

吸烟与胰腺癌发生风险的病例对照研究

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摘要: [目的] 探讨吸烟与胰腺癌发生风险的关系。[方法] 采用 1:1 配对病例对照研究, 病例来源于 2011 年 11 月至 2013 年 2 月间河南省肿瘤医院住院治疗的新发胰腺癌病例, 选取非胰腺癌患者家属为对照组, 对病例组和对照组进行问卷调查。采用单因素和多因素条件 Logistic 回归进行数据分析。[结果] 吸烟($OR=2.57, 95\%CI: 1.07\sim 6.16$)、清晨吸烟($OR=5.50, 95\%CI: 1.22\sim 24.81$)是胰腺癌的危险因素。调整 BMI、糖尿病、胆囊疾病等混杂因素后, 吸烟、清晨吸烟的相对危险度分别为 3.53($95\%CI: 1.30\sim 9.60$), 13.14($95\%CI: 1.45\sim 118.68$); 吸烟年限、每天吸烟支数和吸烟指数与胰腺癌发生风险增大存在趋势关系($P_{趋势}<0.05$)。[结论] 吸烟、尤其是清晨吸烟是胰腺癌的危险因素, 控制烟草是预防胰腺癌的重要措施。

关键词: 胰腺癌; 吸烟; 配对病例对照研究; 条件 Logistic 回归

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Cigarette Smoking and The Risk of Pancreatic Cancer : A Case-control Study

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Abstract: [Purpose] To investigate the relationship between smoking and pancreatic cancer. [Methods] A pair matched case-control study was carried out. New cases of pancreatic cancer were consecutively recruited at Henan Cancer Hospital from November 2011 to February 2013. Matched controls were selected from the family members of non-pancreatic cancer patients. Information was collected by questionnaire. Univariate and multivariate conditional Logistic regression were performed to data analysis. [Results] Smoking ($OR=2.57, 95\%CI: 1.07\sim 6.16$) and smoking in the early morning ($OR=5.50, 95\%CI: 1.22\sim 24.81$) were risk factors of pancreatic cancer. After adjusted for BMI, diabetes mellitus, gallbladder disease, the odds ratio of smoking and smoking in the early morning were 3.5($95\%CI: 1.3\sim 9.8$), 13.0($95\%CI: 1.4\sim 124.5$), respectively. With the increasing of smoking duration, the number of cigarettes per day and smoking index, significant trends were found between these indicators and pancreatic cancer($P_{trend}<0.05$). [Conclusion] Smoking, especially smoking in the early morning are the risk factors of pancreatic cancer. Tobacco control is an important measure for the prevention of pancreatic cancer.

Key words: pancreatic cancer; smoking; matched case-control study; conditional logistic regression

据国际癌症研究中心数据显示 2008 年全球范围内胰腺癌发病人数约 27.87 万, 位居恶性肿瘤发病率的第 13 位, 死亡人数约 26.67 万, 位居恶性肿瘤死亡率的第 8 位^[1]。我国肿瘤登记年报显示 2012 年胰腺癌发病率居全国肿瘤发病顺位的第 7 位, 死

亡顺位的第 6 位^[2]。胰腺癌是恶性度较高的癌症之一, 其早期诊断困难, 病程短, 进展快, 死亡率高, 中位生存时间仅 4~6 个月^[3]。国外多项病例对照研究、队列研究及 Meta 分析证实吸烟是胰腺癌的重要危险因素, 但对于吸烟年限、每天吸烟支数、戒烟等研究结果存在较大差异^[4-11]。国内仅有少量吸烟与胰腺癌发生风险的病例对照研究^[12-14]。本文以医院为基

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础进行病例对照研究,旨在进一步探讨吸烟与胰腺癌发生风险的关系。

1 资料与方法

1.1 研究对象与方法

收集 2011 年 11 月到 2013 年 2 月期间河南省肿瘤医院住院的胰腺癌患者作为病例组,胰腺癌诊断依据如下:(1)有病理标本者;(2)无病理标本者至少有以下两项影像学诊断支持可以确诊为胰腺癌:①CT 提示胰腺局部增大和占位性病变;②B 超提示胰腺有低密度区、胰管扩张及胆总管和胆囊肿大;③内镜下逆行胆胰管造影(ERCP)提示胰管或胆管截然中断、断端变钝、管壁僵硬不规则或有双管征或胰外血管受侵(有血管狭窄、中断);④经皮肝穿刺胆道造影(PTC)示有胆总管偏心狭窄或阻塞;⑤超声内镜提示有胰腺区低密度占位性病变;⑥磁共振胆胰管造影(MRCP)显示胰管或胆总管狭窄、扩张或有占位性病变;(3)手术中探查扪及实性肿物加上至少 1 条影像学证据。

对照组的選擇按照 1:1 匹配方法,从同一病区或其他病区中寻找非胰腺癌患者的家属,要求与病例性别相同、年龄相差<5 岁、居住地区在河南。由于 75 岁以上患者信息收集及对照选取比较困难,本研究未将 75 岁以上胰腺癌患者作为研究对象。所有研究对象均签订知情同意书。

105 对研究对象中,男性 49 对,女性 56 对。病例组平均年龄 59.5 ± 9.3 岁,对照组平均年龄 57.7 ± 9.4 岁。病例组与对照组的基本情况分布差异无统计学意义(Table 1)。

1.2 变量定义

吸烟:按照 1984 年 WHO 关于吸烟调查方法标准化规定;每天吸烟 1 支或 1 支以上,并且连续或者累计 6 个月及以上视为吸烟;戒烟者规定为符合吸烟条件,但调查时已经连续 2 年不吸烟;吸烟指数(smoking index, SI)=每天吸烟支数×吸烟年限。本研究按照四分位间距将吸烟指数分为 4 组:A 组:SI:0~300;B 组:

SI:300~600;C 组:SI:600~840;D 组:SI≥840。

1.3 统计学处理

调查问卷采用 Epidata3.0 软件双人双录入,采用 SAS9.1.3 软件进行数据处理分析。利用单因素 Logistic 回归和多因素 Logistic 回归分析计算 OR 值及其 95%CI。

2 结果

2.1 单因素 Logistic 分析结果

吸烟(OR=2.57, 95%CI:1.07~6.16)、清晨吸烟(OR=5.50, 95%CI:1.22~24.81)与胰腺癌发生存在明显关联;而开始吸烟年龄、吸烟年限、每天吸烟支数、戒烟、被动吸烟与胰腺癌发生风险无统计学关联(Table 2)。

2.2 多因素 Logistic 回归分析结果

调整 BMI、糖尿病、胆囊疾病等混杂因素后显示,吸烟、清晨吸烟的相对危险度分别为 3.53(95%CI:1.30~9.60)、13.14(95%CI:1.45~118.68),吸烟年限增加($P_{趋势}=0.01$)、每天吸烟支数加大($P_{趋势}=0.01$)与胰腺癌的发生风险增加($P<0.05$)(Table 3)。吸烟指数各组之间与胰腺癌无统计学关联,但吸烟指数

Table 1 The general information of cases group and control group

Variable	Case group	Control group	χ^2	P value
Nation			1.33	0.51
Han	103(98.10)	103(98.10)		
Hui	1(0.95)	2(1.90)		
Others	1(0.95)	0		
Education			6.91	0.08
Illiterate	16(15.23)	24(22.86)		
Primary school	40(38.10)	28(26.67)		
Junior high school	24(22.86)	35(33.33)		
Senior high school and above	25(23.81)	18(17.14)		
Marriage			2.05	0.15
Conjugal	96(91.43)	101(96.19)		
Others	9(8.57)	4(3.81)		
Resident district			0.19	0.67
Country	66(62.86)	69(65.71)		
City	39(37.14)	36(34.29)		
BMI(kg/m ²)			1.86	0.06
<18.5	7(6.67)	11(10.48)		
18.5~	74(70.48)	76(72.38)		
24.0~	22(20.95)	16(15.24)		
≥28.0	2(1.90)	2(1.90)		

Table 2 Univariate analysis between smoking and pancreatic cancer

Variable	Case(+) control(+) n	Case(+) control(-) n	Case(-) control(+) n	Case(-) control(-) n	OR(95%CI)	P
Smoking	24	17	6	58	2.57(1.07~6.16)	0.03
Age started smoking (years)						
<30	5	3	5	2	0.60(0.14~2.51)	0.48
≥30	0	0	0	2	—	—
Years of smoking(years)						
<20	2	0	0	60	—	—
20~40	7	9	4	60	2.25(0.69~7.30)	0.18
≥40	3	7	1	60	7.00(0.86~56.89)	0.07
Cigarettes smoked per day(cigarettes/day)						
<10	0	2	1	65	2.00(0.18~22.05)	0.08
10~20	1	6	20	65	3.00(0.61~14.86)	0.18
≥20	4	10	3	65	3.33(0.92~12.11)	0.57
Smoking in morning	6	11	2	4	5.50(1.22~24.81)	0.03
Smoking cessation	6	4	9	5	0.44(0.14~1.44)	0.18
Passive smoking	44	7	7	0	1.46(0.68~3.13)	0.34

Table 3 Multivariate analysis between smoking and pancreatic cancer

Variable	Case (+) control(+) n	Case (+) control(-) n	Case (-) control(+) n	Case (-) control(-) n	OR* (95%CI)	P
Smoking	24	17	6	58	3.53 (1.30~9.60)	0.01
Age started smoking(years)						
<30	5	3	5	2	3.00(0.93~9.71)	0.07
≥30	0	0	0	2	11.37(0.87~149.25)	—
Years of smoking(years)						
<20	2	0	0	60	—	—
20~40	7	9	4	60	3.10(0.83~11.55)	0.09
≥40	3	7	1	60	6.13(0.74~50.67)	0.09
P_{trend}						0.01
Cigarettes smoked per day(cigarettes/day)						
<10	0	2	1	65	2.95(0.14~63.85)	0.49
10~20	1	6	2	65	3.42(0.64~18.25)	0.15
≥20	4	10	3	65	3.81(0.96~15.04)	0.06
P_{trend}						0.01
Smoking in morning	6	11	2	4	13.14(1.45~118.68)	0.02
Smoking cessation	6	4	9	5	0.30(0.08~1.19)	0.09
Passive smoking	44	7	7	0	2.51(0.59~10.65)	0.21

Note: * adjusted for BMI, diabetes mellitus, gallbladder disease

与胰腺癌发生风险的变化差异有统计学意义($P_{趋势}=0.02$)(Table 4)。

3 讨论

吸烟是目前确定的胰腺癌发生的危险因素^[7]。

本研究显示吸烟者患胰腺癌的风险是不吸烟者的3.53倍(95%CI:1.30~9.60),这与大多数吸烟与胰腺癌发生的病例对照研究结果是一致的^[15-17],但部分队列研究显示关联强度相对较弱^[18-21]。有报道表明^[22],随着吸烟量的增加,胰腺癌的发生风险逐渐上升,每天吸烟大于20支的人群患胰腺癌发病风险是不吸

Table 4 Multivariate analysis between smoking index and pancreatic cancer

Smoking index	Case(+) control(+) n	Case(+) control(-) n	Case(-) control(+) n	Case(-) control(-) n	OR* (95%CI)	P
0~300	0	4	1	65	5.73(0.44~74.96)	0.18
300~600	1	4	1	65	5.99(0.55~65.65)	0.07
600~840	1	4	2	65	1.61(0.28~9.26)	0.59
≥840	1	6	2	65	4.21(0.75~23.57)	0.10
<i>P_{trend}</i>						0.02

Note: * adjusted for BMI, diabetes mellitus, gallbladder disease

烟者的 2.6 倍。

本次研究中未发现每天吸烟支数、吸烟年限与胰腺癌的发生存在关联,但两者与胰腺癌的发生风险存在趋势关系($P_{趋势}<0.05$)。随着每天吸烟支数和吸烟年限的增加,胰腺癌发生风险增加。Lin 等^[4]进行的日本人群的队列研究也未发现吸烟量与胰腺癌的发生相关。单独研究吸烟年限和每天吸烟支数不能全面代表吸烟的累积效应与胰腺癌发生风险的关系,故引入吸烟指数,进一步分析吸烟与胰腺癌发生的关系。吸烟指数是研究吸烟累积效应的指标。本研究未发现吸烟指数与胰腺癌的发生存在统计学关联,但吸烟指数与胰腺癌发生风险的变化差异有统计学意义($P_{趋势}=0.02$)。Wynder 提出^[11],烟草致癌物可能通过血液进入胰腺,也可能通过胆汁倒流。有研究显示,吸烟者胰腺中 DNA-致癌物加合物的含量比不吸烟者高。在动物模型中,烟草中的亚硝胺类可诱导胰腺癌,而且烟草中含有其他的致癌物质,如芳香类化合物、多环芳烃、金属镉。烟草中可能只有一种致癌物与胰腺癌相关,也可能是两种或多种致癌物联合作用的结果。吸烟指数增加会导致烟草致癌物的累积暴露,胰腺癌的发生风险就会增加。

本研究中戒烟人群与胰腺癌的发生之间未见明显的相关性。Mirjam 等^[23]关于胰腺癌的队列研究结果显示,戒烟 20 年以后患胰腺癌的风险与不吸烟者相当。也有研究显示,戒烟 5~10 年者胰腺癌的发生风险与不吸烟者相近^[24,25]。但 Silverman 等^[26]进行的病例对照研究显示,戒烟 20 年后胰腺癌的发生风险仍然比未吸烟者高 30%。尽管研究结果存在一些差异,但总体认为戒烟会降低吸烟者胰腺癌的发生风险,认为戒烟是胰腺癌发生的保护因素。随着戒烟年限的延长,胰腺癌的发生风险不断下降。

目前国内外进行的被动吸烟与胰腺癌的发生风险的研究结果存在较大差异。Hassan 等^[27]将被动吸

烟分为儿童时期和成年时期,并且考虑被动吸烟的频率、接受被动吸烟的场所,但均未发现被动吸烟与胰腺癌的发生相关。埃及一项病例对照研究则显示被动吸烟增加了胰腺癌的发生风险 ($OR=6.0$,

$95\%CI:2.4\sim14.8$)^[28],但该研究样本量太小。欧洲进行的大规模的队列研究显示被动吸烟与胰腺癌的发生风险与肺癌相似,具有边缘统计学显著性^[29]。

研究显示,清晨吸烟增加肺癌和其他烟草相关癌症的发生风险^[30,31],但目前仅少量关于清晨吸烟与胰腺癌发生风险的研究^[32]。本研究中,清晨吸烟者患胰腺癌的风险是不吸烟者的 13.14 倍。清晨吸烟是检测尼古丁依赖程度重要指标,清晨醒来立即吸烟人群的血可替丁水平明显高于 30 分钟或者 1 小时后的吸烟者^[33,34],尼古丁及其代谢产物并非致癌物,但具有成瘾性,导致烟草中其他致癌物的持续暴露。Branstetter 等^[35]发现,第一支烟与清晨醒来的时间间隔越短,尿甲基亚硝胺的水平越高。上海的队列研究中,肺癌患者中吸烟者的甲基亚硝胺的水平比不吸烟者高 40%^[36]。因此,致癌物甲基亚硝胺的暴露可能是清晨吸烟与胰腺癌发生的原因,但也可能是由于其他烟草致癌物。由于本研究样本量较小,部分研究结果可能存在偏差,今后工作中需进一步加大样本量,为采取控制烟草措施以预防胰腺癌发生提供科学信息。

参考文献:

- [1] Ferlay J,Shin HR,Bray F,et al. Estimates of worldwide burden of cancer in 2008:GLOBOCAN 2008 [J]. Int J Cancer,2010,127(12):2893-2917.
- [2] He J,Chen WQ. Chinese Cancer Registry Annual Report (2012) [M].Beijing: Military Medical Science Press, 2012.68-87.[赫捷,陈万青.中国肿瘤登记年报(2012)[M].北京:军事医学科学出版社,2012.68-87.]
- [3] Raise the Oncology Branch of Chinese Medical Association Pancreatic Cancer Group. Expert consensus of multi-disciplinary team for pancreatic cancer[J]. Chinese Journal of Oncology,2013,35(5):398-400. [中华医学会肿瘤学分会胰腺癌学组.胰腺癌多学科综合治疗协作组专家共识[J].中华肿瘤杂志,2013,35(5):398-400.]
- [4] Lin Y,Tamakoshi A,Kawamura T,et al. A prospective cohort study of cigarette smoking and pancreatic cancer in Japan[J]. Cancer Causes Control,2002,13(3):249-254.

- [5] Secretan B, Straif K, Baan R, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish[J]. *Lancet Oncol*, 2009, 10(11): 1033–1034.
- [6] Boyle P, Maisonneuve P, Bueno De Mesquita B, et al. Cigarette smoking and pancreas cancer: a case-control study of the search programme of the IARC[J]. *Int J Cancer*, 1996, 67(1): 63–71.
- [7] Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4)[J]. *Ann Oncol*, 2012, 23(7): 1880–1888.
- [8] Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case-control study[J]. *Am J Gastroenterol*, 2007, 102(12): 2696–2707.
- [9] Muscat JE, Stellman SD, Hoffmann D, et al. Smoking and pancreatic cancer in men and women[J]. *Cancer Epidemiol Biomarkers Prev*, 1997, 6(1): 15–19.
- [10] Anderson M, Zolotarevsky E, Cooper K, et al. Alcohol and tobacco lower the age of presentation in sporadic pancreatic cancer in a dose-dependent manner: a multicenter study[J]. *Am J Gastroenterol*, 2012, 107(11): 1730–1739.
- [11] Talamini R, Polesel J, Gallus S, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy[J]. *Eur J Cancer*, 2010, 46(2): 370–376.
- [12] Fang YQ, Zhou GZ, Li ZS, et al. Study on the relationship between pancreatic cancer and life style and diet habits[J]. *Medical Journal of Chinese People's Liberation Army*, 2002, 24(4): 289–291. [方裕强, 周国中, 李兆申, 等. 生活习惯与胰腺癌关系的研究[J]. *解放军医学杂志*, 2002, 27(4): 289–291.]
- [13] Yan D, Wang XY, Xu XJ, et al. Analyses of partial risk factors for pancreatic cancer[J]. *Journal of Xinjiang Medical University*, 2010, 33(8): 928–930. [晏冬, 王喜艳, 徐新建, 等. 胰腺癌部分发病危险因素的分析[J]. *新疆医科大学学报*, 2010, 33(8): 928–930.]
- [14] Xu P, Huang Q, Liu CH, et al. Risk factors for pancreatic cancer: a case-control study [J]. *Tumor*, 2011, 31 (7): 653–657. [许鹏, 黄强, 刘臣海, 等. 胰腺癌危险因素的病例对照研究[J]. *肿瘤*, 2011, 31(7): 653–657.]
- [15] Villeneuve PJ, Johnson KC, Hanley AJ, et al. Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian Enhanced Surveillance System case-control project. *Canadian Cancer Registries Epidemiology Research Group*[J]. *Eur J Cancer Prev*, 2000, 9(1): 49–58.
- [16] Zatonski WA, Boyle P, Przewozniak K, et al. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland [J]. *Int J Cancer*, 1993, 53(4): 601–607.
- [17] Partanen TJ, Vainio HU, Ojajarvi IA, et al. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study[J]. *Cancer Lett*, 1997, 116(1): 27–32.
- [18] Shapiro JA, Jacobs EJ, Thun MJ. Cigar smoking in men and risk of death from tobacco-related cancers[J]. *J Natl Cancer Inst*, 2000, 92(4): 333–337.
- [19] Hirayama T. Epidemiology of pancreatic cancer in Japan [J]. *Jpn J Clin Oncol*, 1989, 19(3): 208–215.
- [20] Harnack LJ, Anderson KE, Zheng W, et al. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study [J]. *Cancer Epidemiol Biomarkers Prev*, 1997, 6(12): 1081–1086.
- [21] Lin Y, Yaqyu K, Ueda J, et al. Active and passive smoking and risk of death from pancreatic cancer: findings from the Japan Collaborative Cohort Study[J]. *Pancreatol*, 2013, 13(3): 279–284.
- [22] Kuzmickiene I, Everatt R, Virviciute D, et al. Smoking and other risk factors for pancreatic cancer: A cohort study in men in Lithuania[J]. *Cancer Epidemiology*, 2013, 37(2): 133–139.
- [23] Heinen MM, Verhage BA, Goldbohm RA, et al. Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study [J]. *Cancer Epidemiol Biomarkers Prev*, 2010, 19(6): 1612–1622.
- [24] Vrieling A, Bueno De Mesquita HB, Boshuizen HC, 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(10): 2394–2403.
- [25] Larsson SC, Permert J, Håkansson N, et al. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts[J]. *Br J Cancer*, 2005, 93(11): 1310–1315.
- [26] Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer[J]. *Br J Cancer*, 1999, 80(11): 1830–1837.
- [27] Hassan MM, Abbruzzese JL, Bondy ML, et al. Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: A case-control study[J]. *Cancer*, 2007, 109(12): 2547–2556.
- [28] Lo A, Soliman AS, El-Ghawalby N, et al. Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk[J]. *Pancreas*, 2007, 35(2): 120–129.
- [29] Vrieling A, Bueno De Mesquita HB, Boshuizen HC, 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(10): 2394–2403.
- [30] Muscat JE, Ahn K, Richie JP, et al. Nicotine dependence phenotype and lung cancer risk[J]. *Cancer*, 2011, 117(23): 5370–5376.
- [31] Muscat JE, Ahn K, Richie JP, et al. Nicotine dependence phenotype, time to first cigarette, and risk of head and neck cancer[J]. *Cancer*, 2011, 117(23): 5377–5382.
- [32] Nakao M, Hosono S, Ito H, et al. Cigarette smoking and pancreatic cancer risk: a revisit with an assessment of the nicotine dependence phenotype[J]. *Asian Pac J Cancer Prev*, 2013, 14(7): 4409–4413.
- [33] Figueiredo VC, Szklo M, Szklo AS, et al. Determinants of salivary cotinine level: a population-based study in Brazil [J]. *Rev Saude Publica*, 2007, 41(6): 954–962.
- [34] Muhammad-Kah RS, Hayden AD, Liang Q, et al. The relationship between nicotine dependence scores and biomarkers of exposure in adult cigarette smokers[J]. *Regul Toxicol Pharmacol*, 2011, 60(1): 79–83.
- [35] Branstetter SA, Muscat JE. Time to first cigarette and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels in adult smokers; National Health and Nutrition Examination Survey (NHANES), 2007–2010[J]. *Cancer Epidemiol Biomarkers Prev*, 2013, 22(4): 615–622.
- [36] Church TR, Anderson KE, Le C, et al. Temporal stability of urinary and plasma biomarkers of tobacco smoke exposure among cigarette smokers[J]. *Biomarkers*, 2010, 15(4): 345–352.