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代谢综合征及其组分与消化系统恶性肿瘤的因果关联:两样本孟德尔随机化研究

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摘要:目的 采用两样本孟德尔随机化(two-sample Mendelian randomization, TSMR)方法,从遗传学角度探索代谢综合征(metabolic syndrome, MetS)及其组分与消化系统恶性肿瘤之间的因果关联,为后者的预防提供新线索。**方法** 基于全基因组关联研究(genome wide association study, GWAS)的汇总数据,将MetS及其组分作为暴露因素,消化系统恶性肿瘤作为结局变量,采用逆方差加权法(inverse variance weighted, IVW)为主要分析方法,加权中位数(weighted median, WM)和MR-Egger为补充分析方法评估因果效应;采用敏感性分析验证研究结果的可靠性。**结果** IVW结果显示,MetS与肝癌(OR=1.357, 95%CI=1.004~1.834, P=0.047)和食管癌(OR=1.001, 95%CI=1.000~1.001, P=0.037)的发生风险增加相关。MetS各组分中,腰围(waist circumference, WC)与胃癌(OR=1.809, 95%CI=1.024~3.196, P=0.041)和食管癌(OR=1.001, 95%CI=1.000~1.002, P=0.020)的发生风险增加相关;高密度脂蛋白(high density lipoprotein, HDL)与结直肠癌(OR=0.789, 95%CI=0.633~0.984, P=0.035)的发生风险降低相关;敏感性分析提示研究结果稳健。**结论** MetS会增加肝癌及食管癌的发生风险。在其各组分中,WC是胃癌及食管癌的发生危险因素,HDL结直肠癌发生的保护因素。

关键词:孟德尔随机化;代谢综合征;消化系统恶性肿瘤;全基因组关联研究;因果关联
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Causal association of metabolic syndrome and its components with digestive system malignancies: a two-sample Mendelian randomized study

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Abstract: Objective To provide new clues for the prevention and treatment of digestive system malignancies by using two sample Mendelian randomization (TSMR) method so as to explore the causal relationship between metabolic syndrome (MetS) and its components and digestive system malignancies from a genetic perspective. **Methods** Based on the summary data of genome-wide association study (GWAS), MetS and its components were used as exposure factors, and digestive system maligancies were used as outcome variables. The inverse variance weighted (IVW) method was used as the main analysis method, and weighted median (WM) and MR Egger were used as supplementary analysis methods to evaluate causal effects. The sensitivity analysis was used to verify the reliability of the research results. **Results** The IVW method showed that MetS is associated with an increased risk of liver cancer (OR = 1.357, 95%CI = 1.004-1.834, P = 0.047) and esophageal cancer (OR = 1.001, 95%CI = 1.000-1.001, P = 0.037). Among the components of MetS, waist circumference (WC) is associated with an increased risk of gastric cancer (OR = 1.809, 95%CI = 1.024-3.196, P = 0.041) and esophageal cancer (OR = 1.001, 95%CI = 1.000-1.002, P = 0.020); High density lipoprotein (HDL) is associated with a reduced risk of colorectal cancer (OR = 0.789, 95% CI = 0.633-0.984, P = 0.035); Sensitivity analysis suggests that the research results are robust. **Conclusion** MetS increases the risk of liver and esophageal cancer, with WC being a risk factor for gastric and esophageal cancer, while HDL is a protective factor for colorectal cancer.

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Key words: Mendelian randomization; Metabolic syndrome; Digestive system malignancies; Genome wide association study; Causal association

消化系统恶性肿瘤包括结直肠癌、胃癌、食管癌、肝癌和胰腺癌,占全球癌症发病率的26%和相关死亡率的35%,严重威胁人们的生命健康[1]。既往研究显示,不良生活习惯、慢性感染及家族性遗传因素是消化系统恶性肿瘤发病的重要危险因素[2-3]。随着生活环境的变化,久坐、不健康饮食等不良生活习惯导致的肥胖可引发血压、血糖及血脂异常等相关代谢紊乱[4],最终增加患癌风险。代谢综合征(metabolic syndrome, MetS)是一种以中心性肥胖、高血压(high blood pressure, HBP)、高血糖、三酰甘油水平升高和高密度脂蛋白(high density lipoprotein, HDL)水平降低为主要特征的临床症候群。有观察性研究发现,MetS可能增加罹患消化系统恶性肿瘤的风险,但具体关系尚不明确[5-6]。Zhan等[7]的荟萃分析显示,MetS与结直肠癌、食管癌、肝癌和胰腺癌的患病风险增加显著相关,但与胃癌无明显关联。Lin等[8]的大型队列研究发现,MetS是胃腺癌的风险因素,与食管腺癌及食管鳞状细胞癌无关。以往的研究多集中在单一因素与消化系统恶性肿瘤的关联,且观察性研究样本量有限,易受混杂因素及反向因果关系的影响。

孟德尔随机化(Mendelian randomization, MR)是一种基于遗传变异的因果推断方法,通过利用大规模全基因组关联研究(genome wide association study, GWAS)数据,并使用与暴露因素强相关的遗传变异作为工具变量(instrumental variables, IVs),如单核苷酸多态性(single nucleotide polymorphisms, SNPs),推断暴露与结局之间的潜在因果关系,可有效减少混杂因素与反向因果关系的影响以及观察性研究的局限性[9-10]。本研究首次使用两样本孟德尔随机化(two-sample Mendelian randomization, TSMR)方法分析探讨MetS及其组分与消化系统肿瘤之间的因果关联,旨在为预防消化系统恶性肿瘤提供新思路。

1 资料与方法

1.1 一般资料

MetS数据来自英国生物银行GWAS汇总数据集,总样本量291 107,包括59 677例MetS患者和231 430名对照(即未患病人群,下同)[11],并提取腰围(waist circumference, WC)、HBP、空腹血糖(fasting blood glucose, FBG)、HDL和TG五项MetS组分数据[12-13]。从医学研究委员会流行病学单位(Medical Research Council Integrative Epidemiology Unit, MRC-IEU)获取WC和HBP的汇总数据,该数据来自英国生物银行的Meta分析[14],其中WC总样本量462 166,HBP总样本量463 010。从IEU-Open GWAS数据库获得FBG的汇总数据,总样本量58 074[15]。HDL和TG的汇总统计数据来自全球脂质遗传学联合会(Global Lipid Genetics Consortium, GLGC),其中HDL总样本量187 167,TG总样本量177 861[16]。结局方面,消化系统恶性肿瘤的GWAS汇总数据来自IEU-Open GWAS数据库[17],其中结直肠癌总样本量218 792例,包括3 022例患者和215 770例对照。胃癌总样本量218 792,包括633例患者和218 159例对照。食管癌总样本量372 756例,包括740例患者和372 106例对照。肝癌总样本量218 792例,包括304例患者和218 488例对照。胰腺癌总样本量218 792例,包括605例患者和218 187例对照。所有数据来源均为欧洲血统。本研究基于公开数据库,所有原始研究均获得伦理批准,不需要额外的知情同意或伦理批准。

1.2 方法

1.2.1 研究设计

本TSMR研究基于以下三个主要假设:①IVs应与暴露密切相关(关联性假设);②IVs与影响暴露和结局的混杂因素无关(独立性假设);③IVs只能通过暴露对结局发生作用,而不能通过其他途径(排他性假设)[18-19]。见图1。

1.2.2 工具变量筛选

首先,以$P<5\times10^{-8}$为显著阈值筛选与表型密切相关的SNPs,并设置运行参数$r^2<0.001$,kb=10 000以去除连锁不平衡。其次,以$F>10$作为标准剔除弱工具变量[20]。计算公式为

$$F=(\beta/\sigma_{\bar{x}})^2,$$

其中β为等位基因效应值,$\sigma_{\bar{x}}$为标准误差[21]。最后,在PhenoScanner V2数据库(http://www.phenoscanner.medschl.cam.ac.uk/)逐个检索选中的SNPs,剔除与混杂因素(性别、年龄、吸烟、饮酒)相关的SNPs[22-24],确保筛选之后的SNPs与混杂因素无关。

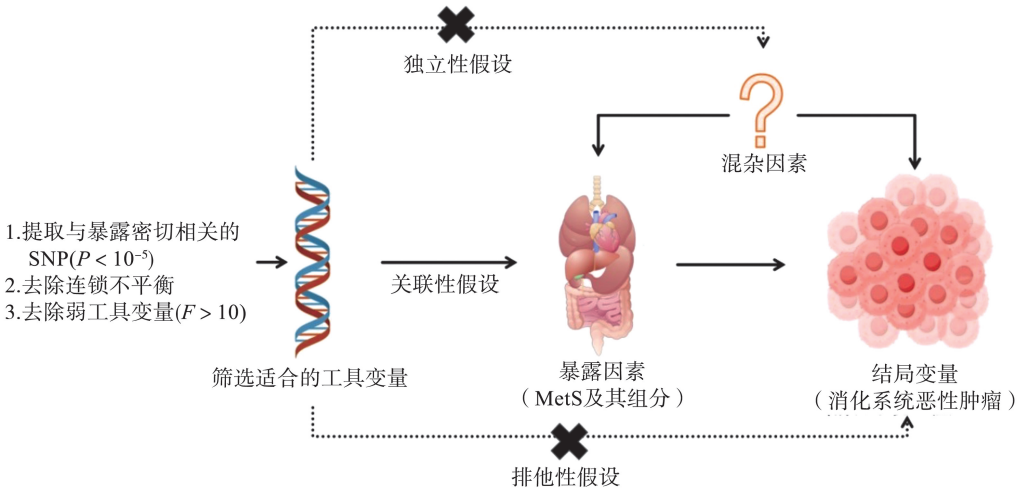

图 1 两样本孟德尔随机化分析示意图

Figure 1 The schematic diagram of two-sample MR analysis

1.3 统计学处理

采用 R 软件(4.3.2 版)，基于 TwoSample MR (版本 0.5.6)和 MR-PRESSO 软件包(版本 1.0)进行统计分析并绘制森林图和散点图。采用逆方差加权法(inverse variance weighted，IVW)作为主要分析方法[25]，MR-Egger 和加权中位数法(weighted median，WM)作为补充方法[26]进行因果推断。采用 Cochran's Q 检验 IVs 之间的异质性，若P<0.05表明存在异质性，并在随后分析中采用 IVW 随机效应模型，否则采用 IVW 固定效应模型[27]。采用 MR Egger 回归截距检测水平多效性，若 P<0.05表明存在水平多效性[28]。采用 MR-PRESSO 法检验离群值，若 P<0.05 表示存在离群值，应剔除并再次进行 MR 分析[29]。采用留一法敏感性分析评估单个 SNP 对整体结果的影响，若剔除任意一个 SNP 都不会导致因果效应产生偏差，证明研究结果稳健[30]。检验水准 α=0.05。

2 结 果

2.1 工具变量筛选结果

共获得 701 个与 MetS 及其组分相关的 SNPs，对应 F 值均>10。剔除具有潜在混杂因素的 SNPs 后，分别保留 91 个与 MetS 相关、250 个与 WC 相关、49 个与 HBP 相关、13 个与 FBG 相关、37 个与 HDL 相关和 21 个与 TG 相关的 SNPs 用于后续分析。

2.2 TSMR 分析结果

IVW 法结果显示，MetS 与肝癌和食管癌的发生呈正相关(P<0.05)；WM 结果显示，MetS 可增加食管癌的患病风险(P<0.05)。见图 2。

暴露因素	结局因素	MR分析方法	P	OR(95%CI)
MetS	结直肠癌	MR Egger	0.677	0.959(0.787~1.168)
MetS		WM	0.870	1.014(0.855~1.203)
MetS		IVW	0.553	0.968(0.871~1.077)
MetS	胃癌	MR Egger	0.749	0.939(0.639~1.380)
MetS		WM	0.738	1.060(0.753~1.493)
MetS		IVW	0.756	0.967(0.785~1.192)
MetS	食管癌	MR Egger	0.060	1.001(1.000~1.001)
MetS		WM	0.005	1.001(1.000~1.001)
MetS		IVW	0.037	1.001(1.000~1.001)
MetS	肝癌	MR Egger	0.847	1.056(0.606~1.841)
MetS		WM	0.522	1.164(0.731~1.852)
MetS		IVW	0.047	1.357(1.004~1.834)
MetS	胰腺癌	MR Egger	0.553	0.886(0.596~1.318)
MetS		WM	0.691	0.935(0.670~1.304)
MetS		IVW	0.349	0.902(0.728~1.119)

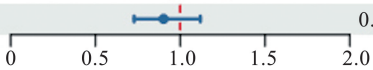

图 2 MetS 结果森林图

Figure 2 Forest plot of MetS

MetS 的各组分中,WC 与胃癌和食管癌的发生呈正相关(P<0.05),见图 3。HDL 与结直肠癌的发生呈负相关(P<0.05),见图 4。散点图结果亦显示出与上述结论相同方向的拟合趋势,见图 5。未发现 MetS、HBP、FBG、TG 与其他消化系统恶性肿瘤之间存在因果关联。

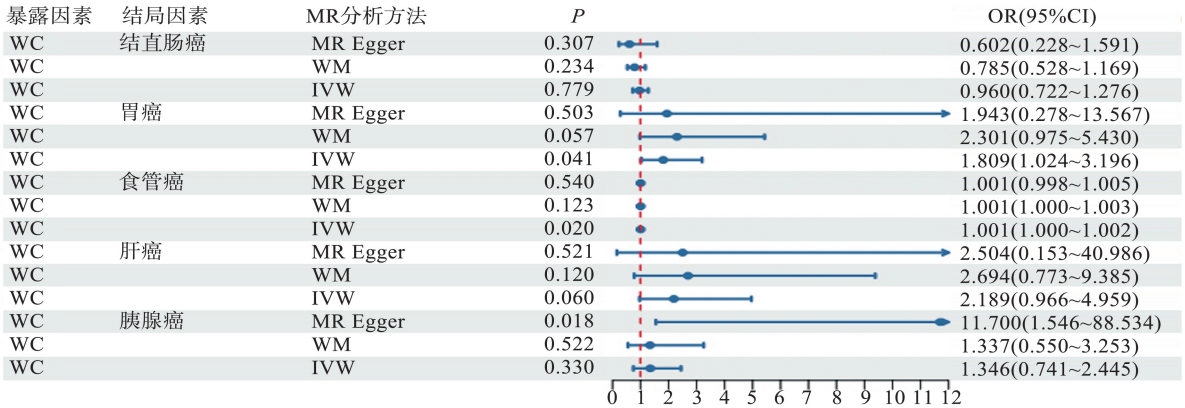

图 3 WC 结果森林图

Figure 3 Forest plot of WC

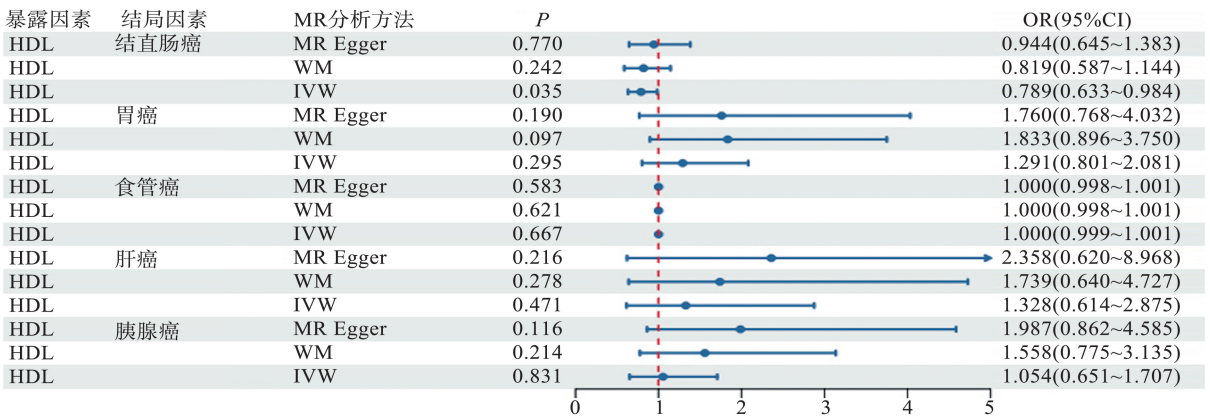

图 4 HDL 结果森林图

Figure 4 Forest plot of HDL

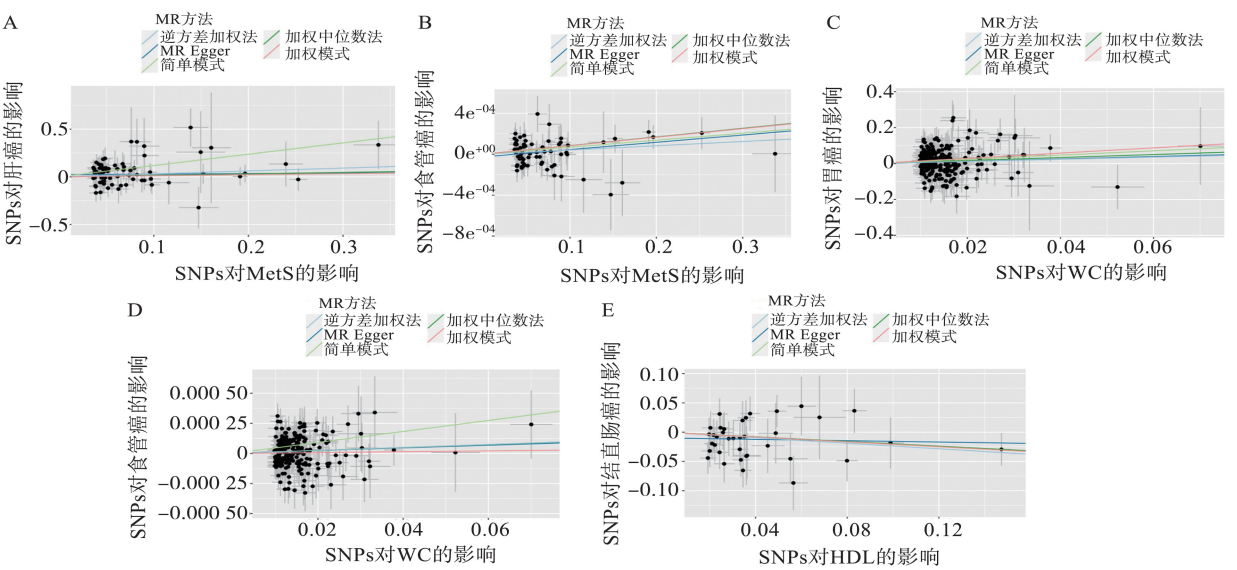

图 5 TSMR 分析散点图

A:MetS 与肝癌;B:MetS 与食管癌;C:WC 与胃癌;D:WC 与食管癌;E:HDL 与结直肠癌。

Figure 5 Scatter plots of TSMR analysis

A: MetS and liver cancer; B: MetS and esophageal cancer; C: WC and gastric cancer; D: WC and esophageal cancer; E: HDL and colorectal cancer.

2.3 敏感性分析结果

Cochran's Q 检验结果显示,TG 和食管癌之间存在异质性($P<0.05$),故采用 IVW 随机效应模型对其因果效应进行检验。MR Egger 回归截距检验发现 MetS、WC、FBG、HDL、TG 与消化系统恶性肿瘤之间均不存在水平多效性($P>0.05$),见表 1。留一法分析结果显示,剔除任意一个 SNP 后,MR 结果依然稳定,表明 MR 分析结果不受任何特定 SNP 的影响。

表 1 异质性检验及多效性检验结果

Table 1 Results of heterogeneity and pliotropy tests

暴露	结局	异质性检验				多效性检验		MR-PRESSO
		MR Egger		IVW		MR Egger		
		Q	P	Q	P	截距	P	P
MetS	结直肠癌	84.229	0.135	84.246	0.153	0.001	0.906	0.734
MetS	胃癌	64.945	0.680	64.978	0.709	0.003	0.857	0.643
MetS	食管癌	57.493	0.790	58.386	0.791	0.000	0.348	0.468
MetS	肝癌	66.036	0.644	67.145	0.640	0.022	0.296	0.365
MetS	胰腺癌	67.984	0.579	67.995	0.612	0.002	0.917	0.571
WC	结直肠癌	261.620	0.081	262.719	0.081	0.007	0.326	0.087
WC	胃癌	228.424	0.536	228.430	0.554	−0.001	0.940	0.534
WC	食管癌	212.566	0.698	212.573	0.714	0.000	0.934	0.691
WC	肝癌	205.664	0.884	205.674	0.893	−0.002	0.922	0.734
WC	胰腺癌	237.322	0.374	242.252	0.309	−0.033	0.295	0.832
HBP	结直肠癌	33.935	0.808	34.467	0.820	0.000	0.470	0.574
HBP	胃癌	47.534	0.331	50.121	0.331	0.017	0.129	0.347
HBP	食管癌	36.852	0.696	42.116	0.510	0.000	0.027	0.543
HBP	肝癌	40.311	0.545	40.667	0.573	0.000	0.554	0.687
HBP	胰腺癌	52.627	0.149	52.631	0.175	−0.002	0.957	0.743
FBG	结直肠癌	4.143	0.966	4.143	0.981	0.000	0.994	0.888
FBG	胃癌	5.211	0.921	5.508	0.939	0.021	0.596	0.274
FBG	食管癌	16.606	0.120	16.646	0.163	0.000	0.874	0.601
FBG	肝癌	6.766	0.818	9.089	0.695	−0.084	0.156	0.341
FBG	胰腺癌	11.010	0.442	11.040	0.525	−0.007	0.866	0.845
HDL	结直肠癌	31.222	0.651	32.496	0.636	−0.010	0.267	0.458
HDL	胃癌	36.469	0.400	37.309	0.409	−0.017	0.375	0.577
HDL	食管癌	25.416	0.789	25.555	0.819	0.000	0.711	0.643
HDL	肝癌	45.744	0.106	47.134	0.101	−0.032	0.309	0.552
HDL	胰腺癌	29.040	0.751	32.359	0.642	−0.035	0.077	0.323
TG	结直肠癌	12.665	0.811	12.807	0.848	−0.007	0.711	0.548
TG	胃癌	12.591	0.815	18.054	0.519	0.088	0.051	0.147
TG	食管癌	32.566	0.019	32.912	0.025	0.000	0.667	0.681
TG	肝癌	17.241	0.507	19.002	0.457	0.072	0.201	0.342
TG	胰腺癌	14.229	0.714	14.229	0.770	0.001	0.981	0.856

3 讨 论

随着人群肥胖率的逐渐增加,MetS 的发病率也逐年攀升,已成为严重危害人类生命健康的全球性公共卫生问题。流行病学调查显示,我国 20 岁及以上人群 MetS 患病率为 31.1%[31]。MetS 不仅是2 型糖尿病和心血管疾病的风险因素[32],也与消化系统恶性肿瘤的发病密切相关[33]。既往研究表明,MetS 与结直肠癌、胰腺癌和肝细胞癌的发生有关[34],但其是否增加胃癌、食管癌的发生风险尚不明确[35]。在 MetS 的各个组分方面,有研究证实肥胖和高血糖是消化系统恶性肿瘤发生发展的重要因素[36],但高血压和血脂异常与消化系统恶性肿瘤之间的联系仍有争议[34]。MetS 促进消化系统恶性肿瘤发生发展可能与其核心病理基础胰岛素抵抗(insulin resistance,IR)有关:①胰岛素受体与机体内胰岛素样生长因子 1(insulin-like growth factor 1, IGF-1)结合可

触发下游细胞信号通路,在诱导癌细胞分裂的同时抑制其凋亡,进而促进癌细胞的增殖[37];②IR 可增加内脏脂肪的积累[38],进而增加促炎细胞因子如白介素-6(interleukin-6, IL-6)的分泌,活化信号转导及转录激活蛋白(signal transducers and activators of transcription, STAT),导致消化系统恶性肿瘤的发生[39]。

已有研究发现,MetS 与肝癌发生密切相关[40],本研究与其结果一致。Shi 等[41]研究表明,MetS 增加了非酒精性脂肪肝(non-alcoholic fatty liver diseases, NAFLD)和携带乙型肝炎病毒(hepatitis B virus, HBV)的患者的肝癌发生风险,NAFLD 是 MetS 的肝脏表现。TG 过度积累于肝脏可导致肝脂肪变性,引起机体炎症和肝细胞损伤,导致肝纤维化,最终发展为肝癌[42]。过多的脂肪积累于肝脏也可引发 IR,上调胰岛素样生长因子(insulin-like growth factor, IGF)表达,促进癌细胞增殖的同时抑制凋亡;胰岛素受体与胰岛素或 IGF 结合可激活 P13K/Akt 和 MAPK 信号通路,增加肝细胞的癌变风险[43]。此外,脂肪组织浸润可导致全身处于慢性低度炎症状态,上调肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和 IL-6 水平,激活丝氨酸苏氨酸激酶(c-Jun N-terminal kinases, JNK)及 STAT 信号通路,促进肝癌发生[44]。HBV 感染亦是肝癌发生的重要因素。Lee 等[45]研究发现,MetS 合并 HBV 感染患者患肝癌的风险增加;Peleg 等[46]研究发现,与无肝脏脂肪疾病的 HBV 感染患者相比,伴肝脏脂质代谢异常的 HBV 感染患者肝癌发生率及死亡率增加,提示 MetS 在乙肝肝硬化的基础上可进一步推进肝脂肪变性及肝纤维化,最终导致肝癌的发生。

Zhang 等[47]通过荟萃分析发现,MetS 与食管腺癌风险有关,但与食管鳞状细胞癌风险无明显关联。Rothwell 等[48]研究表明,MetS 与食管腺癌发病风险呈正相关,与食管鳞状细胞癌发病风险呈负相关。但另有一项针对韩国人群的研究[49]显示,MetS 患者的食管癌,特别是食管鳞状细胞癌的发生风险更高,本研究结果与上述研究部分一致。可能与食管癌发生的区域性有关:食管腺癌是欧洲人群最常见的病理类型,亚洲人群则以食管鳞状细胞癌更为普遍。

Du 等[50]通过 Meta 分析发现,腹部肥胖和食管癌风险增加显著相关。王罡强等[51]和 Sanikini 等[52]的研究均发现腹型肥胖是男性食管胃交界处腺癌的风险因素,本研究结果与上述研究一致。原因可能为腹部肥胖可下调体内有抗炎活性的脂联素的表达水平,且患者脂肪细胞和浸润免疫细胞也可产生炎性细胞因子,导致全身进入炎症状态,形成适合肿瘤发生的微环境[53-54]。

既往研究显示,HDL 水平与结直肠癌的发生风险呈反比[55]。杨刚等[56]的回顾性研究发现,低 HDL 水平是影响结直肠癌术后总生存期的危险因素。van Duijnhoven 等[57]研究显示,HDL 水平每增加 16.6 mg/dL,结直肠癌的患病风险降低 22%,本研究与上述研究结果一致。HDL 是一种脂质运载体,具有调节炎症和抗氧化应激能力,能够有效抑制癌细胞增殖。低 HDL 不仅会导致 TNF-α 及 IL-6 等促炎细胞因子水平上升,形成适合肿瘤细胞生长的炎性微环境[58],还可通过影响肿瘤相关巨噬细胞,加速血管生成,进而促进肿瘤的生长和侵袭[59]。

本研究具有以下局限性:①仅纳入了欧洲人群,结论还需通过在其他人群中开展相关研究进一步验证;②缺乏个体水平的基本信息,使用的消化系统恶性肿瘤汇总数据无法根据相关协变量(例如病理类型、解剖部位等)进行分层分析,因此无法讨论某些亚群体是否会增加罹患消化系统恶性肿瘤的风险,可能导致效应值的偏差;③研究结论仅基于统计学结果,无法进一步探索 MetS 与消化系统恶性肿瘤之间潜在的生物学机制,需要开展相关基础和临床实验加以验证。

综上所述,本研究采用 TSMR 分析,发现 MetS 及其组分与消化系统恶性肿瘤密切相关,提示加强对 MetS 的预防和管理能在一定程度上降低消化系统恶性肿瘤的发病风险,有助于指导人们饮食及生活习惯的选择,为消化系统恶性肿瘤的预防提供了新思路。

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