

基于山东省农村上消化道癌早诊早治项目的食管鳞癌及其癌前病变高危人群预测模型研究

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摘要: [目的] 分析食管鳞癌及其癌前病变的危险因素, 建立并验证食管鳞癌风险预测模型。[方法] 选取 2017 年 3 月至 2020 年 9 月参加山东省“农村上消化道癌早诊早治项目”中 40~69 周岁的人群, 应用 1:4 倾向评分匹配方法(匹配因素: 年龄、性别、收入、教育水平)均衡病例组和对照组基线信息, 纳入病例组 1 410 例, 对照组 5 640 例。将人群按 7:3 随机分为训练集($n=4\ 926$)和验证集($n=2\ 124$), 分别用于建立模型和模型验证。采用 χ^2 检验进行单因素分析, 将 $P<0.1$ 的因素纳入条件 Logistic 回归进行多因素分析, 将筛选出的影响因素建立列线图模型并计算 C 指数以评价模型区分度, 绘制校准曲线评价其一致性。[结果] Logistic 回归分析发现, 有家族史、饮酒、高油炸食品、霉变食品、腌制食品摄入、低肉蛋奶类、豆类食品摄入是食管鳞癌发病的危险因素。建立基于以上 7 项因素的食管鳞癌高危人群列线图模型, 其训练集和验证集的受试者工作特征曲线下面积分别为 0.714(95%CI:0.696~0.733)和 0.722(95%CI:0.704~0.741), 表明该模型具有较好的区分度; 校准图显示预测概率和实际概率较一致, 综合两个指标表明该模型具有较好的预测能力。[结论] 基于环境和生活方式等 7 项因素的食管鳞癌及癌前病变高危人群预测模型具有较好的预测价值, 可用于选择应接受内镜检查的个体和群体, 以促进食管癌的精准筛查, 提高筛查效益。

关键词: 食管鳞癌; 癌前病变; 预测模型; 山东

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A Predictive Model for High Risk Population of Esophageal Squamous Cell Carcinoma and Precancerous Lesions Based on Upper Gastrointestinal Cancer Screening Programme in Rural Areas of Shandong

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Abstract: [Purpose] To establish a predictive model for esophageal squamous cell carcinoma based on the risk factor analysis. [Methods] Subjects aged 40~69 years who participated in the “early diagnosis and early treatment of upper gastrointestinal cancer in rural areas program” in Shandong Province from March 2017 to September 2020 were selected. Propensity score matching method(matching factors: age, gender, income, education level) was used to balance the baseline information between the case and control group, and finally 1 410 cases and 5 640 controls were included. The two groups randomly divided into training set($n=4\ 926$) and verification set($n=2\ 124$) with a ratio of 7 to 3. Chi-square test was used for univariate analysis, and the factors with $P<0.1$ were included in conditional multivariate Logistic regression analysis. The nomogram was established based on the risk factors to evaluate the efficacy of differentiation using the C index and a calibration curve was drawn to evaluate the consistency of the model. [Results] Logistic regression analysis showed that family history of cancer, alcohol drinking, high pickled, fried and moldy food consumption, low meat, egg, milk products and beans consumption were risk factors of esophageal squamous cell carcinoma and precancerous lesions. The area under the receiver operating characteristic (ROC) curve (AUC) of the training set and the validation set was 0.714 (95%CI:0.696~0.733) and

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0.722(95%CI:0.704~0.741), respectively, indicating that the nomogram model established based on 7 risk factors had a good capability of differentiation. The calibration curve showed that the prediction probability was consistent with the actual probability, and the combination of the two indicators showed that the model had a good prediction ability. [Conclusion] The model for prediction of esophageal squamous cell carcinoma and precancerous lesions developed in the study based on environment and life style factors has a good predictive value and can be used to select individuals who should undergo endoscopic examination, which may promote the screening accuracy and improve the screening efficiency for esophageal cancer.

Key words: esophageal squamous cell carcinoma; precancerous lesions; prediction model; Shandong

食管癌是常见高发恶性肿瘤之一。GLOBOCAN 2020^[1]数据显示,2020 年全球食管癌新发病例约 604 100 例,较 2018 年^[2](572 034 例)增加 32 066 例,增长约 5.6%;死亡病例约 544 000 例,发病率和死亡率分别居癌谱第 7 位和第 6 位,其中一半以上的病例分布在中国。虽然我国食管癌发病率和死亡率均有不同程度的下降,但因人口基数庞大,发病和死亡绝对例数仍呈上升趋势^[3]。食管癌预后和肿瘤分期密切相关,2003—2015 年,虽然我国食管癌生存率约 10%的提升,但 5 年生存率仍 30.3%左右^[4]。食管癌早期发现和早期治疗是提高生存率、降低死亡率的重要手段^[5-6],早期食管癌术后患者 5 年生存率可高达 80%~95%^[7-8]。随着上消化道癌早诊早治项目的推广,如何有效识别高危人群,降低筛查成本成为一项新的任务。现有的“全人群”筛查需投入大量直接与间接成本,筛查成本效益仍需提高^[9]。本研究旨在通过探讨食管鳞癌(esophageal squamous cell carcinoma, ESCC)及癌前病变发病危险因素,识别高危个体,建立预测模型,以探索精准筛查的可行性,提高整体筛查效益。

1 资料与方法

1.1 资料来源

筛查流程遵循《上消化道癌筛查及早诊早治项目技术方案(2014 年试行版)》:(1)筛查对象为上消化道癌症高发地区 40~69 岁的人群,参与者签署知情同意书;(2)填写基本信息调查表,同时进行一些基本临床问诊和体检以排除内镜检查禁忌证人群;(3)内镜检查;(4)如果在食管黏膜、贲门区黏膜和胃黏膜发现任何阳性或可疑病灶,在相应区域分别咬取活检,活检标本处理后送病理检查,同时填写病理诊断表;(5)根据临床治疗及随访原则,对患者进行

治疗及随访。患者接受治疗后填写治疗情况登记表,应该治疗的患者如拒绝临床治疗,患者需签署拒绝治疗知情同意书。

基于山东省“农村上消化道癌早诊早治项目”网络数据平台进行数据采集和汇总,选取 2017 年 3 月至 2020 年 9 月参加山东省“农村上消化道癌早诊早治项目”的人群,共收集 107 718 人的人群资料。纳入标准:(1)年龄 40~69 周岁;(2)自愿签署知情同意书;(3)无癌症疾病史(自述);(4)既往 3 年内未接受内镜镜检查(自述)。排除标准:(1)基线信息不全;(2)无确诊病理结果;(3)既往有癌症疾病史。病例的人群选择:病理结果为鳞状上皮重度异型增生及以上(原位癌、鳞癌有可能浸润、黏膜内鳞状细胞癌、浸润性鳞癌)。本研究在设计阶段未按照严格的病例对照设计选择研究人群,故使用个体匹配法。使用 1:4 倾向性评分匹配法(propensity score matching, PSM)匹配病例组和健康对照组,匹配因素:年龄、性别、教育水平和家庭收入,最终纳入病例组 1 410 人,健康对照组 5 640 人,共 7 050 人。将 7 050 人样本按照 7:3 随机分为训练集($n=4\ 926$)和验证集($n=2\ 124$),分别用于建立和验证模型。

1.2 食管鳞癌预测因子的选择

基线问卷包括人口统计学状况[年龄、性别、婚姻状况、体质指数(body mass index, BMI)]、社会经济状况(教育程度、家庭收入)、生活方式(饮水来源、吸烟、饮酒、饮茶等)、饮食偏好(新鲜蔬菜、新鲜水果、肉蛋奶类、腌晒食品、油炸食品、烫热食品、霉变食品等)、肿瘤家族史。利用多重插补法补全身高、体重等缺失数据。根据既往高质量研究、文献综述及流行病学研究结果,确定预测因子。

1.3 统计学处理

采用 Rstudio 4.0.3 进行数据 PSM 及分析,正态分布的资料以 $\bar{x} \pm s$ 表示,非正态分布资料以 M(P25,

P75)表示,分类变量等计数资料用构成比表示,并采用 χ^2 检验进行单因素分析, $P<0.1$ 的因素纳入条件 Logistic 回归分析进行多因素分析,并计算比值比(odds ratio,OR)及 95%置信区间(confidence interval,CI)。 $P<0.05$ (双侧)认为差异有统计学意义。倾向性评分匹配方法为卡钳匹配,卡钳值为 0.02。进行敏感性分析来评价身高、体重等数据缺失补全的前后结果差异。

2 结 果

2.1 研究对象基本资料

匹配前,病例组和对照组在性别、年龄、教育水平、年均收入等差异具有统计学意义($P<0.01$),匹配后,各因素差异无统计学意义($P=1.000$),两组具有可比性(Table 1)。

分析匹配后数据,病例组与对照组中位年龄均为 61(55~65)岁,男性占比 69.72%,初中及以上教育水平者占 51.84%,年均收入>20 000 元者占 65.60%。

2.2 单因素分析

训练集单因素分析结果显示:吸烟、饮酒、饮茶、新鲜水果、肉蛋奶类、豆类食品、腌制食品、油炸食品、霉变食品、肿瘤家族史等因素与食管鳞癌及癌前病变有关($P<0.05$)(Table 2)。

纳入分析的总样本人群 7 050 人中,身高缺失 35 人,体重缺失 70 人,BMI 共缺失 70 人,其中训练

集 BMI 缺失 53 人。BMI 敏感性分析结果显示,BMI 在含缺失数值的单因素分析中 $P>0.05$,和补全后一致,能够证明数据的稳定性和结果的可靠性。

2.3 多因素条件 Logistic 回归分析

以是否患病为因变量,匹配结果为分层变量, $P<0.1$ 的因素纳入多因素条件 Logistic 回归分析,建立回归模型。结果显示,饮酒(OR=2.281,95%CI: 1.900~2.738)、有肿瘤家族史(OR=1.504,95%CI: 1.205~1.878)、腌制食品摄入 ≥ 2 次/周(OR=1.292,95%CI: 1.081~1.544)、油炸食品摄入 ≥ 2 次/周(OR=2.420,95%CI: 1.919~3.053)、霉变食品摄入 ≥ 2 次/周(OR=3.495,95%CI: 1.631~7.492)是食管癌的独立危险因素,肉蛋奶类摄入 ≥ 2 次/周(OR=0.396,95%CI: 0.324~0.484)、豆类食品摄入 ≥ 2 次/周(OR=0.661,95%CI: 0.551~0.794)是食管鳞癌的独立保护因素(Table 3)。

2.4 模型的评价及验证

基于筛选出的 7 项独立因素,建立了预测食管鳞癌危险因素的列线图模型(Figure 1)。训练集和验证集受试者工作特征曲线下面积(area under the curve,AUC)分别为 0.714(95%CI: 0.696~0.733)和 0.722(95%CI: 0.704~0.741),表示模型区分度较好,能较好地识别高危和非高危人群(Figure 2)。通过绘制校准曲线,显示训练集和验证集数据预测概率和实际观察概率均较一致,结果显示模型一致性较好(Figure 3~4)。综合两个指标,本研究建立的列线图预测模型较好。

Table 1 Demographic comparisons between control and case group[n(%)]

Characteristic	Before PSM			After PSM		
	Control group	Case group	P	Control group	Case group	P
Total	106308(98.69)	1410(1.31)		5640(80.00)	1410(20.00)	
Gender						
Male	49547(46.61)	983(69.72)	<0.001	3932(69.72)	983(69.72)	1.000
Female	56761(53.39)	427(30.28)		1708(30.28)	427(30.28)	
Age(years old)						
40~49	27528(25.89)	106(7.52)	<0.001	424(7.52)	106(7.52)	1.000
50~59	44026(41.41)	466(33.05)		1864(33.05)	466(33.05)	
60~69	34754(32.69)	838(59.53)		3352(59.43)	838(59.43)	
Education level						
No more than primary school	45103(42.43)	679(48.16)	<0.001	2716(48.16)	679(48.16)	1.000
Junior high school and above	61205(57.57)	731(51.84)		2924(51.84)	731(51.84)	
Income level(Yuan)						
≤ 20000	32064(30.16)	485(34.40)	<0.001	1940(34.40)	485(34.40)	1.000
>20000	74244(69.84)	925(65.60)		3700(65.60)	925(65.60)	

Note: PSM: propensity score matching

Table 2 Univariate analysis of ESCC and precancerous lesions in training set[n(%)]

Factor	Control group	Case group	χ^2	P
BMI(kg/m ²)				
<18.5	140(3.56)	40(4.01)	5.173	0.160
18.5~23.9	1893(48.18)	506(50.75)		
24.0~28.0	1536(39.09)	379(38.01)		
>28.0	360(9.16)	72(7.22)		
Smoking				
No	2878(73.25)	664(66.60)	23.067	<0.001
Yes(packs/year)				
<30	121(3.08)	24(2.41)		
≥30	930(23.67)	309(30.99)		
Alcohol drinking				
No	2757(70.17)	448(44.93)	222.789	<0.001
Yes	1172(29.83)	549(55.07)		
Tea drinking				
No	2586(65.82)	552(55.37)	37.572	<0.001
Yes	1343(34.18)	445(44.63)		
Source of drinking water				
Tap-water	3285(83.61)	818(82.05)	2.810	0.245
Purified water	271(6.90)	84(8.43)		
Others	373(9.49)	95(9.53)		
Fresh vegetables consumption(times/week)				
<2	157(4.00)	38(3.81)	0.071	0.790
≥2	3772(96.00)	959(96.19)		
Fresh fruits consumption(times/week)				
<2	957(24.36)	369(37.01)	64.723	<0.001
≥2	2972(75.64)	628(62.99)		
Meat,egg,milk consumption(times/week)				
<2	767(19.52)	447(44.83)	274.367	<0.001
≥2	3162(80.48)	550(55.17)		
Beans food consumption(times/week)				
<2	1377(35.05)	537(53.86)	111.484	<0.001
≥2	2552(64.95)	460(46.14)		
Pickled food consumption(times/week)				
<2	2777(70.68)	625(62.69)	23.769	<0.001
≥2	1152(29.32)	372(37.31)		
Hot food consumption(times/week)				
<2	3378(85.98)	861(86.36)	0.097	0.755
≥2	551(14.02)	136(13.64)		
Fried food consumption(times/week)				
<2	3476(88.47)	810(81.24)	36.737	<0.001
≥2	453(11.53)	187(18.76)		
Moldy food consumption(times/week)				
<2	3899(99.24)	977(97.99)	12.218	<0.001
≥2	30(0.76)	20(2.01)		
Family history of cancer				
No	3465(88.19)	807(80.94)	36.278	<0.001
Yes	464(11.81)	190(19.06)		

3 讨论

食管癌早诊早治是提高其生存率降低死亡率的重要手段^[5-6]。因食管癌早期阶段缺乏典型的临床表现,绝大多数患者出现明显症状后就诊已为中晚期,生存率和生存质量大大降低^[8]。我国关于食管鳞癌高危人群预测模型已有部分研究,但均处于探索阶段,未有成熟模型应用^[10-12]。山东省“农村癌症早诊早治项目”自2006年启动,针对40~69岁户籍人口开展基本信息调查,并行内镜检查,对发现的可疑病变进行活体组织病理学检查。本研究以此项目人群为基础,开发了一个基于环境和饮食习惯的因素预测模型,以识别高危个体,助力食管癌精准筛查。

深入了解食管癌的危险因素,对于识别需要筛查的高危个体具有重要意义。本研究结果显示,有肿瘤家族史,饮酒,高油炸食品、霉变食品、腌制食品摄入,低肉蛋奶类、豆类食品摄入是食管鳞癌发病的危险因素。有研究结果显示,有肿瘤家族史、吸烟、饮酒、腌制食品、油炸食品摄入量高是较为充分的食管鳞癌危险因素^[13-20],与本研究部分结果一致。一级和二级亲属肿瘤家族史是多种癌症的危险因素,考虑与基因多态性和遗传多样性有关,其中一项关于基于社区的上消化道癌的随机对照试验证实,肿瘤家族史与食管癌前病变的风险增加有关^[21],和本研究关于肿瘤家族史结论一致。另有研究得出高遗传风险得分显著增加了患食管鳞癌的风险,此外,低遗传风险有高累积风险,表明环境因素在食管

Table 3 Risk factors associated with ESCC and precancerous lesions in the conditional multivariable Logistic regression

Factor	β	S.E	Wald χ^2	P	OR	95%CI
Alcohol drinking	0.824	0.093	78.303	<0.001	2.281	1.900~2.738
Family history of cancer	0.408	0.113	13.011	<0.001	1.504	1.205~1.878
Meat,egg,milk consumption	-0.927	0.102	81.987	<0.001	0.396	0.324~0.484
Beans food consumption	-0.414	0.093	19.618	<0.001	0.661	0.551~0.794
Pickled food consumption	0.256	0.091	7.921	0.005	1.292	1.081~1.544
Fried food consumption	0.884	0.118	55.724	<0.001	2.420	1.919~3.053
Moldy food consumption	1.251	0.389	10.353	0.001	3.495	1.631~7.492

癌发病中起重要作用^[22]。酒精及其代谢产物乙醛具有直接致癌作用,被国际癌症研究署列为食管癌的一级致癌物^[23-24]。多项研究发现,食管癌发病和饮酒呈正相关^[24-25],且食管癌与饮酒有剂量或频率反应关系^[26]。山东人群喜好饮酒,饮酒率高达 36.9%^[27],且饮食偏咸,以农村地区居民自行腌制咸菜或豆酱为甚。本研究人群正在饮酒率为 34.95%,饮酒人群患食管鳞癌及癌前病变风险显著高于不饮酒人群 (OR=

2.281),30.92%人群喜食腌制食品 (OR=1.292),这提示应该进一步加强宣传合理膳食理念,提高居民防癌意识,帮助居民戒烟限酒,少吃或不吃腌制或高盐食品。以往研究显示,经常食用新鲜水果蔬菜、肉蛋奶类是食管癌的保护因素^[21,28]。本研究发现经常食用

肉蛋奶类和豆类是食管癌的保护因素,未发现经常食用新鲜蔬菜和水果的保护作用,考虑是山东省农村地区蔬菜和水果的易获得性,因而差异不明显。

现有的食管鳞癌筛查模型包括非遗传因素、遗传因素、非遗传因素和遗传因素结合三种方式^[29-31]。陈万青等^[11]基于人群的研究开发了食管癌高危人群预测模型,结果显示高危人群发生食管鳞癌的累积风险高于非高危人群,危险比为 3.11。本研究仅从识别

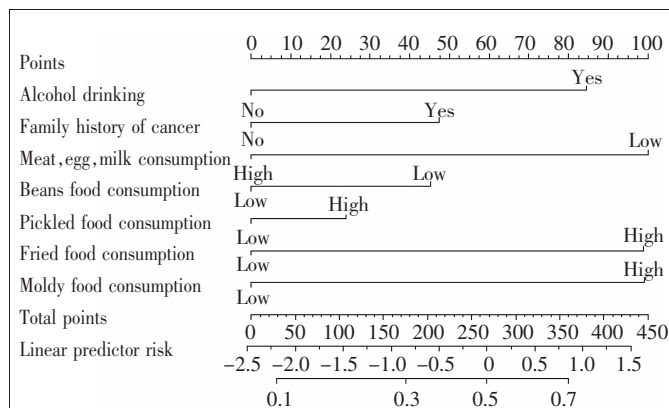


Figure 1 Nomogram model for ESCC and precancerous lesion

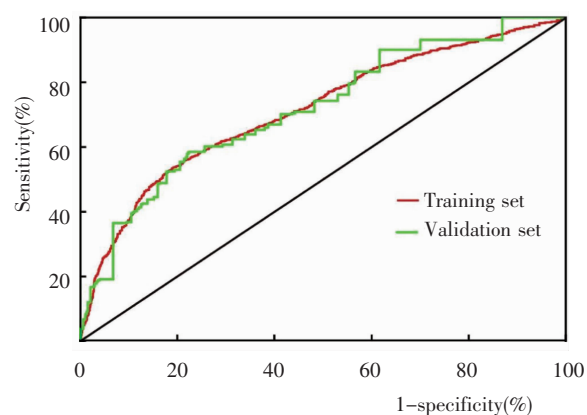


Figure 2 Nomogram model with ROC curve

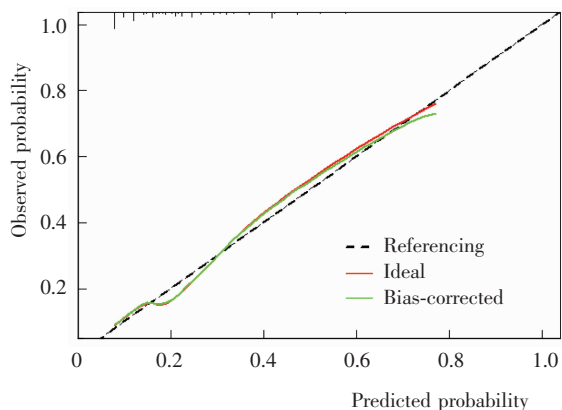


Figure 3 Calibration curve for training set

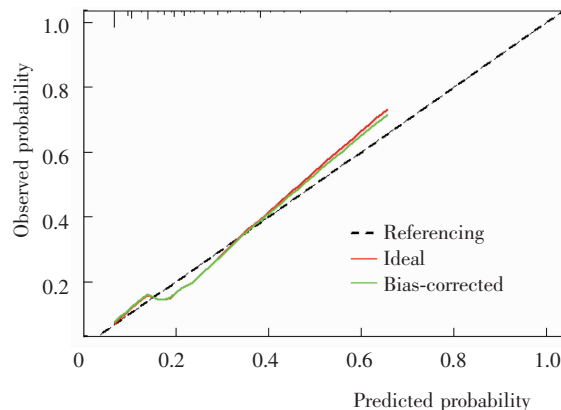


Figure 4 Calibration curve for validation set

高危个体方面做出研究,未评估人群累计发病风险,这可作为本课题进一步研究方向。日本的 Sudo 等^[31]采用病例对照研究设计,构建了以 6 个血清 miRNAs 为预测变量食管鳞癌发病风险预测模型,模型具有极高的预测效能,该模型在验证集中预测食管鳞癌发生的 AUC 高达 1.00(灵敏度、特异度分别为 100%和 98%)。本研究仅从非遗传因素研究得出验证集 AUC 在 0.70~0.90,有一定准确性,但区分度优势不够明显,考虑是和样本人群和暴露因素水平差异性有关。多数食管鳞癌模型仅评价区分度,未评价一致度。本研究从两者综合考虑,对预测高危人群更有优势。伊朗一项高风险地区的食管鳞癌预测模型包含所有已知危险因素,AUC 为 0.77 (95%CI: 0.74~0.80),将过去一年体重减轻再纳入模型后 AUC 增加到 0.87(95%CI:0.85~0.89),但该模型的拟合优度较差(H-L 检验 $P<0.001$)。本研究也同样使用 H-L 拟合优度检验来评估预测概率和观测概率之间的差异, $P<0.05$,拟合优度较差。但根据 2017 年发表于 JAMA 的《临床预测模型的区分度和校准度指南》^[32],H-L 检验有其局限性,当样本量较大时临床上预测的风险和观察到的风险之间的微小差异可能会导致具有统计学意义的 H-L 检验结果,所以指南推荐使用校准图形作为评估校准的最佳方式。本研究最终以校准图形来评估预测概率和观测概率的一致性,两者较一致。

本研究也存在一定的局限性。本研究模型以山东省农村地区 40~69 岁人群为研究对象,是否适用于其他地区、其他人群亟待外部验证。其次,该模型基于人群病例对照研究设计开发,缺少对前瞻性收集结局事件和对暴露因素随访动态观察。

综上所述,本研究运用了一种易使用的模型来识别农村地区的食管鳞癌高风险个体,以提高大规模筛查工作的总体成本效益,降低内镜检查损害风险。该模型可用于选择应接受内镜检查的个体和群体,助力食管癌精准筛查,提高整体筛查效益,促进食管癌二级预防。

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