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Cancer Research on Prevention and Treatment

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引用本文:

包晓丹, 陈法, 刘凤琼, 等. 口腔卫生、蔬菜水果摄入与牙龈癌发病风险的相关性[J]. 肿瘤防治研究, 2018, 45(09): 681–686.

BAO Xiaodan, CHEN Fa, LIU Fengqiong, et al. Correlation of Oral Hygiene, Intake of Vegetables and Fruits with Risk of Gingival Cancer[J]. *Zhong Liu Fang Zhi Yan Jiu*, 2018, 45(09): 681–686.

在线阅读 View online: <https://doi.org/10.3971/j.issn.1000-8578.2018.18.0323>

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口腔卫生、蔬菜水果摄入与牙龈癌发病风险的相关性

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Correlation of Oral Hygiene, Intake of Vegetables and Fruits with Risk of Gingival Cancer
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Abstract: Objective To explore the effects of oral hygiene, vegetables and fruits intake on gingival cancer. **Methods** A case-control study including 131 patients pathologically confirmed as gingival cancer from October 2010 to November 2016 and 669 health controls was performed by questionnaire survey. Unconditional Logistic regression was used to assess the effect of oral hygiene, vegetables and fruits intake on gingival cancer. **Results** Teeth brushing <2 times/day, lacking of teeth, wearing dentures, irregular dental visits and recurrent dental ulceration were risk factors of gingival cancer. We developed a composite oral hygiene score to measure the combined effects of various oral hygiene. The risk of gingival cancer among patients scored 3-5 was 6.991 times(95%CI: 4.267, 11.453) as those scored 0-2. Eating green leafy vegetables <2 times/day, non-green leafy vegetables <2 times/day, fruit <1 time/day were risk factors of gingival cancer. The people scored 3-5 had higher risk of gingival cancer in all subgroups. Furthermore, the people with lower frequency consumption of green leafy vegetables, non-leafy vegetables and fruits had the higher risk of gingival cancer. Multiplicative interaction of green leafy vegetables, non-leafy vegetables, fruits with oral hygiene was observed. **Conclusion** The people with higher oral hygiene index have higher risk of gingival cancer. Eating green leafy vegetables <2 times/day, non-green leafy vegetables <2 times /day, fruit <1 time/day could increase the risk of gingival cancer.

Key word: Gingival cancer; Oral hygiene; Vegetables; Fruits

摘要: 目的 探讨口腔卫生、蔬菜水果摄入与牙龈癌的关系。**方法** 采用病例对照研究,对2010年10月—2016年11月确诊的131例新发牙龈癌患者及669例健康人群进行问卷调查。采用非条件Logistic回归分析探讨口腔卫生及蔬菜水果摄入与牙龈癌发病的关系。**结果** 分析结果显示:刷牙频率<2次/天,缺失牙齿、佩戴假牙、无规律性看牙医及复发性口腔溃疡可增大牙龈癌的发病风险。构建口腔卫生综合指数,分析显示口腔卫生综合指数得分3~5分者患牙龈癌的风险是0~2分者的6.991倍(95%CI: 4.267, 11.453)。此外,进食绿叶蔬菜<2次/天、非绿叶蔬菜<2次/天、水果<1次/天是牙龈癌发病的危险因素。按绿叶蔬菜、非绿叶蔬菜及水果分层,结果显示口腔卫生指数得分3~5分者在各分组中均较0~2分者患牙龈癌的风险更大,并且食用绿叶蔬菜、非绿叶蔬菜及水果的频率较低者患牙龈癌的风险均高于频率较高者。此外,口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果均存在正相乘交互作用。**结论** 口腔卫生综合指数得分越高者患牙龈癌的风险越大,并且进食绿叶蔬菜<2次/天、非绿叶蔬菜<2次/天、水果<1次/天可增大牙龈癌的发病风险。

关键词: 牙龈癌; 口腔卫生; 蔬菜; 水果
中图分类号: R739.8
文献标识码: A
开放科学(资源服务)标识码(OSID):



收稿日期: 2018-03-12; **修回日期:** 2018-03-29
基金项目: 福建省科技厅科研项目(2015J01304); 福建省科技创新联合资金项目(2016Y9033); 福建省卫生计生科研人才培养项目(2017-ZQN-57)
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0 引言

牙龈癌 (gingival cancer, GC) 是一种常见的口腔恶性肿瘤, 在亚洲人群口腔癌发病顺位中位居第二^[1]。目前, 牙龈癌尚无有效的早期诊断技术, 发现时多为晚期^[2]。手术是其主要治疗方式, 但手术易引起颌面部畸形, 严重影响患者的颜面部美观及生活质量, 故探讨牙龈癌的发病影响因素显得尤为重要。有研究发现口腔卫生与牙龈退缩关系密切^[3-4], 而牙龈退缩可增大牙龈癌的发病风险^[5], 因此, 口腔卫生与牙龈癌之间可能存在关联。此外, 有研究显示蔬菜及水果摄入不足会导致维生素C、维生素E等矿物质的缺乏, 进而引发牙周病^[6], 牙周病常伴有牙龈炎及牙龈退缩, 而长期的炎性反应刺激^[7-8]及牙龈退缩^[5]与肿瘤的发生关系密切, 故蔬菜水果摄入不足亦可能与牙龈癌存在关联。本研究旨在福建地区开展牙龈癌的流行病学调查, 探讨口腔卫生及蔬菜水果与牙龈癌的关联, 为牙龈癌的预防和控制提供科学的依据。

1 资料与方法

1.1 研究对象

本研究采用病例对照的研究方法, 选取2010年10月—2016年11月福建医科大学附属第一医院口腔颌面外科牙龈癌患者131例, 作为病例组。病例组的纳入标准: (1) 经病理确诊的牙龈癌新发病例; (2) 可清晰回答问题者。排除继发性肿瘤或良性病变者以及病情危重不能清晰回答问题者。同期选取医院体检人群及社区健康人群, 并排除既往或现患肿瘤疾病者, 按性别、年龄 (± 3 岁) 进行频数匹配选择对照, 最终共纳入669名对照。所有研究对象均在福建本地居住10年以上, 并均签署了知情同意书。

1.2 研究方法

本研究采用统一编制的结构式调查问卷, 由统一培训过的调查员对研究对象进行面对面问卷调查。调查内容主要包含: 一般情况 (年龄、性别、民族、职业、文化程度、婚姻状况、肿瘤家族史、身高、体重等)、吸烟史、饮酒史、口腔卫生 (包括刷牙频率、牙齿缺失、佩戴假牙、规律性看牙医和复发性口腔溃疡等) 及膳食摄入情况等。调查结束后, 由专人负责调查表的审核, 发现问题及时予以纠正, 剔除不合格者。

1.3 术语与定义

(1) 吸烟: 累计吸烟大于100支^[9]; (2) 饮酒: 每周至少1次, 持续6个月以上^[10]; (3) 绿叶蔬

菜: 以鲜嫩的绿叶、叶柄和嫩茎为产品的蔬菜, 主要包括小白菜、生菜、油麦菜、菠菜等; (4) 非绿叶蔬菜: 指除绿叶蔬菜之外的蔬菜, 主要包括菜花、白萝卜、土豆、胡萝卜等; (5) 口腔卫生综合指数: 口腔卫生综合指数由以下5个项目综合评分得到: 刷牙频率: ≥ 2 次/天=0, < 2 次/天=1; 缺失牙齿: 无=0, 有=1; 佩戴假牙: 无=0, 有=1; 规律性看牙医: 有=0, 无=1; 复发性口腔溃疡: 无=0, 有=1。求5个项目总得分 (得分范围: 0~5分), 得分越高表示口腔卫生情况越差。

1.4 统计学方法

使用EpiData3.1对数据进行双核录入, 并进行逻辑纠错, 再随机抽取10%进行复查。采用 χ^2 检验对病例组 and 对照组的一般人口学特征进行均衡性检验, 应用非条件Logistic回归分析口腔卫生相关指标及蔬菜水果与牙龈癌的关系, 并构建口腔卫生综合指数, 分析口腔卫生综合指数与牙龈癌发病的关联。按绿叶蔬菜、非绿叶蔬菜及水果分层, 估算调整OR值及95%CI。最后进行口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果的交互作用分析。统计分析均采用Stata13.0软件包进行, 检验水准 α 为0.05。

2 结果

2.1 一般情况

本研究共纳入131例新发牙龈癌患者, 其中包括117例鳞状细胞癌患者和14例腺癌患者, 年龄为 60.88 ± 13.00 岁。此外, 共纳入健康对照者669例, 年龄为 60.07 ± 12.43 岁。经均衡性检验, 病例组和对照组在年龄、性别、职业、文化程度、婚姻状况、肿瘤家族史等方面均衡可比 ($P > 0.05$), 而在居住地、身体质量指数 (body mass index, BMI) 等方面两组间存在差异, 见表1。

2.2 单因素非条件Logistic回归分析

调整年龄、性别、吸烟、饮酒等因素后, 分析显示刷牙频率 < 2 次/天、缺失牙齿、佩戴假牙、无规律性看牙医、复发性口腔溃疡等因素是牙龈癌的发病危险因素, 调整OR值及95%CI分别为2.843 (1.869, 4.327)、4.949 (2.862, 8.559)、4.066 (2.595, 6.369)、1.858 (1.082, 3.189) 及5.004 (2.077, 12.053), 并且口腔卫生综合指数得分越高者患牙龈癌的风险越大。此外, 进食绿叶蔬菜 < 2 次/天、非绿叶蔬菜 < 2 次/天、水果 < 1 次/天能增大牙龈癌的发病风险, 见表2。

表1 病例组与对照组的一般资料比较

Table1 Comparison of main characters between case and control groups

Variables	Case group n(%)	Control group n(%)	χ^2	P
Age(years)			0.631	0.427
≤60	54(41.22)	301(44.99)		
>60	77(58.78)	368(55.01)		
Gender			3.645	0.056
Male	75(57.25)	322(48.13)		
Female	56(42.75)	347(51.87)		
Occupation			3.136	0.209
Famer	44(33.59)	209(31.24)		
Worker	23(17.56)	85(12.71)		
Staff and others	64(48.85)	375(56.05)		
Education level			0.981	0.612
Illiteracy	15(11.45)	61(9.12)		
Primary-middle school	89(67.94)	452(67.55)		
High school and above	27(20.61)	156(23.33)		
Marital status			2.510	0.113
Married	119(90.84)	632(94.47)		
Other	12(9.16)	37(5.53)		
Residence			5.520	0.019
Rural	63(48.09)	396(59.19)		
Urban	68(51.91)	273(40.81)		
Family history of cancer			0.484	0.487
No	111(84.73)	582(87.00)		
Yes	20(15.27)	87(13.00)		
BMI(kg/m ²)			47.657	<0.001
<18.5	20(15.27)	25(3.74)		
18.5-24	89(67.94)	364(54.41)		
≥24	22(16.79)	280(41.85)		

Notes: BMI: body mass index

2.3 口腔卫生与牙龈癌的分层分析

按绿叶蔬菜、非绿叶蔬菜及水果分层，调整年龄、性别、吸烟、饮酒等因素，结果显示口腔卫生指数得分3~5分者在各分组中均较0~2分者患牙龈癌的风险更高，并且食用绿叶蔬菜<2次/天的OR值为9.198，高于≥2次/天者（其OR值为7.679），食用非绿叶蔬菜<2次/天的OR值为9.809，高于≥2次/天者（其OR值为6.638），食用水果<1次/天的OR值为8.807，高于≥1次/天者（其OR值为4.863），说明食用蔬菜及水果的频率较低者患牙龈癌的风险大于频率较高者，见表3。

2.4 口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果的交互作用分析

分析发现口腔卫生综合指数得分3~5分且食用绿叶蔬菜<2次/天者发生牙龈癌的风险是0~2分且≥2次/天的26.985倍，得分3~5分且食用非绿叶蔬菜<2次/天者发生牙龈癌的风险是0~2分且≥2次/天的23.378倍，得分3~5分且食用水果<1次/天者发生牙龈癌的风险是0~2分且≥1次/天的27.210倍。且相乘交互作用分析显示口腔卫生与绿叶蔬菜、非

绿叶蔬菜及水果均存在正相乘交互作用，提示口腔卫生与蔬菜水果在牙龈癌的发生发展中可能存在协同作用，见表4。

3 讨论

吸烟、饮酒是牙龈癌的主要危险因素^[11-12]，但目前关于口腔卫生与牙龈癌的研究尚少。本研究显示刷牙频率<2次/天，缺失牙齿、佩戴假牙、无规律性看牙医及复发性口腔溃疡可增加牙龈癌的发病风险。因此，纳入此5项口腔卫生指标构建口腔卫生综合指数，综合评价口腔卫生情况与牙龈癌的关系。分析显示口腔卫生综合指数得分3~5分者患牙龈癌的风险是0~2分者的6.991倍（95%CI: 4.267, 11.453）。大量研究表明增加刷牙频率能够预防口腔癌的发生^[13-15]，但亦有研究发现刷牙与口腔癌之间没有统计学关联^[16-17]。本研究结果显示刷牙频率<2次/天能增加牙龈癌的发病风险。乙醇能够诱发牙龈癌的发生^[11]，有研究发现饮酒数小时后仍可在唾液中检测出乙醇残留^[18]，而增加刷牙频率能有效降低口腔中的乙醇残留^[19]，此外，亚硝胺亦是消化道恶性肿瘤的危险因素^[20-21]，刷牙能够降低口腔中的亚硝胺水平^[22]，从而预防口腔恶性肿瘤的发生。本研究显示缺失牙齿、佩戴假牙及复发性口腔溃疡等因素是牙龈癌的发病危险因素，伍俊锋等^[23]研究亦发现这些因素能够增大口腔癌的发病风险。这可能由于缺失牙齿及佩戴假牙所引起的牙齿错位和尖锐边缘导致慢性口腔黏膜溃疡，而长期的炎性因子刺激进一步诱导了肿瘤的发生^[7-8]。因此，定期进行口腔卫生护理、及早治疗口腔溃疡，能防止牙龈黏膜病变，可有效预防牙龈癌的发生。

本研究结果显示较低频率食用蔬菜及水果将增大牙龈癌的发病风险，与刘凤琼等^[24]研究结果基本一致。水果和蔬菜中富含维生素C、维生素E及胡萝卜素等，具有抗氧化和抗增殖活性，能够刺激免疫系统，抑制DNA氧化损伤^[25-26]。十字花科蔬菜富含芥子油苷，而芥子油苷的分解产物（异硫氰酸酯吲哚）已被证明具有抗癌性^[27]。本研究结果还显示口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果间均存在正相乘交互作用，提示口腔卫生与蔬菜水果在牙龈癌的发生发展中可能存在协同作用。维生素C、维生素E等抗氧化剂能够清除机体内的自由基^[28]，研究表明它们可通过降低牙周组织中的氧化应激水平而减少牙周病的发生^[29]。而牙周病常伴有牙龈炎及牙龈退缩，长期的炎性因子刺激^[7-8]以及牙龈退缩^[5]进一步促进了牙龈癌的发生。

表2 牙龈癌患者单因素非条件Logistic回归分析

Table2 Univariate unconditional Logistic regression analysis of gingival cancer patients

Variable	Case group (n(%))	Control group (n(%))	OR(95%CI)	OR(95%CI) ^a
Tobacco smoking				
No	74(56.49)	507(75.78)	1.000	1.000
Yes	57(43.51)	162(24.22)	2.411(1.635,3.554)	2.533(1.415,4.535)
Alcohol drinking				
No	91(69.47)	551(82.36)	1.000	1.000
Yes	40(30.53)	118(17.64)	2.053(1.346,3.129)	1.601(0.942,2.719)
Green vegetables(times/day)				
≥2	58(44.27)	492(73.54)	1.000	1.000
<2	73(55.73)	177(26.46)	3.499(2.380,5.142)	3.311(2.202,4.979)
Non-green leafy vegetables (times/day)				
≥2	54(41.22)	468(69.96)	1.000	1.000
<2	77(58.78)	201(30.04)	3.320(2.259,4.880)	3.057(2.035,4.593)
Fruits (times/day)				
≥1	23(17.56)	287(42.90)	1.000	1.000
<1	108(82.44)	382(57.10)	3.528(2.193,5.675)	3.148(1.919,5.166)
Teeth brushing (times/day)				
≥2	51(38.93)	433(64.72)	1.000	1.000
<2	80(61.07)	236(35.28)	2.878(1.958,4.231)	2.843(1.869,4.327)
Lacking of teeth				
No	24(18.32)	303(45.29)	1.000	1.000
Yes	107(81.68)	366(54.71)	3.691(2.311,5.894)	4.949(2.862,8.559)
Wearing dentures				
No	59(45.04)	490(73.24)	1.000	1.000
Yes	72(54.96)	179(26.76)	3.341(2.274,4.906)	4.066(2.595,6.369)
Regular dental visits				
Yes	19(14.50)	164(24.51)	1.000	1.000
No	112(85.50)	505(75.49)	1.914(1.141,3.211)	1.858(1.082,3.189)
Recurrent dental ulceration				
No	120(91.60)	656(98.06)	1.000	1.000
Yes	11(8.40)	13(1.94)	4.626(2.025,10.568)	5.004(2.077,12.053)
Oral hygiene index ^b				
0-2	44(33.59)	480(71.75)	1.000	1.000
3-5	87(66.41)	189(28.25)	5.022(3.367,7.489)	6.991(4.267,11.453)

Notes: a: adjustment for age, gender, occupation, marital status, education level, residence, family history of cancer, BMI, tobacco smoking and alcohol drinking; b: oral hygiene index was a combination of the following five items: teeth brushing: ≥2 times/day =0, <2 times/day =1; lacking of teeth: No=0, Yes=1; wearing dentures: No=0, Yes=1; regular dental visits: Yes=0, No =1; recurrent dental ulceration: No=0, Yes=1

表3 口腔卫生与牙龈癌的分层分析

Table3 Stratification analysis of oral hygiene and gingival cancer

Oral hygiene index	Case group (n(%))	Control group (n(%))	OR(95%CI)	OR(95%CI) ^a
Green vegetables ≥ 2 times/day				
0-2	20(34.48)	345(70.12)	1.000	1.000
3-5	38(65.52)	147(29.88)	4.459(2.510,7.923)	7.679(3.689,15.985)
Green vegetables < 2 times/day				
0-2	24(32.88)	135(76.27)	1.000	1.000
3-5	49(67.12)	42(23.73)	6.563(3.606,11.941)	9.198(4.352,19.441)
Non-green leafy vegetables ≥ 2 times/day				
0-2	20(37.04)	327(69.87)	1.000	1.000
3-5	34(62.96)	141(30.13)	3.943(2.193,7.088)	6.638(3.126,14.096)
Non-green leafy vegetables < 2 times/day				
0-2	24(31.17)	153(76.12)	1.000	1.000
3-5	53(68.83)	48(23.88)	7.039(3.937,12.586)	9.809(4.849,19.844)
Fruits ≥ 1 times/day				
0-2	8(34.78)	204(71.08)	1.000	1.000
3-5	15(65.22)	83(28.92)	4.608(1.883,11.281)	4.863(1.646,14.366)
Fruits < 1 times/day				
0-2	36(33.33)	276(72.25)	1.000	1.000
3-5	72(66.67)	106(27.75)	5.208(3.292,8.237)	8.807(4.848,16.000)

Notes: a: adjustment for age, gender, occupation, marital status, education level, residence, family history of cancer, BMI, tobacco smoking and alcohol drink-

表4 口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果的交互作用分析

Table4 Interaction of oral hygiene with green vegetables with non-green leafy vegetables and fruits

		Case group(n(%))	Control group(n(%))	OR(95%CI)	OR(95%CI) ^a
Oral hygiene index		Green vegetables (times/day)			
0-2	≥2	20(15.27)	345(51.57)	1.000	1.000
0-2	<2	24(18.32)	135(20.18)	3.067(1.640,5.734)	3.079(1.613,5.878)
3-5	≥2	38(29.01)	147(21.97)	4.459(2.510,7.923)	6.960(3.591,13.488)
3-5	<2	49(37.40)	42(6.28)	20.125(10.926,37.068)	26.985(13.501,53.934)
Multiplicative interaction				2.915(2.279,3.728)	2.834(2.188,3.670)
Oral hygiene index		Non-green leafy vegetables (times/day)			
0-2	≥2	20(15.27)	327(48.88)	1.000	1.000
0-2	<2	24(18.32)	153(22.87)	2.565(1.375,4.785)	2.458(1.290,4.683)
3-5	≥2	34(25.95)	141(21.08)	3.943(2.193,7.088)	5.950(3.035,11.665)
3-5	<2	53(40.46)	48(7.17)	18.053(9.938,32.794)	23.378(11.946,45.753)
Multiplicative interaction				2.065(1.556,2.740)	2.108(1.511,2.942)
Oral hygiene index		Fruits (times/day)			
0-2	≥1	8(6.11)	204(30.49)	1.000	1.000
0-2	<1	36(27.48)	276(41.26)	3.326(1.514,7.308)	3.382(1.511,7.568)
3-5	≥1	15(11.45)	83(12.41)	4.608(1.883,11.281)	7.811(2.998,20.349)
3-5	<1	72(54.96)	106(15.84)	17.321(8.042,37.304)	27.210(11.645,63.582)
Multiplicative interaction				3.198(2.429,4.211)	3.398(2.491,4.636)

Notes: a: adjustment for age, gender, occupation, marital status, education level, residence, family history of cancer, BMI, tobacco smoking and alcohol drinking

本研究也存在一些不足：（1）本研究采用病例-对照的研究方法，回忆偏倚不可避免，但本研究在调查时尽可能地进行了质量控制，遵循严格的纳入和排除标准，选取新发病例，且调查人员均接受了统一培训，在询问食物摄入情况时向研究对象出示彩色食物份量图谱，图谱的辅助能更加有效的降低回忆偏倚的产生。此外，我们在统计分析时注意控制混杂因素的干扰，尽可能将偏倚降至较低水平。（2）本研究样本量较小，因此分析结果仍需进一步增大样本量及利用队列研究加以验证。

综上所述，刷牙频率<2次/天、缺失牙齿、佩戴假牙、无规律性看牙医及复发性口腔溃疡等因素可增加牙龈癌的发病风险，口腔卫生综合指数得分越高者患牙龈癌的风险越大。食用绿叶蔬菜<2次/天、非绿叶蔬菜<2次/天、水果<1次/天是牙龈癌发病的危险因素，并且口腔卫生与绿叶蔬菜、非绿叶蔬菜及水果间均存在正相乘交互作用。

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[编辑: 周永红; 校对: 刘红武]