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「壽美降脂一號膠囊(LipoCol Forte)」降低肝癌風險：一項以傾向分數配對、以全國人口爲對象的世代研究

LipoCol Forte capsules reduce the risk of liver cancer: A propensity score-matched, nationwide, population-based cohort study

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摘要

背景：肝癌是全球五大最常見的癌症之一。降血脂藥物如 statin 類藥物可以降低肝癌的風險，但也可能造成肝損傷。在臨床研究中，LipoCol Forte膠囊(LFC)，一種紅麴製品，已經顯示出顯著的降膽固醇作用和良好的安全性。

目的：本研究旨在評估 LFC 是否降低成年人肝癌的風險，並進行傾向評分配對，以全國人口為對象的世代研究。

方法：使用台灣國民健保研究資料庫的數據，該數據庫包含了台灣 99.99% 人口的電子醫療記錄。在 2010 年 1 月至 2017 年 12 月之間，我們通過傾向評分將 LFC 使用者和非使用者(對照組)以 1:1 的比例進行匹配。所有人至少有 1 年的追蹤資料。統計分析比較了性別、年齡、共病症和處方藥物等人口分布情況。Cox迴歸分析在調整潛在混雜因素後估計了調整後風險比(aHR)。

結果：我們納入了 33231 名 LFC 使用者和 33231 名非 LFC 使用者(對照組)。在研究組和對照組之間並未發現共病症和藥物使用方面的顯著差異(標準化平均差異SMD< 0.05)。追蹤期間，LFC組的肝癌發生率顯著低於對照組(aHR 0.91；95%信賴區間CI：0.86-0.95;P < 0.001)。與非LFC組相比，LFC組的女性(aHR 0.87;95%CI：0.8-0.94；P < 0.001)和男性(aHR 0.93;95%CI：0 .87-0.98;P < 0.01)的肝癌風險均顯著降低。抗腫瘤保護效果也適用於有共病症(包括高血壓、缺血性中風、糖尿病、高脂血症、B 型肝炎感染和C型肝炎感染)的病患。使用 LFC 超過84天的病患與對照組相比，罹患肝癌的風險降低了 0.64 倍(P < 0.001)。與對照組相比，LFC組發展肝癌的風險隨著時間的推移逐漸降低；追蹤時間超過6年的LFC使用者的肝癌發生率最低(27.44 vs 31.49 每1,000人年；aHR 0.75；95%CI：0.68-0.82；P < 0.001)。

結論：這項回溯性世代研究顯示，LFC 對降低肝癌風險具有顯著的保護作用，且具有劑量依存性和時間依存性。

前言

LipoCol Forte 膠囊(LFC)是紅麴的產品，紅麴是利用酵母(主要是紫紅菌株)發酵製成的[1]。亞洲國家和地區，包括中國、日本和台灣，傳統上使用紅麴製作米酒，增加食物調味，並用作食品色素。中醫傳統藥學將紅麴用於助消化劑，促進血液循環和緩解濕氣。這種發酵米含有幾種monacolin、GABA、類黃酮、色素(如Monascorubramine與Rubropunctamine)、聚酮和Dimerumic acid (DMA)[2,3]。Monacolins以其降血脂特性而聞名。特別是 Monacolin K 通過抑制膽固醇合成途徑的速率控制酶 HMG-CoA 降低膽固醇[1]。著名的降脂藥物Lovastatin主要就是Monacolin K。LFC已獲得台灣食藥署核發降血脂的適應症[4]。每顆600毫克的LFC膠囊含有相當於5.76 毫克的 Lovastatin，口服建議劑量是每日兩次[4]。在一項 79名高脂血症患者參與的台灣臨床試驗中，每日兩次服用紅麴膠囊（600毫克）的LFC 療法在 4 週和 8 週後與服用安慰劑者相比顯著降低了低密度脂蛋白（LDL）膽固醇、總膽固醇、甘油三酯和apo B的數值，且無重大的副作用[5]。在另一項有1530名具高血壓和心肌梗塞病史的老年病患參加的中國冠心病二級預防研究中，紅麴的部分萃取物通過降低LDL和總膽固醇數值降低了心血管疾病和

全因死亡的發生率[6]。

根據 2019 年《全球疾病、傷害和危險因素研究報告》，肝癌是全球五大導致失能調整生命年損失的癌症之一[7]。肝癌的危險因素包括病毒性肝炎（例如B型肝炎和C型肝炎）、寄生蟲感染、酒精、毒素（例如黃麴毒素、農藥）和胰島素阻抗[8]。在東亞地區，B型和C型肝炎感染是I肝癌發展的主要原因[8]。非酒精性脂肪肝疾病（NAFLD）已被多項研究報告為肝癌的重要危險因素[9]。與氧化壓力以及脂毒性有關的代謝功能障礙促進了慢性肝炎和纖維化，進而增加了NAFLD相關肝細胞癌（HCC）的風險[9]。最近的研究發現，降血脂治療藥物，如statin類藥物，與較低的HCC風險有關[10]。然而，這些藥物與不良反應，如肝指數上升、肌痛和誘發糖尿病的效應 [11] 相關。當 statin 類藥物與 CYP450 3A4 抑制劑同時使用時，不良藥物反應的風險可能增加，因此一些患者為了減少肌痛和其他藥物相關的毒性風險而停用statin類藥物[11]。

紅麴製品具有類似的降血脂效果，同時具有安全性上的優勢[12]。到目前為止，尚未有研究報導紅麴對肝癌風險的預防作用。我們是第一個提出紅麴萃取物LFC透過降低血脂減少肝癌發生率的研究。鑒於癌症發展需要時間，我們決定使用台灣國民健康保險研究資料庫(NHIRD)的數據進行一項以全人口為基礎的回溯性世代研究，探討LFC使用與肝癌發生之間的關聯。

材料與方法

資料來源與倫理審核

本研究分析的資料來自台灣的全民健保資料庫(NHIRD)，該資料庫成立於1995年，目前包含了高達台灣人口的99.99%，其中包括每位受益人的電子病歷記錄、人口統計資料、住院與門診健康照護資訊、診斷代碼以及處方詳細資料。在2016年之前，NHIRD使用的診斷代碼為國際疾病第九版臨床修訂版(ICD-9-CM)，自2016年起改為第十版(ICD-10)。本研究已獲得中國醫藥大學台中地區的中央區域研究倫理委員會批准(CMUH109-REC2-031(CR2))。NHIRD中包含的個人資料皆以加密方式處理，因此可以免除獲取知情同意的要求。

研究人口

本病例群由2010年1月至2017年12月期間使用LFC(ATC：A047152)的用戶組成。病例群的索引日期定義為首次處方LFC的日期，而對於非使用LFC的對照組，索引日期則為研究期間內的隨機日期。年齡小於20歲、在索引日期之前已被診斷患有肝癌或任何其他癌症，或在使用LFC後的1年內被診斷患有肝癌並在索引日期之前退出保險計劃的患者均被排除。每位病例群中的患者均按照1：1的比例（性別、年齡（每5年一組）、基線共病症、藥物使用以及索引年）與對照組進行頻率匹配（圖1）。

主要結果與相關變數

此研究的主要結果為肝癌（ICD-9-CM代碼155.0、155.1、155.2；ICD-10-CM代碼C220、C221、C228、C229）。本研究的結束日期為患者被診斷患有肝癌、因退出NHIRD或死亡而失去隨訪資料，或截至2017年12月31日止。所有疾病代碼，包括主要結果和基線共病症，均定義為至少2次門診診治或1次住院入院。共病症包括高血壓（I

CD-9-CM 代碼 401-405；ICD-10-CM 代碼 I10、I11.0、I11.9、I12.0、I12.9、I13.0、I13.10、I13.11、I15.0、I15.1、I15.8、I15.9）、冠心病（ICD-9-CM代碼410-414；ICD-10-CM代碼I20.0、I20.1、I20.8、I20.9、I21. I22、I24.1、I24.8、I24.9、I25.1、I25.2）、缺血性中風（ICD-9-CM代碼433、434、436、437；ICD-10-CM代碼I63、I65、I66、I67、I68、G46.3-G46.8）、出血性中風（ICD-9-CM 代碼 430、431、432；ICD-10-CM代碼I60-I62）、糖尿病（ICD-9-CM代碼250；ICD-10-CM代碼E08-E13）、高脂血症（ICD-9-CM代碼272；ICD-10-CM代碼E78）、腎功能不全（ICD-9-CM代碼585、586、588.8、588.9；ICD-10-CM代碼N18、N19、N25.8、N25.9）、肝硬化（ICD-9- CM代碼571.2、571.5、571.6；ICD-10-CM代碼K70.2、K70.30、K70.31、K74.0、K74.1、K74.2、K74.3、K74.4、K74.5、K74.60、K74.69）、酒精性肝損傷（ICD-9-CM 代碼 571.0、571.1、571.3；ICD-10-CM 代碼 K70.0、K70.10、K70.11、K70.40、K70.41、K70.0）、非酒精性脂肪性肝病（ICD-9-CM代碼571.8；ICD-10-CM代碼K74.4、K75.81、K76.0、K76.89）、B型肝炎（HBV）（ICD-9-CM代碼V02.61、070.20、070.22、070.30、070.32；ICD-10-CM代碼Z22.51、B16.2、B16.9、B18.1、B19.10、B19.11）和 C型肝炎（HCV）（ICD-9-CM代碼V02.62、070.41、070.44、070.51、070.54；ICD-10-CM代碼 Z22.52、B17.10、B17.11、B18.2、B19.20、B19.21）均進行了配對。我們還比較了研究組和對照組之間的藥物使用情況，包括statin類藥物（(simvastatin,lovastatin,fluvastatin, atorvastatin, pravastatin and rosuvastatin）、非statin類降脂藥物（cholestyramine, colestipol, colesevelam, nicolar, lipo-nicin,acipimox, probucol, gemfibrozil, bezafibrate, etofibrate, fenofibrate, and ezetimibe等)、aspirin、HBV治療（lamivudine, adefovir, entecavir, telbivudine,tenofovir and peg-interferon α 2a）和HCV治療(Harvoni, Sovaldi, Zepatier ,Maviret, Epclusa, Viekirax plus Exviera, Daklinza, Daklinza plus Sunvepra and Interferon plus Ribavirin），metformin以及thiazolidinedione(TZD) (Pioglitazone and Rosiglitazone).

統計分析

我們使用卡方鑑定比較LFC和非LFC群之間的基線人口統計特徵、共病症和藥物使用情況。類別變數以計數和百分比列出，連續變數的差異以均值和標準差呈現，並使用未配對的司徒頓t檢定評估差異。計算標準化平均差異（SMD）來評估 LFC 使用者與非LFC使用者之間各變數的差異。SMD值小於0.05表示兩個群之間差異微不足道。在本研究中，我們使用單變量和多變量Cox比例風險回歸模型計算風險比（HR）和95%信賴區間（CI）。多變量分析校正年齡、性別、共病症和藥物使用等變數。使用Kaplan-Meier方法估計肝癌的累積發病率，並使用R語言繪製累積發病率曲線。所有統計分析使用SAS統計軟體版本9.4（SAS Institute Inc.，Cary，NC，美國）進行。統計顯著性標準設定為P-value小於0.05。

結果

（表1）顯示了研究人口的基線人口統計特徵和共病症。我們在 LFC 群組中招募了33231名患者，在非LFC群組中招募了33231名對照者。LFC群組和非LFC群組中男性的比例相似(分別為52.46%和52.25%)；相應的平均年齡分別為62.75 ± 13.62歲和63.22 ± 13.60歲。研究對象主要年齡在50歲及以上。在共病症和藥物使用分佈方面，研究群組之間沒有顯著差異（SMD < 0.05）。

根據年齡、性別、共病症和藥物使用等因素分層分析患有肝癌的病人，結果顯示於(表2)中。在校正年齡、性別、共病症和藥物使用等因素後，LFC群組中肝癌的整體發生率顯著低於非LFC群組(每千人年19.26 vs 20.62；aHR 0.91；95% CI: 0.86-0.95；P < 0.001）。與非LFC群組相比，在LFC群組中女性（aHR 0.87；95% CI: 0.8-0.94；P < 0.001）和男性（aHR 0.93；95% CI: 0.87-0.98；P < 0.01）的肝癌風險均顯著降低。在50歲以上的亞組中，LFC使用者相較於非LFC使用者，其患肝癌的風險顯著降低（aHR 0.91；95% CI: 0.87-0.95；P < 0.001）。在針對共病症的分析中，與非LFC群組相比，患有高血壓（aHR 0.89；95% CI: 0.84-0.94；P < 0.001）、缺血性中風（aHR 0.9；95% CI: 0.81-0.99；P < 0.05）、糖尿病（aHR 0.92；95% CI:0.86-0.98；P=0.01）、高血脂症（aHR 0.93；95% CI: 0.87-1；P < 0.05）、B型肝炎病毒（HBV）感染（aHR 0.91；95% CI: 0.84-0.99；P < 0.05）或C型肝炎病毒（HCV）感染（aHR 0.9；95% CI: 0.82-0.98；P < 0.05）的LFC使用者患肝癌的風險顯著降低。在LFC使用其他藥物的患者中，與非LFC群組相比，使用阿斯匹靈（aspirin）（aHR 0.93；95% CI: 0.87-1；P < 0.05）或二甲雙胍（metformin）（aHR 0.92；95% CI: 0.85-0.99；P < 0.05）的患者罹患肝癌風險顯著降低。

如(表3)所示，當分析考慮了使用LFC藥物的天數並校正了人口統計學因素、共病症和藥物使用時，使用LFC藥物少於28天的患者患肝癌的風險降低了0.94倍；使用LFC藥物在28至84天之間的患者患肝癌的風險降低了0.79倍；使用LFC藥物超過84天的患者患肝癌的風險降低了0.64倍。在調整年齡、性別、所有列出的共病症和藥物後，根據每個LFC治療劑量進行分層，我們發現更高的累積LFC劑量和更長的持續服用時間對於預防肝癌的效果最為顯著(aHR 0.46；95% CI: 0.39-0.55)(表4)。當我們進一步將患者根據追蹤持續時間分成三組，包括2-3年、4-6年和6年以上(表5)，與非LFC群組相比，在LFC群組中罹患肝癌的風險隨著時間的推移逐漸下降；使用LFC藥物超過6年的患者中肝癌發生率最低(每千人年27.44 vs 31.49；aHR 0.75；95% CI: 0.68-0.82；P < 0.001。)(圖2)顯示在追蹤8年後，LFC群組的肝癌累積發病率顯著低於非LFC群組(P < 0.001)。

討論

雖然先前的研究已經顯示statin類藥物在降低肝細胞癌(HCC)風險方面具有益處，但這是第一個使用基於全人口的資料庫來顯示LFC藥物的使用在考慮了性別、年齡、共病症和藥物使用後，能顯著降低肝癌風險9%(aHR 0.91)的研究。此外，LFC藥物的保護效果是劑量依賴的，隨著LFC使用時間的延長，肝癌風險逐漸降低。

LFC是紅麴米的產物。紅麴米是一種傳統的中國食品，通過將紅麴黴菌與米一起發

酵而製成。紅麴米的主要活性成分是monacolin K(lovastatin)，該成分在紅麴米產品中包括LFC，具有良好的口服生體利用率[13]，在治療血脂異常和預防脂肪肝方面已被證實有效[14,15]。LFC預防代謝功能障礙的能力表明，該產品可能減少氧化壓力、慢性炎症和脂質毒性，從而預防肝癌的發展[9]。其他研究還指出，紅麴米有助於預防冠心病、糖尿病和癌症[16]。據報導，與紅麴黴菌發酵的米能夠通過降低雄激素合成酶的基因表達並誘導自噬來抑制前列腺癌[17,18]。其他研究還聲稱紅麴米對結腸癌、乳腺癌和肝癌也具有有益作用[19-21]。在另一項研究中，從紅麴米中提取的ankaflavin通過細胞週期阻滯似乎誘導細胞凋亡的方式抑制了人類肝癌細胞HepG2和A549的生長[21]。紅麴黴菌CWT715發酵萃取物在BNL細胞（小鼠肝癌）中表現出抗氧化活性，並通過誘導nm23-H1(非轉移蛋白23-H1)蛋白的表現而具有抗轉移和抗侵襲活性[22,23]。紅麴黴素和紅麴紅色素被報導對人類腎上皮細胞具有抗有絲分裂作用[24]。有趣的是，從與紅麴黴菌發酵的米中提取的氮菌酮化合物在等效濃度下對人類癌細胞表現出選擇性細胞毒性，而對正常細胞則沒有[25,26]。而腸道菌叢失調與肝癌的發生密切相關。較高的厚壁菌/拮抗菌比可能與較高的肝癌風險和nivolumab治療的較低反應相關[27]。紅麴米可以通過減少厚壁菌、拮抗菌和梭菌屬細菌的數量，並增加乳酸菌和隆頭菌屬細菌的數量，調節腸道菌群[28-31]。這種改善腸道菌叢組成的作用表明紅麴米有潛力預防肝癌的發生。因此，我們假設LFC不僅通過降低膽固醇水平，還通過直接的抗腫瘤作用來預防肝癌，可能的機轉包括細胞週期阻滯、抗有絲分裂和腸道菌群調節。

在亞組分析中，LFC使用對於男性和女性的效益都是顯著的，雖然LFC在女性中的保護作用似乎更明顯(aHR 0.87)而在男性中則是(aHR 0.93)。這可能是由於性別在肝癌方面存在差異，例如炎症導致的HCC，在男性發生的頻率比女性更高[32]。此外，性別差異也存在於代謝因子和HCC風險之間的關聯[33]。然而，我們觀察到LFC治療的顯示益處僅在50歲以上的年齡組中表現出來，這反應在較高年齡患者中被診斷出較多的肝癌病例。我們的分析考慮了重要的多重因素，包括所有降脂藥物、aspirin、二甲雙胍和TZD。以往的研究顯示，statin類藥物已經能夠降低肝癌發生率，HR值在0.4到0.72之間[10,34-36]。一項2013年在台灣進行的基於全人口的病例對照研究使用NHIRD數據顯示，statin類藥物使用將HCC的機率降低了28%(aHR 0.72)[36]。該研究還發現，lovastatin、simvastatin和atorvastatin等各種statin類藥物都顯著降低了HCC的風險[36]。在我們的研究中，由於LFC與statin類藥物具有相似的藥理途徑，因此LFC的使用在患有高血壓、冠心病、缺血性中風、出血性中風、糖尿病、HBV和HCV感染等共病症的患者中對抗肝癌的發展具有保護作用。

在沒有重大肝癌風險(例如肝硬化、酒精性肝損傷、非酒精性脂肪肝病、乙型或丙型肝炎感染)的患者中，LFC對於預防肝癌顯示出保護效果（aHRs 0.83-0.9）。我們的結果顯示，即使是被認為處於「低風險」肝癌的患者，使用LFC也是適當的。LFC 對於使用statin類和非statin類降脂藥物的患者都有益處。然而，由於案例數量有限或不同類型的降脂藥物之間存在相似的作用機制，只有非使用statin類降脂藥物的患者達到統計學意義（statin類降脂藥物組的aHR為0.91，非statin類降脂藥物組的aHR為0.9）。

之前已有報告稱阿斯匹林在增加劑量和使用時間的情況下可以降低肝細胞癌的風險[37]，這與我們觀察到的結果相似，aHR範圍在0.61到0.73之間。值得注意的是，即使沒有接受B型或C型肝炎治療的患者仍然可以從LFC使用中獲得顯著的益處（HBV非治療組的aHR為0.83，HCV非治療組的aHR為0.91）。然而，B型和C型肝炎治療組沒有達到統計學意義，這可能是因為B型和C型肝炎的治療減緩了肝癌的進展，潛在地掩蓋了LFC所引起的保護效應。此外，2016年前台灣的全民健康保險並未涵蓋直接作用的抗病毒藥物。因此，在我們的研究中，只納入了8個案例，因此無法得出任何有意義的結論。

研究報告指出二甲雙胍和TZD藥物降低了肝細胞癌的風險，其 aHR 範圍在 0.49 到 0.72之間[38-41]。因此，我們在混雜因素的分析中包含了這些藥物，以排除可能的相互作用。我們觀察到LFC使用和肝癌發生率之間存在明顯的劑量-反應關係，分別為使用LFC不超過28天的患者的aHR為0.94，使用28-84天的患者的aHR為0.79，使用超過84天的患者的aHR為0.64。我們的結果與其他藥物-肝細胞癌預防研究的報告相似[36,38]。在4-6年的子組中，與非使用LFC的患者相比，LFC使用者的肝癌累積發病率逐漸降低(aHR為0.92；$P < 0.05$)，在超過6年的子組中也是如此(aHR為0.75；$P < 0.001$)。這些發現表明，LFC使用降低了長期內發展肝癌的風險。 台灣的全民健康保險（NHI）是一個涵蓋幾乎全國人口的全民醫療保險制度。這個大型數據庫增加了產生具有說服力的患者數據的可能性，並且可以進行性別、年齡、共病症和藥物使用的調整。然而，這項研究也有一些限制需要注意。首先，我們使用ICD-9-CM (2010年至2015年) 和 ICD-10-CM(2016年至2017年)算法來定義由臨床醫師診斷的疾病。我們只包括在單次住院後經過正確ICD-9-CM或ICD-10-CM編碼的患者，或在兩次門診就診後經過編碼，以增加共病診斷的有效性和準確性。肝癌主要結果的診斷是通過Catastrophic Illness Patient Database資料庫進行了雙重檢查。其次，NHIRD數據缺乏重要的潛在混淆因素資訊，包括身體質量指數、肝硬化程度、肝炎病毒載量、酒精消耗、環境/化學暴露和家族病史。此外，生化數據、腹部超聲波報告、電腦斷層報告、肝癌分級和分期在台灣的NHI數據庫研究中無法確定。我們的患者人口特徵，肝硬化、酒精性肝損傷或B型/C型肝炎感染的比例，在各組之間並無顯著差異。因此，肝癌發生的背景風險可能對每個組都相似。然而，通過強調潛在的混淆因素，特別是藥物相互作用方面，我們的分析比之前的NHIRD研究更為先進。第三，儘管我們考慮了所有潛在的混淆因素，但由於本研究的觀察性質，無法直接推斷LFC和肝癌風險之間的因果關係。因此，我們排除了在研究開始後1年內診斷的肝癌。同時，我們也考慮了潛在的機制，如脂質代謝異常、直接抗腫瘤作用和腸道菌叢理論，作為我們發現的解釋，正如之前所提到的。需要進行長期的前瞻性臨床研究來確認我們的結果。

結論

這是第一項研究顯示使用LFC在考慮性別、年齡、共病症和藥物使用的分析中，顯著降低了肝癌風險，降低了9%。LFC的保護效果與劑量有關，因此我們的研究結果顯示，在8年的追蹤期間，LFC治療可能與降低肝癌風險有關。然而，仍需要進行長期研究來確認我們的發現。由於LFC是一種價格便宜且常用的產品，前瞻性臨床試驗是可行且必要的，以確認其對肝癌預防的益處。

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ORIGINAL ARTICLE

Retrospective Cohort Study

LipoCol Forte capsules reduce the risk of liver cancer: A propensity score-matched, nationwide, population-based cohort study

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Abstract

BACKGROUND

Liver cancer is among the top five most common cancers globally. Lipid-lowering drugs such as statins can lower the risk of liver cancer, but may also cause liver damage. LipoCol Forte capsules (LFC), a red yeast rice product, have de-

monstrated significant antihypercholesterolemic effects and a good safety profile in clinical studies.

AIM

To evaluate whether LFC lowers the risk of liver cancer in adults in this propensity score-matched, nationwide, population-based cohort study.

METHODS

We used data from Taiwan's National Health Insurance Research Database, which includes electronic medical records for up to 99.99% of Taiwan's population. LFC users and LFC non-users were matched 1:1 by propensity scores between January 2010 and December 2017. All had follow-up data for at least 1 year. Statistical analyses compared demographic distributions including sex, age, comorbidities, and prescribed medications. Cox regression analyses estimated adjusted hazard ratios (aHRs) after adjusting for potential confounders.

RESULTS

We enrolled 33231 LFC users and 33231 non-LFC users (controls). No significant differences between the study cohorts were identified regarding comorbidities and medications [standardized mean difference (SMD) < 0.05]. At follow-up, the overall incidence of liver cancer was significantly lower in the LFC cohort compared with controls [aHR 0.91; 95% confidence interval (CI): 0.86-0.95; $P < 0.001$]. The risk of liver cancer was significantly reduced in both females (aHR 0.87; 95%CI: 0.8-0.94; $P < 0.001$) and males (aHR 0.93; 95%CI: 0.87-0.98; $P < 0.01$) in the LFC cohort compared with their counterparts in the non-LFC cohort. The antitumor protective effects applied to patients with comorbidities (including hypertension, ischemic stroke, diabetes mellitus, hyperlipidemia, hepatitis B infection and hepatitis C infection). Those using LFC for more than 84 drug days had a 0.64-fold lower risk of liver cancer compared with controls ($P < 0.001$). Compared with controls, the risk of developing liver cancer in the LFC cohort progressively decreased over time; the lowest incidence of liver cancer occurred in LFC users followed-up for more than 6 years (27.44 *vs* 31.49 per 1,000 person-years; aHR 0.75; 95%CI: 0.68-0.82; $P < 0.001$).

CONCLUSION

This retrospective cohort study indicates that LFC has a significantly protective effect on lowering the risk of liver cancer, in a dose-dependent and time-dependent manner.

Key Words: LipoCol Forte capsules; Hyperlipidemia; Liver cancer; Hepatocellular carcinoma; Retrospective cohort study; Taiwan National Health Insurance Research Database

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Core Tip: LipoCol Forte capsules (LFC), a red yeast rice product, have lipid-lowering effects and good safety reports. Lipid-lowering therapies such as statins can lower the risk of liver cancer, but may also cause liver damage. We evaluated whether LFC lowers the risk of liver cancer in adults in this propensity score-matched, nationwide, population-based cohort study. The LFC cohort had a 9% lower incidence of liver cancer compared with controls; this lower risk was dose-dependent and time-dependent, with a 0.64-fold lower risk found in those using LFC for more than 84 drug days. The lowest incidence of liver cancer occurred in LFC users followed-up for more than 6 years.

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INTRODUCTION

LipoCol Forte capsules (LFC) are a product of red yeast rice, which is made by fermenting rice with yeasts, mainly *Monascus purpureus*[1]. Asian countries and territories, including China, Japan and Taiwan, have traditionally used red yeast to make rice wine, increase the intensity of food flavoring and as a food coloring. Traditional Chinese medicine uses red yeast rice as a digestive aid, to promote blood

and dimerumic acid[2,3]. Monacolins are known for their lipid-lowering qualities. In particular, monacolin K lowers cholesterol levels by inhibiting hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA), the rate-controlling enzyme of the cholesterol synthesis pathway[1]. The renowned lipid-lowering drug, lovastatin, is mainly monacolin K. LFC has received approval from the Taiwan Food and Drug Administration for the indication of antihyperlipidemia[4]. Each 600 mg capsule of LFC contains the equivalent of 5.76 mg of lovastatin and the recommended oral dose is twice daily[4]. In a Taiwanese study involving 79 patients with hyperlipidemia, twice-daily dosing with *Monascus purpureus* Went rice therapy (600 mg) LFC significantly reduced levels of low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides and apolipoprotein B levels after 4 and 8 weeks compared with placebo therapy, without any major side effects[5]. In another study involving 1530 elderly patients with hypertension and a history of myocardial infarction enrolled in the Chinese Coronary Secondary Prevention Study, a partial extract of red yeast rice reduced the incidence of cardiovascular events and all-cause mortality by lowering LDL and total cholesterol[6].

The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 reported that liver cancer was among the leading five cancers globally by disability-adjusted life years[7]. Risk factors for liver cancer include viral hepatitis (*e.g.*, hepatitis B and hepatitis C), parasitic infestation, alcohol, toxins (*e.g.*, aflatoxin, pesticides) and insulin resistance[8]. In East Asia, hepatitis B and C infections are major contributors to the development of liver cancer[8]. Nonalcoholic fatty liver disease (NAFLD) has been reported by several studies to be an important risk factor for liver cancer[9]. Metabolic dysfunction related to oxidative stress and lipotoxicity promote the development of chronic liver inflammation and fibrosis, and consequently increase the risk of NAFLD-related hepatocellular carcinoma (HCC)[9]. Recently, lipid-lowering therapies such as statins have been linked to a lower risk for HCC[10]. However, these drugs are associated with unwanted side effects such as elevated liver enzymes, myalgia and diabetogenic effects[11]. The risk of adverse drug reactions can increase when statins are co-administered with cytochrome P450 3A4 inhibitors, so some patients discontinue statins in order to decrease the risk of myopathy and other drug-related toxicities[11].

Similar lipid-lowering effects have been reported with red yeast rice products, with a safety advantage[12]. Up until now, no research has reported the preventive effects of red yeast rice on the risk for liver cancer. We are the first to propose that LFC, a red yeast rice extract, decreases the incidence of liver cancer *via* lipid-lowering benefits. In view of the time-consuming nature of cancer development, we decided to conduct a population-based retrospective cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) for this investigation into the association between LFC use and liver cancer occurrence.

MATERIALS AND METHODS

Data source and ethics approval

The data analyzed in this study were extracted from Taiwan's NHIRD, which was established in 1995 and now includes up to 99.99% of Taiwan's population with their electronic medical records. The database includes demographic data, comprehensive inpatient and outpatient health care information, diagnostic codes, and prescription details for each beneficiary. Prior to 2016, diagnoses in the NHIRD used the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM); since 2016, the Tenth Edition (ICD-10) has been used. This study was approved by the Central Regional Research Ethics Committee of China Medical University, Taichung, Taiwan [CMUH109-REC2-031(CR-2)]. The encrypted nature of all individual information contained in the NHIRD meant that informed patient consent could be waived.

Study population

The case cohort consisted of the LFC users (ATC: A047152) during the period from January 2010 through December 2017. For the case cohort, the index date was defined as the first date with a prescription of LFC, whereas for the LFC non-users the index date was a random date within the study period. Patients aged less than 20 years, who had been diagnosed with liver cancer or any other cancer before the index date, or diagnosed with liver cancer within 1 year of LFC use and withdrew from the insurance program before the index date were excluded. Each patient in the case cohort was frequency-matched with the controls (randomly selected from all NHI beneficiaries aged 20 years and more) at a 1:1 ratio by sex, age (every 5 years span), baseline comorbidities, medicine and the index year (Figure 1).

Main outcome and relevant variables

The main outcome of this cohort study was liver cancer (ICD-9-CM codes 155.0, 155.1, 155.2; ICD-10-CM codes C220, C221, C228, C229). The end date of this study was the date when the patients were diagnosed with liver cancer, were lost to follow-up due to withdrawal from the NHIRD or death, or until December 31, 2017. All disease codes including main outcomes and baseline comorbidities were

defined as at least 2 clinic visits or 1 inpatient admission. Comorbidities included hypertension (ICD-9-CM codes 401-405; ICD-10-CM codes I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I15.0, I15.1, I15.8, I15.9), coronary heart disease (ICD-9-CM codes 410-414; ICD-10-CM codes I20.0, I20.1, I20.8, I20.9, I21.

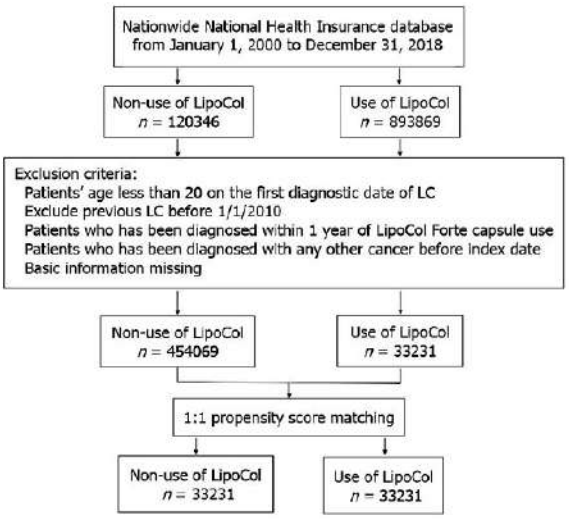

Figure 1 Flow chart of the enrollment of study subjects. LC: Liver cancer.

I22, I24.1, I24.8, I24.9, I25.1, I25.2), ischemic stroke (ICD-9-CM codes 433, 434, 436, 437; ICD-10-CM codes I63, I65, I66, I67, I68, G46.3-G46.8), hemorrhagic stroke (ICD-9-CM codes 430, 431, 432; ICD-10-CM codes I60-I62), diabetes mellitus (ICD-9-CM code 250; ICD-10-CM codes E08-E13), hyperlipidemia (ICD-9-CM code 272; ICD-10-CM code E78), renal insufficiency (ICD-9-CM codes 585, 586, 588.8, 588.9; ICD-10-CM codes N18, N19, N25.8, N25.9), cirrhosis (ICD-9-CM codes 571.2, 571.5, 571.6; ICD-10-CM codes K70.2, K70.30, K70.31, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69), alcoholic liver damage (ICD-9-CM codes 571.0, 571.1, 571.3; ICD-10-CM codes K70.0, K70.10, K70.11, K70.40, K70.41, K70.0), NAFLD (ICD-9-CM code 571.8; ICD-10-CM codes K74.4, K75.81, K76.0, K76.89), hepatitis B virus (HBV) infection (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, 070.32; ICD-10-CM codes Z22.51, B16.2, B16.9, B18.1, B19.10, B19.11) and hepatitis C virus (HCV) infection (ICD-9-CM codes V02.62, 070.41, 070.44, 070.51, 070.54; ICD-10-CM codes Z22.52, B17.10, B17.11, B18.2, B19.20, B19.21) were matched. We also compared medication use between the study groups for statins (simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin), non-statin lipid-lowering drugs (cholestyramine, colestipol, colesevelam, nicolar, lipo-nicin, acipimox, probucol, gemfibrozil, bezafibrate, etofibrate, fenofibrate, and ezetimibe), aspirin, HBV treatments (lamivudine, adefovir, entecavir, telbivudine, tenofovir and peg-interferon α-2a) and HCV treatments (Harvoni, Sovaldi, Zepatier, Maviret, Epclusa, Viekirax plus Exviera, Daklinza, Daklinza plus Sunvepra and Interferon plus Ribavirin), metformin and thiazolidinedione (TZD) (Pioglitazone and Rosiglitazone).

Statistical analysis

We used the Chi-square test to compare baseline demographic characteristics, comorbidities and medication status between the LFC and non-LFC cohorts. Categorical variables are listed as counts and percentages; the differences in continuous variables are presented as the means and standard deviations, and were evaluated using the unpaired Student's *t*-test. The standardized mean difference (SMD) was calculated to assess the difference of each variable between the LFC users and non-LFC users. An SMD value of less than 0.05 indicated a negligible difference between the two cohorts. In this study, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) in univariate and multivariate Cox proportional hazard regression models. Multivariate analysis adjusted for the variables of age, sex, comorbidities and medications. The Kaplan–Meier method was used to estimate the cumulative incidence of liver cancer; the cumulative incidence curve was plotted by R software. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, United States) was used for all statistical analyses. Statistical significance was set as a *P* value of less than 0.05.

Table 1 Demographic characteristics and comorbidities for non-LipoCol Forte capsules users and LipoCol Forte capsules user populations in Taiwan between 2010 and 2017

Variables	Non-LFC users (*n* = 33231)		LFC users (*n* = 33231)		SMD
	n	%	*n*	%	
Sex					
Female	15869	47.75	15798	47.54	0.004
Male	17362	52.25	17433	52.46	0.004
Age (yr)					
20-29	300	0.90	319	0.96	0.006
30-39	1434	4.32	1545	4.65	0.016
40-49	3677	11.07	3816	11.48	0.013
> 50	27820	83.72	27551	82.91	0.022
mean (SD)	63.22	13.60	62.75	13.62	0.035

Comorbidities					
Hypertension	21195	63.78	20825	62.67	0.023
Coronary heart disease	11255	33.87	10972	33.02	0.018
Ischemic stroke	6902	20.77	6784	20.41	0.009
Hemorrhagic stroke	816	2.46	939	2.83	0.023
Diabetes mellitus	12348	37.16	12172	36.63	0.011
Hyperlipidemia	16793	50.53	16196	48.74	0.036
Renal insufficiency	4028	12.12	4007	12.06	0.002
Cirrhosis	2585	7.78	2643	7.95	0.007
Alcoholic liver damage	2554	7.69	2606	7.84	0.006
Nonalcoholic fatty liver disease	1648	4.96	1825	5.49	0.024
HBV infection	3239	9.75	3342	10.06	0.010
HCV infection	2061	6.20	2196	6.61	0.017
Medications					
Statin	12008	36.13	11666	35.11	0.022
Non-statin lipid-lowering drug	6339	19.08	6161	18.54	0.014
Aspirin	15564	46.84	15330	46.13	0.014
HBV treatment	1531	4.61	1572	4.73	0.006
HCV treatment	7	0.02	10	0.03	0.006
Metformin	8674	26.10	8469	25.49	0.014
Thiazolidinediones	2533	7.62	2483	7.47	0.006

Student's *t*-test. LFC: LipoCol Forte capsules; SMD: Standardized mean difference (a standardized mean difference of 0.05 or less indicates a negligible difference); SD: Standard deviation; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

RESULTS

Baseline demographics and comorbidities of the study population are shown in Table 1. We enrolled 33231 patients in the LFC cohort and 33231 controls in the non-LFC cohort. Similar proportions in the LFC cohort and non-LFC cohort were male (52.46% and 52.25%, respectively); corresponding mean ages were 62.75 ± 13.62 years and 63.22 ± 13.60 years, respectively. The study subjects were predominantly aged 50 years and over. No significant differences between the study cohorts were observed for the distributions of comorbidities and medications (SMD < 0.05).

Analyses stratified for demographic characteristics, comorbidities and medications in the patients with liver cancer are shown in Table 2. In analyses adjusting for age, sex, comorbidities and medications, the overall incidence of liver cancer was significantly lower in the LFC cohort than in the non-LFC cohort (19.26 *vs* 20.62 per 1000 person-years; aHR 0.91; 95%CI: 0.86-0.95; $P < 0.001$). The risk of liver cancer was significantly reduced in both females (aHR 0.87; 95%CI: 0.8-0.94; $P < 0.001$) and males

Table 2 Incidence rates, hazard ratios and 95% confidence intervals of liver cancer, stratified by sex, age, comorbidities and medications, comparing LipoCol Forte capsules users with non-LipoCol Forte capsules users

	Non-LFC users			LFC users			Crude			Adjusted		
Variable	Event	Person-years	IR	Event	Person-years	IR	cHR	95%CI	Pvalue	aHR[1]	95%CI	Pvalue
Overall	3848	186604	20.62	3700	192122	19.26	0.89	(0.85,0.94)[c]	< 0.001	0.91	(0.86, 0.95)[c]	< 0.001
Sex												
Female	1416	91487	15.48	1267	94190	13.45	0.83	(0.77,0.9)[c]	< 0.001	0.87	(0.8, 0.94)[c]	< 0.001
Male	2432	95117	25.57	2433	97932	24.84	0.93	(0.88,0.99)[a]	0.014	0.93	(0.87,0.98)[b]	0.008
Age (yr)												
20-29	11	1884	5.84	9	2054	4.38	0.67	(0.27, 1.68)	0.396	0.61	(0.24, 1.59)	0.313
30-39	68	8881	7.66	77	9854	7.81	0.96	(0.69, 1.34)	0.827	0.79	(0.56, 1.11)	0.178
40-49	285	22392	12.73	290	23617	12.28	0.95	(0.8, 1.12)	0.508	0.91	(0.77, 1.07)	0.249
> 50	3484	153447	22.71	3324	156597	21.23	0.89	(0.85,0.94)[c]	< 0.001	0.91	(0.87, 0.95)[c]	< 0.001
Comorbidities												
Hypertension												
No	1169	69398	16.85	1281	73107	17.52	1	(0.92, 1.08)	0.910	0.93	(0.86, 1.01)	0.090
Yes	2679	117206	22.86	2419	119015	20.33	0.85	(0.81,0.9)[c]	< 0.001	0.89	(0.84,0.94)[c]	< 0.001

Coronary heart disease											
No	2455	124923	19.65	2413	130037	18.56	0.9	(0.85,0.95)[c]	< 0.001	0.88	(0.84,0.94)[c]	< 0.001
Yes	1393	61681	22.58	1287	62085	20.73	0.89	(0.83,0.96)[b]	0.004	0.94	(0.87, 1.02)	0.143
Ischemic stroke												
No	3002	149577	20.07	2983	154633	19.29	0.92	(0.87,0.97)[b]	0.001	0.91	(0.86,0.96)[c]	< 0.001
Yes	846	37027	22.85	717	37489	19.13	0.8	(0.73,0.89)[c]	< 0.001	0.9	(0.81,0.99)[a]	0.033
Hemorrhagic stroke												
No	3738	182382	20.50	3586	187046	19.17	0.89	(0.85,0.94)[c]	< 0.001	0.9	(0.86,0.95)[c]	< 0.001
Yes	110	4222	26.05	114	5076	22.46	0.86	(0.66, 1.12)	0.265	1	(0.76, 1.32)	0.992
Diabetes mellitus												
No	2023	119363	16.95	1972	124172	15.88	0.9	(0.84,0.96)[c]	< 0.001	0.89	(0.84,0.95)[c]	< 0.001
Yes	1825	67241	27.14	1728	67950	25.43	0.9	(0.84,0.96)[b]	0.001	0.92	(0.86,0.98)[a]	0.010
Hyperlipidemia												
No	1986	92314	21.51	1980	98628	20.08	0.9	(0.84,0.96)[c]	< 0.001	0.89	(0.83,0.94)[c]	< 0.001
Yes	1862	94290	19.75	1720	93494	18.40	0.89	(0.83,0.95)[c]	< 0.001	0.93	(0.87,1)[a]	0.040
Renal insufficiency												
No	3319	165852	20.01	3221	170964	18.84	0.9	(0.86,0.95)[c]	< 0.001	0.9	(0.85,0.94)[c]	< 0.001
Yes	529	20752	25.49	479	21158	22.64	0.86	(0.76,0.97)[a]	0.016	0.96	(0.85, 1.1)	0.580
Cirrhosis												
No	2514	174893	14.38	2314	180074	12.85	0.84	(0.8,0.89)[c]	< 0.001	0.83	(0.79,0.88)[c]	< 0.001
Yes	1334	11711	113.91	1386	12048	115.04	0.98	(0.91, 1.06)	0.606	1	(0.93, 1.08)	0.921
Alcoholic liver damage												
No	3297	173575	19.00	3164	178842	17.69	0.89	(0.84,0.93)[c]	< 0.001	0.88	(0.84,0.93)[c]	< 0.001
Yes	551	13029	42.29	536	13281	40.36	0.95	(0.85, 1.07)	0.432	1	(0.88, 1.13)	0.970
Nonalcoholic fatty liver disease												
No	3553	177753	19.99	3404	182155	18.69	0.89	(0.85,0.94)[c]	< 0.001	0.9	(0.86,0.94)[c]	< 0.001
Yes	295	8851	33.33	296	9967	29.70	0.86	(0.73, 1.01)	0.06	0.92	(0.78, 1.09)	0.322
HBV infection												
No	2604	170246	15.30	2501	175001	14.29	0.89	(0.84,0.94)[c]	< 0.001	0.88	(0.83,0.93)[c]	< 0.001
Yes	1244	16359	76.05	1199	17121	70.03	0.89	(0.82,0.96)[b]	0.003	0.91	(0.84,0.99)[a]	0.025
HCV infection												
No	2784	176772	15.75	2658	181323	14.66	0.89	(0.84,0.94)[c]	< 0.001	0.88	(0.83,0.93)[c]	< 0.001
Yes	1064	9832	108.22	1042	10799	96.49	0.85	(0.78,0.92)[c]	< 0.001	0.9	(0.82,0.98)[a]	0.016
Medication												
Statins												
No	2693	120440	22.36	2681	125954	21.29	0.91	(0.87,0.97)[b]	0.001	0.91	(0.86,0.96)[c]	< 0.001
Yes	1155	66164	17.46	1019	66168	15.40	0.84	(0.77,0.92)[c]	< 0.001	0.92	(0.84, 1)	0.058
Non-statin lipid-lowering drugs												
No	3203	151343	21.16	3080	157120	19.60	0.89	(0.85,0.93)[c]	< 0.001	0.9	(0.86,0.95)[c]	< 0.001
Yes	645	35261	18.29	620	35003	17.71	0.92	(0.82, 1.03)	0.135	0.94	(0.84, 1.05)	0.295
Aspirin												
No	1947	101738	19.14	1935	105708	18.31	0.91	(0.86,0.97)[b]	0.004	0.88	(0.83,0.94)[c]	< 0.001
Yes	1901	84866	22.40	1765	86414	20.43	0.88	(0.82,0.94)[c]	< 0.001	0.93	(0.87,1)[a]	0.043
HBV treatment												
No	2971	179610	16.54	2788	184920	15.08	0.87	(0.82,0.91)[c]	< 0.001	0.83	(0.79,0.88)[c]	< 0.001
Yes	877	6994	125.40	912	7203	126.62	0.97	(0.89, 1.07)	0.592	0.99	(0.9, 1.09)	0.807
HCV treatment												
No	3843	186594	20.60	3697	192084	19.25	0.89	(0.86,0.94)[c]	< 0.001	0.91	(0.87,0.95)[c]	< 0.001
Yes	5	10	487.00	3	39	77.83	0.21	(0.04, 1.07)	0.060	NA	NA	1
Metformin												
No	2471	140106	17.64	2413	145474	16.59	0.9	(0.85,0.96)[c]	< 0.001	0.9	(0.85,0.95)[c]	< 0.001
Yes	1377	46498	29.61	1287	46648	27.59	0.89	(0.82,0.96)[b]	0.002	0.92	(0.85,0.99)[a]	0.033
Thiazolidinediones												
No	3453	173105	19.95	3331	178541	18.66	0.89	(0.85,0.94)[c]	< 0.001	0.91	(0.87,0.95)[c]	< 0.001
Yes	395	13499	29.26	369	13581	27.17	0.9	(0.78,1.04)	0.141	0.89	(0.77, 1.03)	0.110

[1]Adjusted in multivariate analysis by sex, age, comorbidities and medications.

[a]$P < 0.05$.

[b]$P < 0.01$.

[c]$P < 0.001$.

LFC: LipoCol Forte capsules; IR: Incidence rate per 1000 person-years; cHR: Crude hazard ratio; aHR: Adjusted hazard ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Not available.

As shown in Table 3, when analyses assessed the risk of developing liver cancer stratified by days of LFC use and adjusted for demographic factors, comorbidities and medications, the risk of liver cancer was 0.94-fold lower among patients using LFC for fewer than 28 drug days; 0.79-fold lower among those using LFC for any time between 28 and 84 drug days and 0.64-fold lower among those using LFC for more than 84 drug days with medication consumption. After adjusting for age, sex, all comorbidities and medications listed, stratified with each dose of LFC treatment, we found that a higher cumulative dosage of LFC and longer duration had the most protective effects against the development of liver cancer (aHR 0.46; 95%CI: 0.39-0.55) (Table 4). When we further stratified the patients by duration of follow-up into three groups including 2-3 years, 4-6 years and beyond 6 years (Table 5), the risk of developing liver cancer in the LFC cohort progressively decreased over time compared with the risk in the non-LFC cohort; the lowest incidence of liver cancer occurred in LFC users followed-up for more than 6 years (27.44 *vs* 31.49 per 1000 person-years; aHR 0.75; 95%CI: 0.68-0.82; $P < 0.001$). Figure 2 shows the significantly lower cumulative incidence of liver cancer in the LFC cohort compared with the non-LFC cohort after 8 years of follow-up ($P < 0.001$).

DISCUSSION

Although previous studies have shown a benefit with statins in reducing the risk of HCC, this is the first study using a population-based database to show that LFC use significantly decreased the risk of liver cancer by 9% (aHR 0.91) in analyses adjusted for sex, age, comorbidities and medication use. Furthermore, the protective effect of LFC use was dose-dependent, with a progressively lower risk of liver cancer seen with prolonged LFC use.

LFC is a product of red yeast rice. Red yeast rice is a traditional Chinese food that is created by fermenting a red yeast strain (most commonly *Monascus purpureus*) with rice. The major active component in red yeast rice is monacolin K (lovastatin), which has demonstrated good oral bioavailability in red yeast rice products, including LFC[13], and has proven efficacy in the management of dyslipidemia and prevention of steatohepatitis[14,15]. The ability of LFC to prevent metabolic dysfunction suggests that this product may reduce oxidative stress, chronic inflammation and lipid toxicities, and thus prevent liver cancer development[9]. Other research has also suggested that red yeast rice helps to prevent coronary heart disease, diabetes mellitus and cancer[16]. Rice fermented with *Monascus purpureus* reportedly inhibits prostate cancer by decreasing gene expression of androgen-synthesizing enzymes and inducing autophagy[17,18]. Other research also claims beneficial effects of red yeast rice in colon cancer, breast cancer and liver cancers[19-21]. In another study, ankaflavin extracted from *Monascus*-fermented red rice inhibited the growth of human cancer cell lines Hep G2 and A549 by cell cycle arrest and appeared to induce apoptosis[21]. *Monascus purpureus* CWT715 fermented extract has demonstrated antioxidation activity in the BNL cell line (mouse liver cancer) and antimigratory, antiinvasive activities in SK-Hep-1 human hepatocarcinoma cells by inducing nm²3-H1 (non-metastasis protein 23-H1) protein expression[22,23]. Rubropunctamine and monascorubramine, the red *Monascus* pigments, reportedly induce antimitotic effects on immortalized human kidney epithelial cells[24]. Interestingly, azaphilone compounds extracted from rice fermented with *Monascus purpureus* have shown selective cytotoxicity in human cancer cells and not in normal cells at equivalent concentrations[25,26]. Dysbiosis is correlated to liver carcinogenesis. A higher Firmicutes/Bacteroidetes ratio might be associated with a higher liver cancer risk and lower response rate to nivolumab treatment [27]. Red yeast rice can modulate gut microbiota by decreasing *Firmicutes*, *Bacteroidetes*, and *Clostridium* species and increasing *Lactobacillus* and *Ruminococcacea*[28-31]. This amelioration of gut microbiota composition shows that red yeast rice has the potential to prevent liver cancer occurrence. Thus, we hypothesized that LFC can prevent liver cancer not only by lowering cholesterol levels, but also *via* direct antitumor effects with possible mechanisms including cell cycle arrest, antimitotic and gut microbiota modulation.

In subgroup analysis, the benefit of LFC use was significant in both males and females, although LFC appeared to be more protective in females (aHR 0.87) than in males (aHR 0.93). This might be due to sex differences in liver cancer, as for instance is the case with inflammation-driven HCC, which occurs more often in males than in females[32]. Moreover, gender differences exist in the association between metabolic factors and HCC risk[33]. However, we observed significant benefits with LFC treatment only in the over-50-year-old age group, reflected by the larger numbers of cases diagnosed with liver cancers in older-aged patients. Our analyses adjusted for important confounding factors including all lipid-lowering drugs, aspirin, metformin and TZD. Statins have been shown in previous studies to reduce the occurrence of liver cancer, with HRs ranging from 0.4 to 0.72[10,34-36]. A 2013 population-based, case-control study conducted in Taiwan using NHIRD data revealed that statin use reduced the likelihood of HCC by 28% (aHR 0.72)[36]. The same study also identified that the individual statins lovastatin, simvastatin and atorvastatin all significantly lowered the risk of HCC[36]. In our study, the fact that LFC shares a similar pharmacological pathway to that of statins meant that LFC use protected against the development of liver cancer in patients with comorbidities including hypertension, coronary heart disease, ischemic stroke, hemorrhagic stroke, diabetes mellitus, HBV and HCV infection. In patients

Table 3 Incidence and hazard ratios of liver cancer, stratified by the duration of LipoCol Forte capsules use

Variable	*n*	PY	IR	cHR	95%CI	*P* value	aHR[1]	95%CI	*P* value
Non-use of LipoCol Forte capsules as reference	3848	186604	20.621	1.00	Reference		1.00	Reference	
LipoCol Forte capsules									
< 28 d	3115	161794	19.253	0.9	(0.86, 0.94)[c]	< 0.001	0.94	(0.89, 0.98)[b]	0.006
28-84 d	533	27871	19.124	0.87	(0.79, 0.95)[b]	0.002	0.79	(0.72, 0.87)[c]	< 0.001
> 84 d	52	2457	21.165	0.99	(0.75, 1.3)	0.925	0.64	(0.48, 0.84)[b]	0.001

[1]Adjusted in multivariate analysis by sex, age, comorbidities and medications.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
PY: Person-years; IR: Incidence rate per 1000 person-years; cHR: Crude hazard ratio; aHR: Adjusted hazard ratio.

Table 4 Cox proportional hazard model estimated hazard ratio among cumulative dose of LipoCol Forte capsules

Variable	*n*	PY	IR	cHR	95%CI	*P* value	aHR[1]	95%CI	*P* value
Non-use of LFC as reference	3848	186604.2	20.6212	1.00	(Reference)	-	1.00	(Reference)	-
LFC dose (g)									
< 91	3182	158379	20.09	0.94	(0.9, 0.98)[b]	0.0089	0.98	(0.94, 1.03)	0.4435
91-179	366	21568	16.97	0.77	(0.69, 0.86)[c]	<0.001	0.69	(0.62, 0.77)[c]	< 0.001
> 179	152	12175	12.48	0.55	(0.47, 0.65)[c]	<0.001	0.46	(0.39, 0.55)[c]	< 0.001

[1]Adjusted in multivariate analysis by sex, age, comorbidities and medications.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
LFC: LipoCol Forte capsules; PY: Person-years; IR: Incidence rate per 1000 person-years; cHR: Crude hazard ratio; aHR: Adjusted hazard ratio.

Table 5 The risk of liver cancer by stratified follow-up years

Follow-up time	Non-LFC users			LFC users			cHR	95%CI	aHR[1]	95%CI
	n	PY	IR	*n*	PY	IR				
2-3 yr	1367	93294	14.65	1332	92819	14.35	0.98	(0.91, 1.06)	1.01	(0.93, 1.09)
4-6 yr	1554	63868	24.33	1401	64063	21.87	0.9	(0.84, 0.97)[b]	0.92	(0.86, 0.99)[a]
> 6 yr	927	29442	31.49	967	35241	27.44	0.77	(0.7, 0.84)[c]	0.75	(0.68, 0.82)[c]

[1]Adjusted in multivariate analysis by sex, age, comorbidities and medications.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
LFC: LipoCol Forte capsules; PY: Person-years; IR: Incidence rate per 1000 person-years; cHR: Crude hazard ratio; aHR: Adjusted hazard ratio.

without major liver cancer risks such as cirrhosis, alcoholic liver damage, NAFLD, HBV or HCV infection, LFC showed protective effects against liver cancer (aHRs 0.83-0.9). Our results suggest that LFC use is also appropriate for patients who are considered to be at "low risk" of liver cancer. LFC use was beneficial in users of both statin and non-statin lipid-lowering drugs. However, statistical significance was achieved only by the non-users (aHR 0.91 in the statin cohort and aHR 0.9 in the non-statin lipid-lowering drug cohort), due to limited case numbers or fewer synergistic effects because of similar mechanisms between the different classes of lipid-lowering agents. Aspirin has previously been reported to reduce the risk of HCC with increasing dose and duration[37], which is similar to what we observed, with aHRs ranging from 0.61 to 0.73. Notably, patients not receiving HBV or HCV treatment still derived significant benefit from LFC use (aHR 0.83 in the HBV non-treatment cohort and aHR 0.91

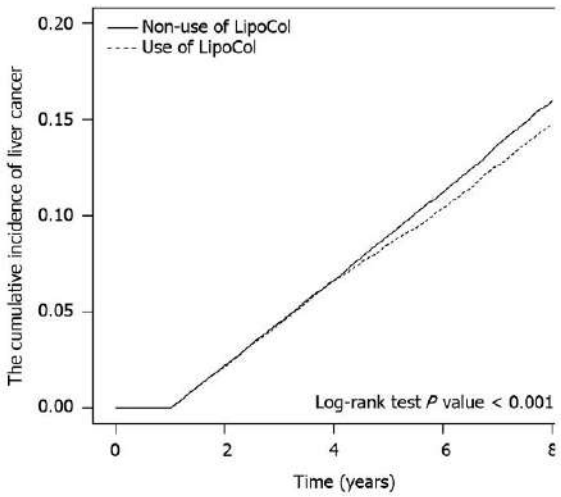

Figure 2 Kaplan-Meier analysis shows the cumulative incidence of liver cancer for patients using LipoCol Forte capsules in comparison with non-users during follow-up lasting more than 8 years.

in the HCV non-treatment cohort). However, the HBV and HCV treatment groups did not reach statistical significance, which is likely due to the treatment of HBV and HCV reducing the progression of liver cancer and potentially masking the LFC-induced protective effect. Moreover, Taiwan's NHIRD did not cover direct-acting antiviral agents in HCV treatment until 2016. Consequently, we only enrolled 8 cases in our cohort study and are therefore unable to formulate any meaningful conclusion. Studies have reported that metformin and TZD lower the risk of HCC, with aHRs ranging from 0.49 to 0.72[38-41]. Thus, we included these drugs in our analyses of confounding factors, to exclude the possibility of an interaction. We observed a significant dose-dependent association between LFC use and the incidence of liver cancer, with aHRs of 0.94, 0.79 and 0.64, respectively, for patients who used LFC for up to 28 d, 28-84 d, or more than 84 d. Our result is similar to reports from other drug-HCC prevention investigations[36,38]. We also report progressively lower cumulative incidence values of liver cancer among LFC users compared with non-LFC users in the 4-6-year subgroup (aHR 0.92; $P < 0.05$) and in the over 6 years subgroup (aHR 0.75; $P < 0.001$). These findings indicate that LFC use reduces the risk of liver cancer development in the long-term.

Taiwan's NHI is a universal healthcare system that covers nearly all of the country's population. The large database enhances the possibility of producing conclusive patient data, with adjustment for sex, age, comorbidities and medication use. However, several limitations must be noted with this study. First, we used the ICD-9-CM (from 2010 to 2015) and the ICD-10-CM (from 2016 to 2017) algorithms to define diseases diagnosed by clinical physicians. We included only patients with correct ICD-9-CM or ICD-10-CM coding after a single inpatient admission, or after two outpatient clinical visits, to increase the validity and accuracy of comorbidity diagnoses. The major outcome of liver cancer diagnosis was double-checked using the Registry for Catastrophic Illness Patient Database. Second, the NHIRD data lack important information on potential confounding factors, including body mass index, cirrhosis severity, hepatitis viral load, alcohol consumption, environmental/chemical exposure, and family history. Furthermore, biochemical data, abdominal ultrasound reports, computed tomography reports, grading and staging of liver cancer, cannot be defined in Taiwan's NHI database studies. The demographic characteristics of our patients, the proportions with cirrhosis, alcoholic liver damage or HBV/HCV infection, were not significantly different between the groups. Thus, the background risk of liver cancer occurrence was likely similar for each group. However, by highlighting potential confounding factors, especially the aspect of drug interactions, our analysis is more advanced than previous NHIRD studies. Third, although we took all potential confounding factors into account, a causal relationship between LFC and liver cancer risk could not be directly inferred owing to the observational nature of this study. Thus, we excluded liver cancers diagnosed within 1 year of study commencement. We also considered potential mechanisms in the management of dyslipidemia, direct antitumor effects and microbiota theories as explanations of our findings, as mentioned earlier. Longer-term, prospective clinical studies are needed to confirm our findings.

CONCLUSION

This is the first study to show that LFC use significantly decreases the risk of liver cancer by 9% in analyses adjusted for sex, age, comorbidities, and medication use. The protective effect of LFC was dose-dependent. Thus, our results of this cohort study suggest that LFC therapy may be associated with

reducing risk of liver cancer over an 8-year follow-up. However, long-term studies are needed to confirm our findings. Since LFC is a cheap and commonly used product, prospective clinical trials are feasible and necessary to confirm its beneficial effects on the prevention of liver cancer.

ARTICLE HIGHLIGHTS

Research background

Liver cancer is among the top five most common cancers globally. Anti-lipid therapies such as statins lowered risk of liver cancer. Lipid-lowering drugs such as statins can lower the risk of liver cancer, but may also cause liver damage. LipoCol Forte capsules (LFC), a red yeast rice product, have demonstrated significant antihypercholesterolemic effects and a good safety profile in clinical studies.

Research motivation

We evaluated whether using LFC lowers the risk of liver cancer.

Research objectives

The objective of this study was to evaluate whether LFC lowers the risk of liver cancer in adults, by analyzing data from Taiwan's National Health Insurance Research Database (NHIRD) in a propensity score-matched, nationwide, population-based cohort study.

Research methods

Patients using LFC and those not using LFC (controls) between January 2010 and December 2017 were selected from Taiwan's NHIRD and matched 1:1 by propensity scores. Statistical analyses assessed between-group demographic differences by sex, age, comorbidities, and prescribed medications.

Research results

We enrolled 33231 patients in the LFC cohort and 33231 controls. The overall incidence of liver cancer was significantly lower in the LFC cohort compared with controls (aHR 0.91; $P < 0.001$). The risk of liver cancer was significantly reduced in both females and males in the LFC cohort compared with their counterparts in the non-LFC cohort. There was a 0.64-fold lower liver cancer risk among those using LFC for more than 84 drug days. The risk of developing liver cancer in the LFC cohort progressively decreased over time; the lowest incidence of liver cancer occurred in LFC users followed-up for more than 6 years.

Research conclusions

This retrospective cohort study indicates that LFC has a significantly protective effect against the development of liver cancer, in a dose-dependent and time-dependent manner.

Research perspectives

Since LFC is a cheap and commonly used product, prospective clinical trials are feasible and necessary to confirm its beneficial effects in the prevention of liver cancer.

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FOOTNOTES

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: The datasets generated for this study are available on request to the corresponding author.

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