肥胖与原发性肝癌关系的流行病学研究进展

李卓颖[1,2,3]，项永兵[1,2,3]
（1.复旦大学公共卫生学院，上海 200032；2.上海交通大学医学院附属仁济医院癌基因及相关基因国家重点实验室，上海 200032；3.上海市肿瘤研究所，上海 200032）

摘　要：原发性肝癌是常见的恶性肿瘤之一。近年来，肥胖与肝癌之间的关系逐渐受到公众和流行病学家的重视。该文对全身性肥胖、脂肪分布以及成年期体重改变与肝癌发病、预后关系的流行病学研究进行了综述。首先，介绍了传统的体质指数、腰围、腰臀比等指标以及成年早期肥胖和成年期体重改变与肝癌关系之间的研究进展；其次，针对一些较新的身体成分测量手段（如双能X线吸收法、计算机断层扫描、磁共振等）在肥胖与肝癌关系中的应用进行了简要描述；最后，由于肥胖和多种代谢紊乱关系密切，因此对2型糖尿病、代谢综合征、非酒精性脂肪肝病等与原发性肝癌之间的关系也进行了概述。

关键词：原发性肝癌；肥胖；脂肪分布；危险因素；流行病学研究；队列研究
中图分类号：R730.1；R735.7　　**文献标识码**：A　　**文章编号**：1004-0242(2021)09-0711-10
doi：10.11735/j.issn.1004-0242.2021.09.A012

Progress on Epidemiologic Studies for the Relationship Between Adiposity and Primary Liver Cancer

LI Zhuo-ying[1,2,3], XIANG Yong-bing[1,2,3]
(1. School of Public Health, Fudan University, Shanghai 200032, China; 2. State Key Laboratory of Oncogenes and Related Genes, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200032, China; 3. Shanghai Cancer Institute, Shanghai 200032, China)

Abstract: Primary liver cancer is one of the most common malignancies. Recently, the association between adiposity and liver cancer has gradually attracted the attention of the public and epidemiologists. The current review systematically summarized the epidemiological studies on the relationship between general obesity, fat distribution and adult weight change with the incidence and prognosis of primary liver cancer. Firstly, the research progress on the relationship between traditional anthropometrics such as body mass index, waist circumference, waist-to-hip ratio, obesity in early adulthood and adult weight change with liver cancer were introduced. Secondly, the application of some new body composition measurement methods (such as dual-energy X-ray absorptiometry, computed tomography, magnetic resonance imaging, etc.) on the relationship between adiposity and liver cancer is briefly described. Finally, the association of type 2 diabetes mellitus, metabolic syndrome and non-alcoholic fatty liver disease with primary liver cancer is also briefly reviewed, as adiposity is closely associated with many metabolic disorders.

Key words: primary liver cancer; adiposity; fat distribution; risk factor; epidemiologic study; cohort study

原发性肝癌（以下简称肝癌）是全球常见的恶性肿瘤之一。国际癌症研究署（International Agency for Research on Cancer，IARC）公布的最新统计数据显示[1]，2020年全球肝癌新发病例数估计约为90.6万，死亡病例数约为83.0万；肝癌新发病例数和死亡例数在所有肿瘤中分别排第6位和第3位。男性肝癌的发病率和死亡率均远高于女性，2020年全球男性肝癌的世界人口标化发病率为14.1/10万，标化死亡率为12.9/10万；女性肝癌的世界人口标化发病率为5.2/10万，标化死亡率为4.8/10万。除了性别差异，肝癌的发病率在不同国家、地区间差异较大。

收稿日期：2021-05-19；修回日期：2021-06-28
基金项目：国家重点研发计划项目(2016YFC1302503)
通信作者：项永兵，E-mail：ybxiang@shsci.org

东亚地区的肝癌发病率最高，2020年世界人口标化发病率达17.8/10万；而发病率最低的中亚地区则仅为3.0/10万。过去40年间，一些发病率水平较高的国家（中国、日本、新加坡、菲律宾等）肝癌标化发病率逐渐下降，而原本发病率较低的国家（美国、德国、加拿大、澳大利亚等）肝癌发病率则快速上升[2]。肝癌的预后很差，最新的全球癌症生存趋势监测（CONCORD-3）数据显示，2000—2014年全球肝癌的5年净生存率（net survival rate）在5%~30%之间；2010—2014年我国人群肝癌的5年净生存率为14%左右[3]。

目前已知的肝癌主要危险因素包括乙型肝炎病毒（hepatitis B virus，HBV）和丙型肝炎病毒（hepatitis C virus，HCV）感染、过量酒精摄入、黄曲霉毒素、马兜铃酸和肝吸虫感染等[4]。以上危险因素的地域分布可部分解释低收入、欠发达国家的肝癌发病率远高于发达国家这一现象[1]。然而，却不足以解释近年来一些西方发达国家肝癌发病率的快速上升[5-6]。近年来，肥胖及其相关的一系列代谢紊乱与肝癌之间的关系逐渐受到重视。非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）已成为全球第一位慢性肝病，在我国的发病率仅次于慢性乙型肝炎[7-8]。NAFLD包括了一系列的肝脏损害，由较轻微的单纯肝脏脂肪变性到较严重的非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH）。NASH的特征是明显的肝细胞脂肪浸润、炎症、坏死和纤维化，可引起肝硬化，并最终导致肝细胞癌（hepatocellular carcinoma，HCC）[9]。肥胖可引起肝脏代谢改变，促进炎症反应，和NAFLD/NASH关系密切，更有学者认为NAFLD/NASH是代谢综合征（metabolic syndrome，MetS）在肝脏中的表现[10]。2020年3月，国际专家共识建议将NAFLD更名为代谢相关脂肪性肝病（metabolic associated fatty liver disease，MAFLD）[11]。

世界卫生组织的调查数据显示，2016年全球18岁及以上的成年人中，约19亿人体质指数（body mass index，BMI）>25 kg/m^2（超重），其中超过6.5亿人BMI>30 kg/m^2（肥胖）[12]。其中，高收入西方国家的肥胖人数占比最高，男女性分别占全球肥胖总人数的33%和26%[13]。从1980年到2013年，世界范围内成年男性超重的比例从28.8%增加到36.9%，成年女性超重的比例从29.8%增加到38.0%[14]。发达国家的超重/肥胖率在30年间均远高于世界平均水平。因此，肥胖及其引起的NAFLD有可能是导致西方发达国家近十年来肝癌发病率显著上升的原因之一[9,15]。

本文将综述肥胖与原发性肝癌关系的流行病学研究进展，重点关注证据级别较高的系统综述/Meta分析以及大型前瞻性队列研究、巢式病例—对照研究等；并简要阐述2型糖尿病（type 2 diabetes mellitus，T2DM）、NAFLD以及MetS等肥胖相关代谢性疾病与肝癌之间的关系，为进一步的研究提供重要参考。

1 肥胖和肝癌发病的关系

肥胖水平的评估一般从脂肪组织的“数量”和“位置”两方面进行，即全身性肥胖（overall obesity）指标和脂肪分布（fat distribution）指标两类。体重和BMI是评价全身性肥胖最常用的指标；脂肪分布情况常用腰围（waist circumference，WC）、腰臀比（waist-to-hip ratio，WHR）和臀围（hip circumference，HC）等指标进行评价。另外，不同年龄的肥胖水平以及肥胖随时间的动态变化情况也逐渐受到关注。

1.1 全身性肥胖与肝癌发病的关系

世界癌症研究基金会（World Cancer Research Fund，WCRF）2018年发布的专家报告显示，目前已有充足的证据认为多余身体脂肪是肝癌的危险因素[16]。上述结论基于大量以BMI作为测量指标的流行病学研究证据。2007年发表的一项纳入了11项前瞻性队列研究的Meta分析发现，肥胖者（BMI≥30 kg/m^2）发生肝癌的风险是正常体重者的1.89倍，95%置信区间（confidence interval，CI）为1.51~2.36[17]。截至目前，已有近30项前瞻性队列研究[18-48]和10余篇系统综述/Meta分析[17,47,49-56]对BMI与肝癌发病之间的关系进行了分析。2021年发表的最新一项评估BMI与肝癌发病关系的Meta分析共纳入了28个前瞻性队列研究，样本量达814万人。结果提示，与体重正常者相比，超重/肥胖（BMI≥25 kg/m^2）者发生肝癌的相对危险度（relative risk，RR）为1.69（95%CI：1.50~1.90）[56]。然而，多项Meta分析的结果均提示，现有研究之间存在显著的异质性[49-51,53-54]，可能的异质性来源包括性别、种族、基线健康状况等。BMI与肝癌

的关联在男性、白人和有慢性肝病史的人群当中似乎较强。美国一项前瞻性队列的研究结果显示，男性人群中 BMI（每增加 5 kg/m²）与肝癌的 RR 为 1.26（95%CI：1.12~1.42），而女性人群中仅为 1.06（95% CI：0.90~1.25）[33]；另一项巢式病例对照研究结果也提示男性人群中 BMI（每增加 5 kg/m²）与肝癌的关联强度高于女性（男性 OR=1.37，95%CI：1.14~1.66；女性 OR=1.28，95%CI：1.03~1.58）[46]。一项针对多种族人群的前瞻性队列研究结果表明，BMI 与高加索人、日本裔和拉丁裔男性的 HCC 密切相关，而在黑人男性中无此关联 [46]。WCRF 的专家报告也提示，BMI（每增加 5 kg/m²）与肝癌的关联在欧洲人群中要强于亚洲人群（欧洲 RR=1.59，95%CI：1.35~1.87；亚洲 RR=1.18，95% CI：1.04~1.34）[16]。2006 年一项针对酒精性/HCV 感染引起的肝硬化患者的研究发现，BMI>30 kg/m² 者发生 HCC 的风险是正常体重者的 2.8 倍（95%CI：2.0~4.0）[45]。2008 年中国台湾地区针对 HCV 感染者的研究发现，相对于 BMI<23.0 kg/m² 的研究对象，BMI>30.0 kg/m² 的人发生 HCC 的风险高达 4.13 倍（95%CI：1.38~12.4）[23]。上述两项研究得到的关联强度估计值均显著高于从健康人群中得到的结果。

1.2 脂肪分布与肝癌发病的关系

由于 BMI 仅能代表整体肥胖的程度，无法反映人体脂肪组织的分布情况，而不同部位的脂肪组织在生理功能、代谢活性等方面并不一致[57]。因此，能够更好反映人体脂肪分布的身体测量指标如 WC、HC、WHR 和腰围身高比（waist-to-height ratio，WHtR）[58]等逐渐受到重视。尤其在 WC 被纳入 MetS 的诊断标准之后，越来越多的研究开始关注 WC 与各种健康结局之间的关系[59]。

2013 年欧洲一项基于人群的大型多中心前瞻性队列研究（European Prospective Investigation into Cancer and Nutrition，EPICN）首次报道了不同的脂肪分布指标与 HCC 和肝内胆管细胞癌（intrahepatic cholangiocarcinoma，ICC）发病风险之间的关系，结果显示较高的 WC、HC、WHR 和 WHtR 均与 HCC 发病风险增加有关；且 WC、WHR 和 WHtR 在调整 BMI 之后结果仍然有统计学意义，提示中心性肥胖可能是独立于全身性肥胖的危险因素[32]。除 EPICN 研究之外，目前还有数项前瞻性队列研究对脂肪分布指标与肝癌的关系进行了分析[22,30,37,48,60-62]，以及一项剂量—反应 Meta 分析对 WC 与肝癌关系的队列研究进行了汇总[63]。目前，WC 与肝癌发病之间的关联基本得到了大部分研究的支持，但 HC、WHR、WHtR 等指标的分析结果并不一致。另外，由于 WC、HC、WHtR 等脂肪分布指标与 BMI 高度相关，要将脂肪分布的额外作用从全身性肥胖当中分离出来并不容易，常规的多因素调整方法可能存在共线性问题。因此脂肪分布与肝癌发病的关系仍需要进一步的探讨。

1.3 成年早期肥胖和成年期体重改变与肝癌发病的关系

目前对于肥胖与肝癌关系的研究多基于中年期的调查资料，人们对于生命早期肥胖以及体重的动态变化与肝癌的关系并不了解。虽然已有数个前瞻性队列研究分析了青少年时期肥胖与肝癌风险之间的关系，但研究结果并不一致[32,64-68]。例如美国国立卫生研究院退休人员协会饮食与健康研究（National Institutes of Health-American Association of Retired Persons Diet and Health study，NIH-AARP）[64]、丹麦一项基于学校健康记录的研究[66]、瑞典一项 120 万男性的研究[67]以及以色列一项 230 万青少年的研究[65]，都支持青春期或成年早期肥胖可增加肝癌的发病风险。但我国的上海女性健康队列（Shanghai Women's Health Study，SWHS）[48]、欧洲的 EPIC 研究[32]以及日本的一项多中心前瞻性队列研究（Japan Collaborative Cohort，JACC）[68] 并不支持 20 岁肥胖与肝癌发病之间的关系。

成年期体重变化与肝癌关系的研究结果也并不一致。例如上海一项基于 13 万人的前瞻性队列研究和欧洲一项多中心的前瞻性队列研究结果均不支持成年期体重增长和肝癌的关系[20,69]。但有 4 项研究则得出了具有统计学意义的结果，体重最高组相比于最低组的 RR 值分别在 1.69~2.48 之间[32,48,64,68]。由于目前几项研究在研究设计、病例样本量大小、暴露测量方法、随访时间长短和统计分析方法等方面存在诸多差异，结果不太适宜直接进行比较。因此，生命早期肥胖、成年期体重的动态变化与肝癌发病风险之间的关系仍需要更多的研究证据支持。

2 肥胖与肝癌预后的关系

随着肥胖对肝癌发病的作用得到逐步确认，肥胖与肝癌预后之间的关系自然也逐渐受到重视。目前已有一些研究探讨了 BMI 与肝癌预后之间的关系，但结果并不一致[70-71]。部分研究发现 BMI 较高的肝癌患者，预后反而好于体重正常的患者；而另一部分研究则提示 BMI 和肝癌预后之间并无显著的关联。2014 年一项 Meta 分析结果提示，BMI 与 HCC 患者的总生存期或无进展生存期之间并无关联；与腹腔积液、胆汁泄漏和 30 天死亡率等并发症的发生率也无关，但 BMI 较高的患者伤口感染的发生率较高[71]。2020 年一项纳入了 10 578 例 HCC 患者的研究发现，超重的男性患者预后好于正常体重者，但在女性病例中 BMI 与预后之间并无关联[72]。

肥胖可升高发病风险但对疾病预后又具有保护作用的现象被称为“肥胖悖论(obesity paradox)”，这在心血管疾病、呼吸系统疾病、糖尿病和部分恶性肿瘤(肺癌、胃癌等)中也有报道[73-74]。目前认为导致“肥胖悖论”出现的可能原因包括：①反向因果关联；②吸烟等混杂因素调整不充分而导致的残余混杂；③选择偏倚；④BMI 难以区分内脏脂肪、皮下脂肪和骨骼肌等不同身体组成成分[75-76]。从现有报道来看，孟德尔随机化是一种运用遗传变异作为工具变量以控制混杂的分析方法[77-78]，可为反向因果关联和残余混杂等问题提供一些解决思路。

3 其他身体成分测量方法在肥胖与肝癌关系研究中的应用

由于 BMI、WC 等身体测量指标只是对脂肪的间接测量，其结果并不仅仅代表脂肪含量，还容易受到肌肉量、骨骼结构等身体成分的影响，在老年人、运动员等特殊人群中尤为明显。身体成分分析技术的快速发展可将肥胖与健康结局关系的研究拓展至更加精细的层面[79]。近年来，一些基于影像学的身体成分测量手段，包括双能 X 线吸收法(dual-energy X-ray absorptiometry，DXA)、磁共振扫描(magnetic resonance imaging，MRI)和计算机断层扫描(computed tomography，CT)等，已逐渐开始得到应用[80-81]。

DXA 可以测量脂肪质量、瘦体重和骨密度，操作简便快速，但有轻微辐射，目前是身体成分测量的金标准[82]；CT 和 MRI 不仅可在器官、组织层面准确测量脂肪组织的含量，还可得到脂肪组织的密度、分布特征以及肌间脂肪浸润情况等大量信息，且常常是肝癌患者诊断时的常规检查项目，可以为肥胖和肝癌预后关系的研究提供十分有用的信息。但由于上述方法的开展成本和技术门槛较高，目前仅有少量基于医院病例的小样本回顾性研究[74]，主要观察结局为肝癌的预后情况。2015 年，日本一项回顾性队列研究分析了身体成分测量指标与 HCC 预后的关系，利用 1 257 例 HCC 患者诊断时的 CT 检查结果，测量了内脏脂肪含量、皮下脂肪含量、骨骼肌含量和肌肉衰减程度等身体成分指标，结果发现骨骼肌减少、肌间脂肪沉积和内脏脂肪可以独立预测 HCC 患者的预后情况[70]。日本另一项纳入了 606 例 HCC 患者的研究发现，术前内脏脂肪含量较高与肝癌肝切除术后不良预后密切相关[83]。一项针对 678 例肝硬化患者的回顾性研究发现，高内脏脂肪含量会增加男性肝硬化患者患 HCC 的风险，并和肝移植术后肝癌的复发独立相关[84]。

生物电阻抗分析法(bioelectrical impedance analysis，BIA)是一种基于电学的身体成分分析方法，主要基于脂肪和瘦组织含水量不同、电阻不同这一原理，利用多个电极和微弱电流来测定人体的总水分、脂肪质量和瘦体重[85-86]。BIA 法测量方便、安全无创、成本较低，适合在大型前瞻性队列研究中使用，但容易受到进食、饮水、运动等影响人体水合状态的因素影响，准确性不如上述三种基于影像学的测量方法[80]。目前仅有一项队列研究分析了 BIA 测定的体脂百分比(percent body fat，BF%)与肝癌发病风险之间的关系，但该研究结果并不支持 BF%与肝癌发病风险之间的关系(BF%每增加 5%的 RR=0.97，95%CI：0.89~1.06)[30]。

4 肥胖相关代谢性疾病与肝癌之间的关系

脂肪组织是人体重要的代谢器官，与高血压、冠心病、血脂异常、T2DM、MetS 等全身代谢性疾病密

切相关。目前一般认为肥胖是这些系统性代谢疾病的危险因素，而T2DM、MetS等有可能是肥胖—肝癌关系的中介变量。

T2DM与肝癌发病的关系已经在不同人群中得到了验证[87]。2013年，上海一项研究首次在中国人群中报道了T2DM与肝癌发病之间的关系，结果显示T2DM可显著增加中国人群的肝癌发病风险，男、女性的多因素调整危险比(hazard ratio，HR)分别为1.63(95%CI：1.06~2.51)和1.64(95%CI：1.03~2.61)[88]。2018年美国一项多中心前瞻性队列研究[47](结局为ICC，HR=1.81，95%CI：1.33~2.46)和2018年中国一项多中心前瞻性队列研究[89](结局为HCC，HR=1.49，95%CI：1.30~1.70)也得出相同的结论。一项Meta分析结果提示，T2DM与男性HCC发病的关系比女性更为密切[90]。T2DM的病程长短可能也与HCC的发病风险相关，但T2DM严重程度或血糖控制情况与HCC发病之间的关系尚不清楚[91]。

MetS是一组包括了高血压、血脂异常、胰岛素抵抗等在内的复杂的代谢紊乱症候群[59]。现有研究支持MetS与肝癌发病风险之间的关联[28,92-93]。一项Meta分析提示，MetS与男性肝癌发病风险增加有关，但在女性肝癌中结果并不一致[93]。值得注意的是，上述多种代谢紊乱症候群往往同时出现，有研究提示多种代谢危险因素之间可能存在一定的协同作用。作为MetS的肝脏表现[10,94]，NAFLD/NASH与肝癌的关系已经得到确认。目前认为大多数NAFLD相关的HCC与酒精性肝病引起的HCC类似，都是经由肝硬化发展而来的。但也有研究提示，大约42%的NAFLD相关HCC病例并没有经历肝硬化过程[95-96]。因此，对于未出现肝硬化表现的NAFLD患者也应当进行早期干预，以减少HCC的发生。

5 肥胖与肝内胆管癌的关系

ICC是原发性肝癌次常见的病理类型，约占全部病例数的10%~15%[1]。近年来，ICC的发病率在全球大多数国家均呈上升趋势。2020年一项研究显示，中国的ICC发病率从1993—1997年的0.14/10万上升至2008—2012年的0.63/10万，年均变化百分比(annual average percent change，AAPC)达11.1%[97]。由于国际疾病分类把HCC、ICC以及其他罕见的肝脏肿瘤统一编码为原发性肝癌（ICD-9编码155/ICD-10编码C22），目前绝大多数流行病学研究通常将HCC和ICC合并分析，或主要关注HCC，而针对发病率较低的ICC进行的单独研究则非常有限。考虑到HCC与ICC起源于不同细胞，在病因和生物学方面存在异质性，肥胖在ICC发病和预后过程中的作用可能与HCC存在一些区别。目前已有流行病学研究提示肥胖与ICC的发病之间也存在关联[47,98-99]。例如2018年美国一项多中心前瞻性队列研究提示肥胖（BMI≥30 kg/m^2）可使ICC的发病风险升高81%（95%CI：1.33~2.46）[47]。2017年一项基于美国肿瘤登记资料的研究结果显示，肥胖与ICC的发病相关，关联存在统计学意义（RR=1.42，95%CI：1.22~1.66）[99]。但也有研究并不支持两者之间的关联[32,100-101]。由于肥胖和ICC之间的生物学机制目前尚不明确，两者的关系仍需要进一步研究。

6 肥胖与肝癌关系的生物学机制

肥胖与肝癌关系的生物学机制还未完全阐明，目前认为主要与胰岛素抵抗、慢性炎症和氧化应激、脂肪细胞因子分泌异常以及肠道菌群改变有关[102]。

肥胖（尤其是中心性肥胖）与肝脏脂肪堆积密切相关，大量的脂肪堆积可引起肝脏代谢异常，从而导致高胰岛素血症和慢性炎症状态等[103-104]。高胰岛素水平可通过磷酸肌醇-3-激酶/蛋白激酶B和Ras/丝裂原活化蛋白激酶途径直接促进癌细胞的增殖和存活[105]；此外，胰岛素样生长因子（IGF-Ⅰ和IGF-Ⅱ）在肿瘤的形成、生长和转移中也发挥着重要作用[106]。

肥胖患者的肝脂肪堆积可促进炎症反应的激活，诱导HCC的起始和发展所必需的促炎分子（趋化因子和细胞因子）产生[107-108]。趋化因子及其受体可促进癌细胞增殖、炎性微环境形成、免疫逃避和血管生成等过程[108]。持续的肝脏炎症可导致肝实质损伤、氧化应激和代偿性的肝细胞再生/增殖。

除此之外，脂肪组织本身就是一种内分泌器官，可分泌大量的激素和蛋白质[109]。已有研究提示，这些生长因子、脂肪因子水平的变化与多种恶性肿瘤密切相关[110-111]。瘦素、脂联素、抵抗素等脂肪因子在食物摄入和营养素代谢、胰岛素敏感性、炎症、应激

和骨骼生长方面都发挥着重要作用[102]。脂肪因子分泌失衡还与肝纤维化密切相关[112-113]。

7 总结与展望

中年期全身性肥胖与肝癌发病的关系已经得到许多大规模流行病学研究的确认，中心性肥胖和成年期体重增长在肝癌发病过程中可能也发挥着重要作用。但肥胖与肝癌预后之间的关系尚未明确。下一步研究可重点关注脂肪分布情况与肝癌预后之间的关系，以及探讨肥胖与肝细胞癌、肝内胆管癌关系的生物学机制。

参考文献：

[1] Sung H，Ferlay J，Siegel RL，et al. Global cancer statistics 2020：GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin，2021，71(3)：209-249.

[2] Petrick JL，Florio AA，Znaor A，et al. International trends in hepatocellular carcinoma incidence，1978-2012 [J]. Int J Cancer，2020，147(2)：317-330.

[3] Allemani C，Matsuda T，Di Carlo V，et al. Global surveillance of trends in cancer survival 2000—14 (CONCORD-3)：Analysis of individual records for 37，513，025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries [J]. Lancet，2018，391 (10125)：1023-1075.

[4] El-Serag HB. Hepatocellular carcinoma[J]. N Engl J Med，2011，365(12)：1118-1127.

[5] Liu Z，Jiang Y，Yuan H，et al. The trends in incidence of primary liver cancer caused by specific etiologies：results from the global burden of disease study 2016 and implications for liver cancer prevention[J]. J Hepatol，2019，70 (4)：674-683.

[6] Dasgupta P，Henshaw C，Youlden DR，et al. Global trends in incidence rates of primary adult liver cancers：a systematic review and meta-analysis[J]. Front Oncol，2020，10：171.

[7] Estes C，Anstee QM，Arias-Loste MT，et al. Modeling NAFLD disease burden in China，France，Germany，Italy，Japan，Spain，United Kingdom，and United States for the period 2016-2030[J]. J Hepatol，2018，69(4)：896-904.

[8] Zhou F，Zhou J，Wang W，et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018：a systematic review and meta-analysis[J]. Hepatology，2019，70(4)：1119-1133.

[9] Alzahrani B，Iseli TJ，Hebbard LW. Non-viral causes of liver cancer：does obesity led inflammation play a role?[J]. Cancer Lett，2014，345(2)：223-229.

[10] Siegel AB，Zhu AX. Metabolic syndrome and hepatocellular carcinoma：two growing epidemics with a potential link [J]. Cancer，2009，115(24)：5651-5661.

[11] Eslam M，Sanyal AJ，George J，et al. MAFLD：a consensus-driven proposed nomenclature for metabolic associated fatty liver disease [J]. Gastroenterology，2020，158 (7)：1999-2014. e1.

[12] 世界卫生组织. 肥胖和超重[EB/OL]. [2021-06-27]. https：//www.who.int/zh/news-room/fact-sheets/detail/obesity-and-overweight.
World Health Organization. Obesity and overweight [EB/OL]. [2021-06-27].https：//www.who.int/zh/news-room/fact-sheets/detail/obesity-and-overweight.

[13] Sung H，Siegel RL，Torre LA，et al. Global patterns in excess body weight and the associated cancer burden[J]. CA Cancer J Clin，2019，69(2)：88-112.

[14] Ng M，Fleming T，Robinson M，et al. Global，regional，and national prevalence of overweight and obesity in children and adults during 1980-2013：a systematic analysis for the Global Burden of Disease Study 2013 [J]. Lancet，2014，384(9945)：766-781.

[15] Michelotti GA，Machado MV，Diehl AM. NAFLD，NASH and liver cancer[J]. Nat Rev Gastroenterol Hepatol，2013，10(11)：656-665.

[16] World Cancer Research Fund/American Institute for Cancer Research. Continuous update project expert report 2018. Body fatness and weight gain and the risk of cancer [EB/OL]. [2021-06-18]. https：//www.wcrf.org/dietandcancer/body-fatness-and-weight-gain/.

[17] Larsson SC，Wolk A. Overweight，obesity and risk of liver cancer：a meta-analysis of cohort studies [J]. Br J Cancer，2007，97(7)：1005-1008.

[18] Andreasson A，Carlsson AC，Önnerhag K，et al. Waist/hip ratio better predicts development of severe liver disease within 20 years than body mass index：a population-based cohort study [J]. Clin Gastroenterol Hepatol，2017，15(8)：1294-1301. e2.

[19] Bhaskaran K，Douglas I，Forbes H，et al. Body-mass index and risk of 22 specific cancers：a population-based cohort study of 5. 24 million UK adults [J]. Lancet，2014，384 (9945)：755-765.

[20] Bjørge T，Häggström C，Ghaderi S，et al. BMI and weight

changes and risk of obesity-related cancers: a pooled European cohort study [J]. Int J Epidemiol, 2019, 48 (6): 1872–1885.

[21] Borena W, Strohmaier S, Lukanova A, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578, 700 adults[J]. Int J Cancer, 2012, 131(1): 193–200.

[22] Campbell PT, Newton CC, Freedman ND, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U. S. adults[J]. Cancer Res, 2016, 76(20): 6076–6083.

[23] Chen CL, Yang HI, Yang WS, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan [J]. Gastroenterology, 2008, 135(1): 111–121.

[24] Gribsholt SB, Cronin-Fenton D, Veres K, et al. Hospital-diagnosed overweight and obesity related to cancer risk: a 40-year Danish cohort study[J]. J Intern Med, 2020, 287(4): 435–447.

[25] Inoue M, Kurahashi N, Iwasaki M, et al. Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC study cohort Ⅱ)[J]. Cancer Causes Control, 2009, 20(5): 741–750.

[26] Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women [J]. Int J Cancer, 2008, 123(8): 1892–1896.

[27] Kliemann N, Murphy N, Viallon V, et al. Predicted basal metabolic rate and cancer risk in the European Prospective Investigation into Cancer and Nutrition [J]. Int J Cancer, 2020, 147(3): 648–661.

[28] Nderitu P, Bosco C, Garmo H, et al. The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: a study in the Swedish AMORIS cohort[J]. Int J Cancer, 2017, 141(6): 1148–1160.

[29] Ohishi W, Fujiwara S, Cologne JB, et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study [J]. Cancer Epidemiol Biomarkers Prev, 2008, 17(4): 846–854.

[30] Pang Y, Kartsonaki C, Turnbull I, et al. Adiposity in relation to risks of fatty liver, cirrhosis and liver cancer: a prospective study of 0.5 million Chinese adults [J]. Sci Rep, 2019, 9(1): 785.

[31] Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362, 552 Swedish men [J]. Cancer Causes Control, 2006, 17(7): 901–909.

[32] Schlesinger S, Aleksandrova K, Pischon T, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort [J]. Int J Cancer, 2013, 132(3): 645–657.

[33] Setiawan VW, Lim U, Lipworth L, et al. Sex and ethnic differences in the association of obesity with risk of hepatocellular carcinoma [J]. Clin Gastroenterol Hepatol, 2016, 14(2): 309–316.

[34] Setiawan VW, Wei PC, Hernandez BY, et al. Disparity in liver cancer incidence and chronic liver disease mortality by nativity in Hispanics: the multiethnic cohort [J]. Cancer, 2016, 122(9): 1444–1452.

[35] Song X, Pukkala E, Dyba T, et al. Body mass index and cancer incidence: the Finrisk study [J]. Eur J Epidemiol, 2014, 29(7): 477–487.

[36] Stocks T, Bjørge T, Ulmer H, et al. Metabolic risk score and cancer risk: pooled analysis of seven cohorts [J]. Int J Epidemiol, 2015, 44(4): 1353–1363.

[37] Wang L, Jin G, Yu C, et al. Cancer incidence in relation to body fatness among 0. 5 million men and women: findings from the China Kadoorie Biobank [J]. Int J Cancer, 2020, 146(4): 987–998.

[38] Yi SW, Choi JS, Yi JJ, et al. Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: a prospective cohort study in Korea[J]. Cancer, 2018, 124(13): 2748–2757.

[39] 郭兰伟, 李霓, 王刚, 等. BMI 与恶性肿瘤发病风险的前瞻性队列研究[J]. 中华流行病学杂志, 2014, 35(3): 231–236.
Guo LW, Li N, Wang G, et al. Body mass index and cancer incidence: a prospective cohort study in northern China[J]. Chinese Journal of Epidemiology, 2014, 35(3): 231–236.

[40] 刘通, 魏垚臣, 梁明杨, 等. 不同体质量指数与消化系统肿瘤发病关系的多中心回顾性研究: 附 95177 例报告[J]. 中华消化外科杂志, 2019, 18(1): 74–82.
Liu T, Wei YC, Liang MY, et al. Correlation between different body mass indexs and incidence of digestive carcinoma: a multicentre retrospective study(a report of 95177 cases) [J]. Chinese Journal of Digestive Surgery, 2019, 18 (1): 74–82.

[41] Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U. S. adults [J]. N Engl J Med, 2003, 348(17): 1625–1638.

[42] Batty GD, Shipley MJ, Jarrett RJ, et al. Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study[J]. Int J Obes, 2005, 29(10): 1267–1274.

[43] Kuriyama S, Tsubono Y, Hozawa A, et al. Obesity and risk of cancer in Japan[J]. Int J Cancer, 2005, 113(1): 148–157.

[44] Rapp K,Schroeder J,Klenk J,et al. Obesity and incidence of cancer:a large cohort study of over 145,000 adults in Austria[J]. Br J Cancer,2005,93(9):1062-1067.
[45] N'kontchou G,Paries J,Htar MTT,et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis [J]. Clin Gastroenterol Hepatol,2006,4 (8):1062-1068.
[46] Petrick JL,Freedman ND,Demuth J,et al. Obesity,diabetes,serum glucose,and risk of primary liver cancer by birth cohort,race/ethnicity,and sex:multiphasic health checkup study[J]. Cancer Epidemiol,2016,42:140-146.
[47] Petrick JL,Thistle JE,Zeleniuch-Jacquotte A,et al. Body mass index,diabetes and intrahepatic cholangiocarcinoma risk:the Liver Cancer Pooling Project and meta-analysis [J]. Am J Gastroenterol,2018,113(10):1494-1505.
[48] Li ZY,Li HL,Ji XW,et al. Dose-response association between adiposity and liver cancer incidence:a prospective cohort study among non-smoking and non-alcohol-drinking Chinese women [J].Cancer Epidemiol Biomarkers Prev,2021,30(6):1200-1207.
[49] Wang Y,Wang B,Shen F,et al. Body mass index and risk of primary liver cancer:a meta-analysis of prospective studies[J]. Oncologist,2012,17(11):1461-1468.
[50] Xue K,Li FF,Chen YW,et al. Body mass index and the risk of cancer in women compared with men:a meta-analysis of prospective cohort studies [J]. Eur J Cancer Prev,2017,26(1):94-105.
[51] Rui R,Lou J,Zou L,et al. Excess body mass index and risk of liver cancer:a nonlinear dose-response meta-analysis of prospective studies[J]. PLoS One,2012,7(9):e44522.
[52] Yang C,Lu YF,Xia H,et al. Excess body weight and the risk of liver cancer:systematic review and a meta-analysis of cohort studies[J]. Nutr Cancer,2020,72(7):1085-1097.
[53] Chen Y,Wang X,Wang J,et al. Excess body weight and the risk of primary liver cancer:an updated meta-analysis of prospective studies [J]. Eur J Cancer,2012,48 (14):2137-2145.
[54] Yao KF,Ma M,Ding GY,et al. Meta-analysis reveals gender difference in the association of liver cancer incidence and excess BMI[J]. Nutr Cancer,2017,8(42):72959-72971.
[55] Gupta A,Das A,Majumder K,et al. Obesity is independently associated with increased risk of hepatocellular cancer-related mortality:a systematic review and meta-analysis[J]. Am J Clin Oncol,2018,41(9):874-881.
[56] Sohn W,Lee HW,Lee S,et al. Obesity and the risk of primary liver cancer:a systematic review and meta-analysis [J].Clin Mol Hepatol,2021,27(1):157-174.
[57] Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin [J].Proc Jpn Acad Ser B Phys Biol Sci,2010,86(2):131-141.
[58] Ashwell M. Obesity risk:importance of the waist-to-height ratio[J]. Nurs Stand,2009,23(41):49-54;quiz 55.
[59] Grundy SM. Metabolic syndrome update [J].Trends Cardiovasc Med,2016,26(4):364-373.
[60] Florio AA,Campbell PT,Zhang X,et al. Abdominal and gluteofemoral size and risk of liver cancer:the Liver Cancer Pooling Project[J]. Int J Cancer,2020,147(3):675-685.
[61] Pang Y,Kartsonaki C,Guo Y,et al. Central adiposity in relation to risk of liver cancer in Chinese adults:a prospective study of 0.5 million people[J]. Int J Cancer,2019,145(5):1245-1253.
[62] Wei L,Li N,Wang G,et al. Waist circumference might be a predictor of primary liver cancer:a population-based cohort study[J]. Front Oncol,2018,8:607.
[63] Rahmani J,Kord Varkaneh H,Kontogiannis V,et al. Waist circumference and risk of liver cancer:a systematic review and meta-analysis of over 2 million cohort study participants[J]. Liver Cancer,2020,9(1):6-14.
[64] Yang B,Petrick JL,Kelly SP,et al. Adiposity across the adult life course and incidence of primary liver cancer:the NIH-AARP cohort[J]. Int J Cancer,2017,141(2):271-278.
[65] Furer A,Afek A,Sommer A,et al. Adolescent obesity and midlife cancer risk:a population-based cohort study of 2.3 million adolescents in Israel[J]. Lancet Diabetes Endocrinol,2020,8(3):216-225.
[66] Berentzen TL,Gamborg M,Holst C,et al. Childhood body size and the risk of hepatocellular carcinoma[J]. J Hepatol,2012,56:S49.
[67] Hagström H,Tynelius P,Rasmussen F. High BMI in late adolescence predicts future severe liver disease:a national,population-based cohort study in 1.2 million men [J]. J Hepatol,2017,66(1):S71.
[68] Li Y,Yatsuya H,Yamagishi K,et al. Body mass index and weight change during adulthood are associated with increased mortality from liver cancer:the JACC study [J]. J Epidemiol,2013,23(3):219-226.
[69] Jia G,Shu XO,Liu Y,et al. Association of adult weight gain with major health outcomes among middle-aged Chinese persons with low body weight in early adulthood[J]. JAMA Netw Open,2019,2(12):e1917371.
[70] Fujiwara N,Nakagawa H,Kudo Y,et al. Sarcopenia,intramuscular fat deposition,and visceral adiposity indepen-

dently predict the outcomes of hepatocellular carcinoma[J]. J Hepatol,2015,63(1):131-140.

[71] Rong X,Wei F,Geng Q,et al. The association between body mass index and the prognosis and postoperative complications of hepatocellular carcinoma:a meta-analysis [J]. Medicine,2015,94(31):e1269.

[72] Cha B,Yu JH,Jin YJ,et al. Survival outcomes according to body mass index in hepatocellular carcinoma patient: analysis of nationwide cancer registry database [J]. Sci Rep,2020,10(1):8347.

[73] Prado CM,Gonzalez MC,Heymsfield SB. Body composition phenotypes and obesity paradox [J]. Curr Opin Clin Nutr Metab Care,2015,18(6):535-551.

[74] Cespedes Feliciano EM,Kroenke CH,Caan BJ. The obesity paradox in cancer:how important is muscle?[J]. Annu Rev Nutr,2018,38:357-379.

[75] Rothman KJ. BMI-related errors in the measurement of obesity[J]. Int J Obes,2008,32 Suppl 3:S56-S59.

[76] Lee DH,Giovannucci EL. The obesity paradox in cancer: epidemiologic insights and perspectives [J]. Curr Nutr Rep,2019,8(3):175-181.

[77] Sekula P,Del Greco MF,Pattaro C,et al. Mendelian randomization as an approach to assess causality using observational data [J]. J Am Soc Nephrol,2016,27(11): 3253-3265.

[78] Emdin CA,Khera AV,Kathiresan S. Mendelian randomization[J]. JAMA,2017,318(19):1925-1926.

[79] Brown JC,Cespedes Feliciano EM,Caan BJ. The evolution of body composition in oncology-epidemiology,clinical trials,and the future of patient care:facts and numbers [J]. J Cachexia Sarcopenia Muscle,2018,9(7):1200-1208.

[80] Di Sebastiano KM,Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer [J]. Appl Physiol Nutr Metab,2012,37(5):811-821.

[81] Strulov Shachar S,Williams GR. The obesity paradox in cancer-moving beyond BMI [J]. Cancer Epidemiol Biomarkers Prev,2017,26(1):13-16.

[82] Plank LD. Dual-energy X-ray absorptiometry and body composition [J]. Curr Opin Clin Nutr Metab Care,2005,8 (3):305-309.

[83] Hamaguchi Y,Kaido T,Okumura S,et al. Preoperative visceral adiposity and muscularity predict poor outcomes after hepatectomy for hepatocellular carcinoma [J]. Liver Cancer,2019,8(2):92-109.

[84] Montano-Loza AJ,Mazurak VC,Ebadi M,et al. Visceral adiposity increases risk for hepatocellular carcinoma in male patients with cirrhosis and recurrence after liver transplant[J]. Hepatology,2018,67(3):914-923.

[85] Kyle UG,Bosaeus I,De Lorenzo AD,et al. Bioelectrical impedance analysis—part I:review of princi ples and methods[J]. Clin Nutr,2004,23(5):1226-1243.

[86] Kyle UG,Bosaeus I,De Lorenzo AD,et al. Bioelectrical impedance analysis—part Ⅱ:utilization in clinical practice[J]. Clin Nutr,2004,23(6):1430-1453.

[87] El-Serag HB,Hampel H,Javadi F. The association between diabetes and hepatocellular carcinoma:a systematic review of epidemiologic evidence[J]. Clin Gastroenterol Hepatol,2006,4(3):369-380.

[88] Yang WS,Shu XO,Gao J,et al. Prospective evaluation of type 2 diabetes mellitus on the risk of primary liver cancer in Chinese men and women[J]. Ann Oncol,2013,24 (6):1679-1685.

[89] Pang Y,Kartsonaki C,Turnbull I,et al. Diabetes,plasma glucose,and incidence of fatty liver,cirrhosis,and liver cancer:a prospective study of 0. 5 million people[J]. Hepatology,2018,68(4):1308-1318.

[90] Ohkuma T,Peters SaE,Woodward M. Sex differences in the association between diabetes and cancer:a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events [J]. Diabetologia, 2018,61(10):2140-2154.

[91] El-Serag HB,Tran T,Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma [J]. Gastroenterology,2004,126(2):460-468.

[92] Jinjuvadia R,Patel S,Liangpunsakul S. The association between metabolic syndrome and hepatocellular carcinoma:systemic review and meta-analysis[J]. J Clin Gastroenterol,2014,48(2):172-177.

[93] Esposito K,Chiodini P,Colao A,et al. Metabolic syndrome and risk of cancer:a systematic review and meta-analysis [J]. Diabetes Care,2012,35(11):2402-2411.

[94] Marengo A,Rosso C,Bugianesi E. Liver cancer:connections with obesity,fatty liver,and cirrhosis[J]. Annu Rev Med,2016,67:103-117.

[95] Ertle J,Dechêne A,Sowa JP,et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis[J]. Int J Cancer,2011,128(10): 2436-2443.

[96] Guzman G,Brunt EM,Petrovic LM,et al. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis?[J]. Arch Pathol

Lab Med,2008,132(11):1761–1766.
[97] Florio AA,Ferlay J,Znaor A,et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012[J]. Cancer,2020,126(11):2666–2678.
[98] Welzel TM,Graubard BI,El-Serag HB,et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States:a population-based case-control study[J]. Clin Gastroenterol Hepatol,2007,5(10):1221–1228.
[99] Petrick JL,Yang B,Altekruse SF,et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the united states:a population-based study in seer-medicare [J]. PloS One,2017,12(10):e0186643.
[100] Welzel TM,Mellemkjaer L,Gloria G,et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population:a nationwide case-control study[J]. Int J Cancer,2007,120(3):638–641.
[101] Clements O,Eliahoo J,Kim JU,et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma:a systematic review and meta-analysis[J]. J Hepatol,2020,72(1):95–103.
[102] Aleksandrova K,Stelmach-Mardas M,Schlesinger S. Obesity and liver cancer [J]. Recent Results Cancer Res,2016,208:177–198.
[103] Wree A,Kahraman A,Gerken G,et al. Obesity affects the liver-the link between adipocytes and hepatocytes [J]. Digestion,2011,83(1–2):124–133.
[104] Eguchi Y,Mizuta T,Sumida Y,et al. The pathological role of visceral fat accumulation in steatosis,inflammation,and progression of nonalcoholic fatty liver disease [J]. J Gastroenterol,2011,46 Suppl 1:70–78.
[105] Tanaka S,Mohr L,Schmidt EV,et al. Biological effects ofhuman insulin receptor substrate-1 overexpression in hepatocytes[J]. Hepatology,1997,26(3):598–604.
[106] LeRoith D,Baserga R,Helman L,et al. Insulin-like growth factors and cancer[J]. Ann Intern Med,1995,122(1):54–59.
[107] Qiao L,Li X. Role of chronic inflammation in cancers of the gastrointestinal system and the liver:where we are now [J]. Cancer Lett,2014,345(2):150–152.
[108] Marra F,Tacke F. Roles for chemokines in liver disease [J]. Gastroenterology,2014,147(3):577–594,e571.
[109] Greenberg AS,Obin MS. Obesity and the role of adipose tissue in inflammation andmetabolism[J]. Am J Clin Nutr,2006,83(2):461S–465S.
[110] Calle EE,Kaaks R. Overweight,obesity and cancer:epidemiological evidence andproposed mechanisms [J]. Nat Rev Cancer,2004,4(8):579–591.
[111] Aleksandrova K,Nimptsch K,Pischon T. Influence of obesity and related metabolicalterations on colorectal cancer risk[J]. Curr Nutr Rep,2013,2(1):1–9.
[112] Jung UJ,Choi MS. Obesity and its metabolic complications:the role of adipokines and the relationship between obesity,inflammation,insulin resistance,dyslipidemia andnonalcoholic fatty liver disease [J]. Int J Mol Sci,2014,15(4):6184–6223.
[113] Abenavoli L,Peta V. Role of adipokines and cytokines in non-alcoholic fatty liverdisease[J]. Rev Recent Clin Trials,2014,9(3):134–140.