cancer) (N=178). The number of individuals with alcoholism was assessed through the questionnaire which explicitly asked the participants whether or not they had "ever had alcoholism" and if so, the "age when diagnosed."

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the 939 cases and 440 controls. Within the 939 cases, 34 individuals reported ever having severe acne (3.6%) and of the 440 controls, 10 individuals reported ever having severe acne (2.3%). Among those that had had teenage acne, the majority for both cases and controls classified their acne as mild (86.1% and 86.8%) respectively. Both cases and controls who had had adult acne also mostly classified their acne as mild (96.2% and 95.5%) respectively. Most of the participants did not have cystic acne (96.5% for cases and 96.6% for controls). The mean ages of the cases (63.92) and controls (59.91) were similar, with the majority of participants of white race (89.4% of cases and 88.2% of controls). Cases had lower recent BMI (mean=23.7 kg/m^2) compared to controls (mean=26.0 kg/m^2) ($p=3.55 \times 10^{-10}$). Cases also completed fewer years of schooling compared to controls ($p=1.14 \times 10^{-3}$), were less likely to be taking menopausal hormones (p=0.02), more likely to have diabetes ($p=3.45 \times 10^{-17}$), and more likely to have pancreatitis ($p=1.78 \times 10^{-12}$). The remaining characteristics were similar between cases and controls (Table 1).

Acne Variables

We did not observe a statistically significant association between history of severe acne at any age and risk of pancreatic cancer (fully-adjusted OR=1.42, 95% CI: 0.65, 3.09) compared to the reference category (none or mild acne). (Table 2). Similarly, compared to subjects reporting mild or no acne, a statistically significant association was not observed for subjects reporting severe teenage acne (fully-adjusted OR=1.60, 95% CI: 0.67, 3.80, p-trend=0.13), severe adult acne (fully-adjusted OR=1.23, 95% CI: 0.32, 4.76, p-trend=0.99), and cystic acne (fully-adjusted OR=1.37, 95% CI: 0.71, 2.67).

When stratified by sex, there was some indication that the association with history of severe acne may be stronger in men; however, p values for heterogeneity were not statistically significant for any of the acne variables (Table 3). Similarly, there were no statistically significant differences when stratified by age and the p values for heterogeneity were not statistically significant for any of the acne variables (Table 4). In additional sensitivity analyses, we did not observe appreciable differences in the interpretation of our results when excluding spousal controls, cases who had more than just pancreatic cancer (excluding those with basal cell non-melanoma skin cancer), or individuals with histories of alcoholism or pancreatitis.

Discussion

In this study, we did not observe a statistically significant association between "ever severe" acne and pancreatic cancer. This was also true of the associations between severe teenage and adult acne and cystic acne and pancreatic cancer risk. Therefore, it cannot be concluded that severe acne increases risk for pancreatic cancer in this study. Further, we did not observe evidence of significant interactions by age or sex.

Our "ever severe" minimally adjusted OR=1.67 and adjusted OR=1.42 and although this magnitude of association is consistent with previously published ORs for acne and cancer risk at other cancer sites, only 44 individuals out of the 1379 in the study sample (3.19%) reported ever having severe acne. Therefore, even though there were many cases in the study, we had limited statistical power to detect more modest associations. However, the magnitudes of association themselves are consistent with those previously published. Platz et al. looked at acne and risk of prostate cancer and found a multivariable-adjusted relative risk (RR) of 1.70 with a 95% CI of 1.03, 2.80.[17] Additionally, Zhang et al. found that a significant association was observed in meta-analysis between acne in adolescence and prostate cancer risk within the cohort studies with an OR of 1.51 and 95% CI of 1.19-1.93.[18] Murphy et al. utilized data from the Sister Study, a large prospective cohort of women who had sisters diagnosed with breast cancer but were cancer free themselves. They found that a diagnosis of having severe acne was associated with having a higher risk of breast cancer (HR 1.23) especially in women diagnosed with severe acne before the age of 18 (HR 1.40).[19] Another study hypothesized that acne may predict risk of hormone-related cancers. Hazard ratios were estimated for cancers of the breast, thyroid, large bowel and rectum (colorectal), ovary, cervix, endometrium, skin (melanoma), and lymphocytes (non-Hodgkin lymphoma) for women who had had severe teen acne. After adjustment for previously

known risk factors of each cancer, among women with a history of severe teenage acne, the hazard ratio was increased (multivariable-adjusted HR=1.44, 95% CI 1.03-2.01) for melanoma, and for breast cancer (HR=1.17, 95% CI 1.03-1.32).[20] By analogy, there could also be associations between severe acne and pancreatic cancer risk; this cancer site was not addressed in the eight-site study. Further studies with larger numbers of participants with severe acne are needed.

There are a few limitations with the present study including the aforementioned power and sample size and the fact that acne was self-reported by participants. Self-reported data can be unreliable especially since severity of acne can be subjective. In the future, studies could include pictures for subjects to choose from that would best represent the severity of acne they experienced. This would allow for a more objective determination. Additionally, since the data were collected after diagnosis, there is a chance of recall bias as well. Most of the study participants were in their 60's and details about teenage and adult acne could be difficult to remember and contribute to information that is not sufficiently accurate. Hospital-based controls are also not ideal, though perhaps may mitigate some degree of recall bias because of their involvement with patients at the hospital. Since for this tertiary care institution there is no clearly defined population from which cases emerge, using hospital-based controls allowed us to enroll individuals who are likely to be similar in background characteristics to the cases. However, more future population-based studies are needed.

It is also important to note that although the latency of pancreatic cancer is long and acne usually occurs earlier in life, it is still worth exploring early life exposures since no prior research has been performed in this specific area. Since there are interesting mechanisms in play related to both acne and pancreatic cancer risk like inflammation, this study design is appropriate for the

purpose of hypothesis generation. Although our results were not statistically significant, it is possibly a function of the small sample size. Our observed associations have similar magnitudes to ones in prior studies which suggests that this question warrants further research in larger studies. In the future, other studies could focus on acquiring more individuals who have severe acne (obtained through means other than self-report) to study what may be smaller associations.

Table 1: Baseline Characteristics

Characteristic	Case-Control Status		p
	Case (N =939)	Control (N =440)	
Ever Severe Acne			0.18
Not Severe	905 (67.8)	430 (32.2)	
Severe	34 (77.3)	10 (22.7)	
Missing	0 (0)	0 (0)	
Severity of Teen Acne			0.39
Mild/None	808 (86.1)	382 (86.8)	
Moderate	102 (10.9)	50 (11.4)	
Severe	29 (3.1)	8 (1.8)	
Missing	0 (0)	0 (0)	
Severity of Adult Acne			0.75
Mild/none	903 (96.2)	420 (95.5)	
Moderate	27 (2.9)	16 (3.6)	
Severe	9 (1.0)	4 (0.9)	
Missing	0 (0)	0 (0)	
Cystic			0.92
No, N/A	906 (96.5)	425 (96.6)	
Yes	33 (3.5)	15 (3.4)	
Missing	0 (0)	0 (0)	
Age			
Mean	63.92	59.91	
Min	32	27	
Max	90	89	
SD	11.01	11.52	
Gender			0.93
Male	491 (52.3)	229 (52.1)	
Female	448 (47.7)	211 (48)	
Missing	0 (0)	0 (0)	
BMI			3.55×10^{-10}
<18.5	46 (4.9)	8 (1.8)	
18.5-24.9	434 (46.2)	141 (32.1)	
25-29.9	266 (28.3)	178 (40.5)	
30-34.9	72 (7.7)	57 (13.0)	
>35	21 (2.2)	21 (2.2)	
Missing	100 (10.7)	35 (8.0)	
BMI			
Mean	23.72	25.96	
Min	13.87	13.87	
Max	49.23	44.70	
SD	5.27	5.55	
Smoking Status			0.39
Non-smoker	442 (47.1)	218 (49.6)	
Smoker	497 (52.9)	222 (50.5)	
Missing	0 (0)	0 (0)	

Ever had Alcoholism			0.99
No Alcoholism	924 (98.4)	433 (98.4)	
Alcoholism	15 (1.6)	7 (1.6)	
Missing	0 (0)	0 (0)	
Race/Ethnicity			0.86
White	839 (89.4)	388 (88.2)	
Black	43 (4.6)	21 (4.8)	
Asian	33 (3.5)	17 (3.9)	
Other	23 (2.5)	14 (3.2)	
Missing	1 (0.1)	0 (0)	
Education			1.14×10^{-3}
<12 Years	61 (6.5)	8 (1.8)	
12 Years	169 (18)	73 (16.6)	
12-16 Years	397 (42.3)	189 (43)	
>16 Years	312 (33.2)	170 (38.6)	
Missing	0 (0)	0 (0)	
Hysterectomy			0.79
No	838 (89.2)	391 (88.9)	
Yes	100 (10.7)	49 (11.1)	
Missing	1 (0.1)	0 (0)	
Oophorectomy			0.90
No	848 (90.3)	399 (90.7)	
Yes	85 (9.1)	41 (9.3)	
Missing	6 (0.6)	0 (0)	
Birth Control			0.07
No	611 (65.1)	269 (61.1)	
Yes	129 (13.7)	76 (37.1)	
Missing	199 (21.2)	95 (21.6)	
Estrogen			0.02
No	814 (86.7)	360 (81.8)	
Yes	121 (12.9)	78 (17.7)	
Missing	4 (0.4)	2 (0.5)	
Diabetes			3.45×10^{-17}
No	668 (71.1)	403 (91.6)	
Yes	271 (28.9)	37 (8.4)	
Missing	0 (0)	0 (0)	
Pancreatitis			1.78×10^{-12}
No	817 (87.0)	437 (99.3)	
Yes	114 (12.1)	3 (0.7)	
Missing	8 (0.9)	0 (0)	

Table 2. Adjusted Odds Ratios for Association Between Acne Variables and Pancreatic Cancer Risk

Characteristic	939 Cases	440 Controls	Minimally Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)	P for trend
Severity of Ever Acne					
Not severe	905	430	1.00	1.00	
Severe	34	10	1.67 (0.81, 3.43)	1.42 (0.65, 3.09)	
Severity of Teen Acne					
Mild/none	808	382	1.00	1.00	0.13
Moderate	102	50	1.08 (0.75, 1.56)	1.26 (0.85, 1.84)	
Severe	29	8	1.75 (0.79, 3.91)	1.60 (0.67, 3.80)	
Severity of Adult Acne					
Mild/none	903	420	1.00	1.00	0.99
Moderate	27	16	0.91 (0.48, 1.73)	0.90 (0.46, 1.75)	
Severe	9	4	1.14 (0.34, 3.78)	1.23 (0.32, 4.76)	
Cystic Acne					
No, N/A	906	425	1.00	1.00	
Yes	33	15	1.27 (0.67, 2.38)	1.37 (0.71, 2.67)	

[1] Minimally adjusted for age, race, and sex
[2] Fully adjusted for age, race, sex, BMI, education, and diabetes

Table 3. Interactions by Sex

Characteristic	491 Cases	229 Controls	Adjusted OR[3] (95% CI)
Men (N=720)			
Severity of Ever Acne			
Not severe	472	227	1.00
Severe	19	2	3.98 (0.86, 18.4)
Severity of Teen Acne			
Mild/none	412	198	1.00
Moderate	62	29	1.30 (0.77, 2.19)
Severe	17	2	3.77 (0.8, 17.77)
Severity of Adult Acne			
Mild/none	477	225	1.00
Moderate	10	3	1.06 (0.27, 4.26)
Severe	4	1	1.30 (0.12, 13.98)
Cystic Acne			
No, N/A	475	225	1.00
Yes	16	4	2.18 (0.65, 7.31)

Characteristic	448 Cases	211 Controls	Adjusted OR[4] (95% CI)
Women (N=659)			
Severity of Ever Acne			
Not severe	433	203	1.00
Severe	15	8	0.75 (0.28, 2.02)
Severity of Teen Acne			
Mild/none	396	184	1.00
Moderate	40	21	1.14 (0.63, 2.06)
Severe	12	6	0.80 (0.26, 2.48)
Severity of Adult Acne			
Mild/none	426	195	1.00
Moderate	17	13	0.89 (0.41, 1.92)
Severe	5	3	1.06 (0.20, 5.51)
Cystic Acne			
No, N/A	431	200	1.00
Yes	17	11	1.17 (0.51, 2.67)

Variables	P-heterogeneity
Severity of Teen	0.18
Severity of Adult	0.60
Cystic Acne	0.26
Ever Acne	0.08

[3] Fully adjusted for age, race, sex, BMI, education, and diabetes
[4] Fully adjusted for age, race, sex, BMI, education, and diabetes

Table 4. Interactions by Age

Characteristic	100 Cases	80 Controls	Adjusted OR[5] (95% CI)
Participants under 50 (N=180)			
Severity of Ever Acne			
Not severe	96	76	1.00
Severe	4	4	0.33 (0.05, 2.11)
Severity of Teen Acne			
Mild/none	80	69	1.00
Moderate	16	9	1.41 (0.55, 3.62)
Severe	4	2	0.66 (0.08, 5.63)
Severity of Adult Acne			
Mild/none	95	73	1.00
Moderate	4	5	0.57 (0.14, 2.38)
Severe	1	2	0.12 (0.00, 3.70)
Cystic Acne			
No, N/A	90	75	1.00
Yes	10	5	1.10 (0.32, 3.71)

Characteristic	839 Cases	360 Controls	Adjusted OR[6] (95% CI)
Participants 50 and older (N=1199)			
Severity of Ever Acne			
Not severe	809	354	1.00
Severe	30	6	2.06 (0.78, 5.44)
Severity of Teen Acne			
Mild/none	728	313	1.00
Moderate	86	41	1.15 (0.75, 1.75)
Severe	25	6	1.78 (0.66, 4.80)
Severity of Adult Acne			
Mild/none	808	347	1.00
Moderate	23	11	0.95 (0.43, 2.06)
Severe	8	2	3.00 (0.47, 19.19)
Cystic Acne			
No, N/A	816	350	1.00
Yes	23	10	1.35 (0.60, 3.02)

Variables	P-heterogeneity
Severity of Teen	0.88
Severity of Adult	0.06
Cystic Acne	0.86
Ever Acne	0.12

[5] Fully adjusted for age, race, sex, BMI, education, and diabetes
[6] Fully adjusted for age, race, sex, BMI, education, and diabetes

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