· 论　著 ·

# 髓过氧化物酶在吸烟与胰腺癌发病关系中的作用

付新新[1,2]，李兆申[1,2]，金震东[2]，陈海涛[1,2]，朱　伟[1,2]，蔡全才[1,2]*

1. 第二军医大学临床流行病学与循证医学中心，上海 200433

2. 第二军医大学长海医院消化内科，上海 200433

[摘要]　**目的**　探讨髓过氧化物酶（MPO）在吸烟与胰腺癌发病关系中的作用。**方法**　采用病例-对照研究设计。病例组为 71 例经病理证实的新发胰腺导管腺癌患者，对照组为 71 例按照性别、年龄进行匹配的健康人群。采用自制调查表进行面对面问卷调查。调查内容包括年龄、性别、体质指数（BMI）、吸烟、饮酒、糖尿病史等。采集研究对象治疗前的静脉血，采用酶联免疫分析方法检测其血浆 MPO 浓度。以对照组 MPO 浓度的中位数作为界值，将研究对象 MPO 浓度分为高和低两组。采用多元非条件 Logistic 回归分析方法分别探讨吸烟与胰腺癌、吸烟与高 MPO 浓度胰腺癌、吸烟与低 MPO 浓度胰腺癌的关系。**结果**　在控制年龄、性别、饮酒、BMI 的情况下，吸烟者发生胰腺癌的风险升高（$OR=2.74$，95%CI：1.12-6.74；$P=0.028$）；将病例组按照 MPO 浓度（196 IU/L）进行分层后，发现吸烟与高 MPO 浓度胰腺癌有关（$OR=3.81$，95%CI：1.17-12.44；$P=0.026$），但与低 MPO 浓度胰腺癌无相关（$OR=2.51$，95%CI：0.82-7.72；$P=0.108$）。**结论**　吸烟可能导致胰腺癌的发病风险升高。血浆 MPO 浓度升高可能在吸烟与胰腺癌关系中起作用。

[关键词]　胰腺肿瘤；吸烟；髓过氧化物酶；病例对照研究

[中图分类号]　R 735.9　　　[文献标志码]　A　　　[文章编号]　0258-879X(2012)02-0183-03

## Role of myeloperoxidase in relationship between smoking and risk of pancreatic cancer

FU Xin-xin[1,2]，LI Zhao-shen[1,2]，JIN Zhen-dong[2]，CHEN Hai-tao[1,2]，ZHU Wei[1,2]，CAI Quan-cai[1,2]*

1. Department of Gastroenterology，Changhai Hospital，Second Military Medical University，Shanghai 200433，China

2. Center for Clinical Epidemiology and Evidence Based Medicine，Second Military Medical University，Shanghai 200433，China

[Abstract]　**Objective**　To study the role of myeloperoxidase (MPO) in the relationship between smoking and risk of pancreatic cancer. **Methods**　A case-control study was adopted in the present study. Totally 71 patients with newly diagnosed pancreatic ductal adenocarcinoma (pathologically confirmed) and 71 age- and sex-matched healthy persons were included. All the subjects were interviewed using a self-designed questionnaire concerning the age, sex, body mass index (BMI), smoking, alcohol consumption, and history of diabetes mellitus. The venous blood samples were collected from patients before treatment and enzyme-linked immunosorbent assay was used to measure the plasma MPO；the subjects were divided into high and low MPO groups based on the median MPO value of controls. Unconditional logistic regression model was used to study the relationship of smoking with risk of pancreatic cancer, risk of pancreatic cancer with high plasma MPO, and risk of pancreatic cancer with low plasma MPO. **Results**　After adjusted for age, sex, alcohol consumption, and BMI, smoking significantly increased the risk of pancreatic cancer ($OR=2.74$，95%CI：1.12-6.74；$P=0.028$). Besides, smoking was also significantly associated with increased risk of pancreatic cancer with high plasma MPO ($>196$ IU/L) ($OR=3.81$，95%CI：1.17-12.44；$P=0.026$)，and was not significantly associated with the risk of pancreatic cancer with low plasma MPO ($\leqslant196$ IU/L) ($OR=2.51$，95%CI：0.82-7.72；$P=0.108$). **Conclusion**　Smoking may increase the risk of pancreatic cancer. High plasma MPO level may play an important role in the relationship between smoking and risk of pancreatic cancer.

[Key words]　pancreatic neoplasms；smoking；myeloperoxidase；case-control studies

[Acad J Sec Mil Med Univ，2012，33(2)：183-185]

　　胰腺癌是恶性程度最高的肿瘤之一，病死率约为 98%[1]，近年来其发病率呈明显上升的趋势[2]。由于缺乏早期诊断方法和有效的治疗手段，其确诊后的平均生存时间不超过 6 个月，5 年生存率低于 5%[3]。针

对病因采取有效措施可望降低其发病率和疾病负担。

　　吸烟是胰腺癌的危险因素之一,然而其致病机制迄今未明[3-4]。研究认为,吸烟可使人血液中髓过氧化物酶(MPO)的浓度升高[5]。MPO存在于大多数白细胞亚种(包括中性白细胞和单核细胞)的嗜苯胺蓝颗粒和一些组织细胞的亚型中[6],与炎症和氧化应激关系密切,在机体免疫功能方面起着重要作用[7]。已有研究表明,MPO基因高表达可能导致胰腺癌的发病风险升高[8]。因此,推测MPO可能在吸烟与胰腺癌的关系中起到一定作用。本研究采用病例-对照研究方法,探讨MPO在吸烟与胰腺癌关系中的作用。

# 1　材料和方法

1.1　研究对象　病例组为来我院就诊的经病理证实的新发胰腺导管腺癌连续病例,对照组为按照年龄、性别进行匹配的来我院体检的健康人群。

1.2　调查内容及方法　采用自制调查表进行面对面问卷调查。调查内容包括年龄、性别、体质指数(BMI)、饮酒、吸烟、糖尿病史等。

1.3　血标本采集及检测方法　采集研究对象静脉血5 ml(病例为入院后治疗前标本),放置在EDTA抗凝管中,在2 h内以3 000 r/min离心15 min后取血浆,分装保存于−80℃冰箱中待测。采用美国RD公司的人MPO ELISA试剂盒检测研究对象血浆中的MPO浓度。

1.4　统计学处理　采用SPSS 19.0统计软件进行分析。计量资料以$\bar{x} \pm s$表示。以对照组MPO浓度的中位数作为界值,将研究对象MPO浓度分为高和低两组。在吸烟与胰腺癌、吸烟与高或低MPO浓度胰腺癌的关系中,单因素分析采用$\chi^2$检验,多因素分析采用非条件Logistic回归分析方法。上述所有分析均为双侧检验,检验水准($\alpha$)为0.05。

# 2　结　果

2.1　研究对象一般情况　病例组共纳入71例胰腺导管腺癌患者,其中33例(46.5%)患者血浆MPO浓度>196 IU/L。对照组纳入71例年龄、性别与病例组匹配的健康人群。研究对象的年龄、性别、BMI、饮酒、吸烟、糖尿病情况见表1。

2.2　吸烟与胰腺癌关系　单因素分析结果显示,吸烟者发生胰腺癌的风险升高($OR = 2.033$,95%CI:$0.996 \sim 4.152$,$P = 0.050$)。多因素分析结果表明,在控制年龄、性别、饮酒、BMI的情况下,吸烟者发生胰腺癌的风险升高($OR = 2.74$,95%CI:$1.12 \sim 6.74$;$P = 0.028$)。见表2。

### 表1　研究对象特征
### Tab 1　Characteristics of the study population

| Group | N | Age(year) | Male n(%) | BMI (kg · m$^{-2}$) | Alcohol drinking n(%) | Smoking n(%) | DM n(%) |
|---|---|---|---|---|---|---|---|
| Control | 71 | 59.1±9.7 | 41(57.7) | 23.7±4.4 | 25(35.2) | 18(25.4) | 0(0) |
| MPO | 71 | 59.3±9.2 | 41(57.7) | 22.5±3.1 | 22(31.0) | 29(40.8) | 7(9.9) |
| High | 33 | 58.7±8.7 | 19(57.6) | 22.8±3.2 | 12(36.4) | 15(45.5) | 5(15.2) |
| Low | 38 | 59.7±9.6 | 22(57.9) | 22.3±3.0 | 10(26.3) | 14(36.8) | 2(5.3) |

MPO:Myeloperoxidase;BMI:Body mass index;DM:Diabetes mellitus

### 表2　病例-对照比较的多因素分析
### Tab 2　Multivariable analysis of case-control comparisons

| Variable | Case vs control | | Case with high MPO vs control | | Case with low MPO vs control | |
|---|---|---|---|---|---|---|
| | OR(95%CI) | P value | OR(95%CI) | P value | OR(95%CI) | P value |
| Smoking | | | | | | |
| Yes | 2.74(1.12-6.74) | 0.028 | 3.81(1.17-12.44) | 0.026 | 2.51(0.82-7.72) | 0.108 |
| No | 1(Reference) | | 1(Reference) | | 1(Reference) | |
| Sex | | | | | | |
| Female | 1.57(0.64-3.86) | 0.329 | 2.15(0.65-7.13) | 0.210 | 1.39(0.43-4.51) | 0.589 |
| Male | 1(Reference) | | 1(Reference) | | 1(Reference) | |
| Alcohol drinking | | | | | | |
| Yes | 0.79(0.35-1.78) | 0.571 | 1.00(0.37-2.67) | 0.992 | 0.70(0.24-2.01) | 0.508 |
| No | 1(Reference) | | 1(Reference) | | 1(Reference) | |
| Continuous variables | | | | | | |
| Age(year) | 1.00(0.96-1.04) | 0.985 | 0.99(0.95-1.04) | 0.809 | 1.01(0.97-1.05) | 0.747 |
| BMI(kg · m$^{-2}$) | 0.92(0.84-1.02) | 0.110 | 0.96(0.85-1.07) | 0.433 | 0.91(0.81-1.02) | 0.105 |

MPO:Myeloperoxidase;BMI:Body mass index

2.3　吸烟与高 MPO 浓度胰腺癌关系　单因素分析结果显示,吸烟与高 MPO 浓度胰腺癌明显相关($OR$=2.45,95％CI：1.03～5.85；$P$=0.040)。控制年龄、性别、饮酒、BMI 后,吸烟仍然升高高浓度 MPO 胰腺癌的发生风险($OR$=3.81,95％CI：1.17～12.44；$P$=0.026)。见表2。

2.4　吸烟与低 MPO 浓度胰腺癌关系　单因素分析结果显示,吸烟与低 MPO 浓度胰腺癌无相关($OR$=1.72,95％CI：0.74～4.01；$P$=0.209)。多因素分析结果表明,吸烟未能升高低 MPO 浓度胰腺癌的发生风险($OR$=2.51,95％CI：0.82～7.72；$P$=0.108)。见表2。

## 3　讨　论

目前研究认为,吸烟是胰腺癌明确的危险因素之一,其相对危险度($OR$)为 2～3[9-12]。本研究结果与上述研究报道相一致,在控制年龄、性别、糖尿病、饮酒等因素后,吸烟者发生胰腺癌的相对危险度为 2.74。然而,吸烟导致胰腺癌发病风险升高的机制尚不清楚。

研究证实,吸烟可使人血液中 MPO 浓度升高[5],其可能机制为：吸烟可为人体提供氰化物($CN^-$)[13],促使人体内发生由 MPO 催化的如下反应：$CN^- + OSCN^- \rightarrow SCN^- + OCN^-$,$SCN^- + H_2O_2 \rightarrow HOSN^-$。$HOSN^-$ 是比 HClO 更强的氧化剂,能促进更强的炎症反应发生,对宿主组织造成更大的破坏,因此,MPO 浓度升高可能会使患胰腺癌的危险度升高。也有文献提出 MPO 是组成抗菌系统中吞噬体的一部分,是在脱颗粒过程中被释放入吞噬体的,是 $MPO$-$H_2O_2$-氯化物系统的重要组成部分[7]。这一系统的最初产物是 HClO,接着生成氯气、氯胺类、羟基、单态氧和臭氧,这些毒性物质可被释放到细胞外,可攻击正常组织从而导致炎性疾病甚至肿瘤的发生[7]。

已有多项研究证实 MPO 与肿瘤关系密切[8,14-17]。Medeiros 等[14]的研究发现,急性白血病与骨髓中高浓度 MPO 关系密切。Kodurua 等[15]的研究证实 MPO 与甲状腺癌的发生有关。更多研究探讨了 MPO 基因突变与肺癌关系,发现导致 MPO 低表达的基因突变可以降低肺癌发病风险[16-17]。已有研究发现,MPO 基因高表达可能导致胰腺癌的发病风险升高[8]。

综上所述,吸烟是胰腺癌的明确危险因素,吸烟可能导致外周血 MPO 浓度升高,高 MPO 浓度可能导致胰腺癌发病风险升高,推测 MPO 可能在吸烟与胰腺癌的关系中起到一定作用。本研究结果证实了上述推测。发现吸烟与高 MPO 浓度胰腺癌有关,但与低 MPO 浓度胰腺癌无关,提示高 MPO 浓度可能在吸烟与胰腺癌关系中扮演重要角色。本研究结果有助于进一步阐明吸烟与胰腺癌关系,这对于胰腺癌预防具有重要意义。

## 4　利益冲突

所有作者声明本文不涉及任何利益冲突。

[参 考 文 献]

[1]　Jemal A,Siegel R,Ward E,Murray T,Xu J,Thun M J. Cancer statistics,2007[J]. CA Cancer J Clin,2007,57:43-66.

[2]　Parkin D M,Bray F,Ferlay J,Pisani P. Global cancer statistics,2002[J]. CA Cancer J Clin,2005,55:74-108.

[3]　Lowenfels A B,Maisonneuve P. Epidemiology and risk factors for pancreatic cancer[J]. Best Pract Res Clin Gastroenterol,2006,20:197-209.

[4]　Koorstra J B M,Hustinx S R,Offerhaus G J A,Maitra A. Pancreatic carcinogenesis[J]. Pancreatology,2008,8:110-125.

[5]　Ozcaka O,Bicakci N,Pussinen P,Sorsa T,Kose T,Buduneli N. Smoking and matrix metalloproteinases,neutrophil elastase and myeloperoxidase in chronic periodontitis[J]. Oral Dis,2010,17:68-76.

[6]　Nicholls S J,Hazen S L. Myeloperoxidase and cardiovascular disease [J]. Arterioscler Thromb Vasc Biol,2005,25:1102-1111.

[7]　Klebanoff S J. Myeloperoxidase:friend and foe[J]. J Leukoc Biol,2005,77:598-625.

[8]　Wheatley-Price P,Asomaning K,Reid A,Zhai R,Su L,Zhou W,et al. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma[J]. Cancer,2008,112:1037-1042.

[9]　Vrieling A,Bueno-de-Mesquita H B,Boshuizen H C,Michaud D S,Severinsen M T,Overvad K,et al. Cigarette smoking,environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition[J]. Int J Cancer,2010,126:2394-2403.

[10]　Talamini R,Polesel J,Gallus S,Dal Maso L,Zucchetto A,Negri E,et al. Tobacco smoking,alcohol consumption and pancreatic cancer risk:a case-control study in Italy[J]. Eur J Cancer,2010,46:370-376.

[11]　Raimondi S,Maisonneuve P,Lowenfels A B. Epidemiology of pancreatic cancer:an overview[J]. Nat Rev Gastroenterol Hepatol,2009,6:699-708.

[12]　Brand R E,Greer J B,Zolotarevsky E,Brand R,Du H,Simeone D,et al. Pancreatic cancer patients who smoke and drink are diagnosed at younger ages[J]. Clin Gastroenterol Hepatol,2009,7:1007-1012.

[13]　Lemma K,Ashby M T. Reactive sulfur species:kinetics and mechanism of the reaction of hypothiocyanous acid with cyanideto give dicyanosulfide in(aqueous solution)[J]. Chem Res Toxicol,2009,22:1622-1628.

[14]　Medeiros B C,Kohrt H E,Arber D A,Bangs C D,Cherry A M,Majeti R,et al. Immunophenotypic features of acute myeloid leukemia with inv(3)(q21q26.2)/t(3;3)(q21;q26.2)[J]. Leuk Res,2010,34:594-597.

[15]　Kodurua B,Tejaswini A,Thakur A,Kamath S U,Shenoy K R,Kamath U,et al. Indicators of oxidative stress in thyroid cancer [J]. Indian J Biochem Biophys,2010,47:121-123.

[16]　Cascorbi I,Henning S,Brockmöller J,Gephart J,Meisel C,Müller J M,et al. Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant －463A of the myeloperoxidase gene[J]. Cancer Res,2000,60:644-649.

[17]　Schabath M B,Spitz M R,Hong W K,Delclos G L,Reynolds W F,Gunn G B,et al. A myeloperoxidase polymorphism associated with reduced risk of lung cancer[J]. Lung Cancer,2002,37:35-40.

[本文编辑]　尹　荼