

生物活性食物成份与消化系统肿瘤

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■背景资料

消化道肿瘤为最常见的肿瘤之一, 随着人民生活水平的提高和工业化城市化进程, 其发病率和死亡率逐步提高, 因此胃癌, 结直肠癌的防治日益受到重视. 除了遗传因素和环境因素外, 消化道肿瘤与饮食、营养物质等密切联系.

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摘要

消化道肿瘤为最常见的肿瘤之一, 随着人民生活水平的提高和工业化城市化进程, 其发病率和死亡率逐步提高, 因此胃癌, 结直肠癌的防治日益受到重视. 除了遗传因素和环境因素外, 消化道肿瘤与饮食、营养物质等密切联系. 生物活性食物成份不仅满足人体必需的营养物质, 而且可以影响身体健康状况. 目前研究已表明, 生物活性食物成份中含有的抗氧化维生素、硒、纤维素等对于消化道肿瘤具有有效的防治作用. 现将对这些营养成份的作用及其机制的研究进展作一综述.

关键词: 生物活性食物成份; 消化道肿瘤; 维生素; 硒; 纤维素

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0 引言

消化道肿瘤发病率高, 危害性大. 其中胃腺癌是包括中国在内的亚洲国家中最常见的癌症^[1]. 在美国大肠癌患者5 a生存率仅为62%, 成为美国第二大死亡病因^[2]. 因此消化道肿瘤的预防和治疗成为研究热点. 目前认为除遗传因素、环境因素外, 饮食中的营养物质也与肿瘤的发生有关^[3-5], 其中叶酸、抗氧化维生素、微量元素硒等可降低癌症的发生^[6-7]. 将这种既能满足人体必需的营养成份又有益于身体健康的食物成份称为生物活性食物成份^[8]. 通过研究生物活性食物成份的作用机制可有效地预防肿瘤, 或与传统的抗肿瘤药物合用以加强疗效.

1 维生素

胃癌的发生与饮食有一定的联系, 其中就包括

维生素的摄入量^[9-12]. 在一项中国舟山的病例对照研究中发现高蛋白、高饱和脂肪酸、高胆固醇的饮食者胃癌发生率较高, 而维生素A, 不饱和脂肪酸及维生素C, 维生素E是胃癌发生的保护因素^[13-15]. Kim *et al*^[9]发现饮食中高摄入植物油、叶酸、抗氧化剂(维生素A, 维生素C, 维生素E)是胃癌的保护因素. 对于*H pylori*感染者, 维生素A, C, E的摄入量与胃癌发生率呈负相关, 当长期大量摄入以上2种或3种维生素时, 这种负相关性更明显. 因此鼓励*H pylori*感染者多摄入抗氧化维生素.

胃癌细胞中全反式维甲酸(ATRA)影响肿瘤相关蛋白p62的表达^[16-17]. 在实验细胞中p62多浓缩于胞质基质, 经5 d 50 mmol/L ATRA处理后细胞生长受抑制, 不仅p62表达下降, 蛋白也由胞质易位至胞核. p62与IGF-II mRNA结合表明他可能参与IGF-II mRNA转录后过程, 并调节IGF-II的表达使细胞增殖. 通常认为维生素A在代谢、ATRA作用下通过视黄酸受体(RAR)与维甲酸反应元件(RARE)介导基因转录^[18], 目前存在一定争议. Park及其同事研究维生素A在HCT-15(ATRA敏感)、HCT-116(ATRA抵抗)癌细胞株中的抑制能力, 未检测到维生素A代谢生成的ATRA或活化的类维生素A类. 尽管HCT-116, WiDR细胞中有少量维生素A转变为ATRA, 却不至于抑制细胞生长. 因此认为维生素A是通过新的非依赖于RAR机制来抑制自细胞生长, 主要是影响细胞周期, 而不是直接诱导凋亡、分化和坏死. 既然维生素A与胃癌发生关系密切, 那么其不同衍生物对胃癌影响有多大区别呢? 以瑞士雌鼠为例, 用苯并芘诱发贲门癌, 同时比较维生素A1、复合物及类胡萝卜素的抗癌效果, 结果发现胡萝卜醇、维生素A2抗癌效果更甚, 但其最佳剂量与肿瘤抑制的相关性还需进一步实验证明^[19].

对于结直肠腺癌, 血浆中维生素A、维生素E浓度同样也有防治作用^[20], 这种防治作用似乎与性别有关, 男性患者效果更明显^[21-23]. Wakai *et al*^[22]检测了116例大肠癌患者血清中的微量元

素,发现男性血清中类胡萝卜素水平较高者发病率较低,女性中结果相反。同时发现血清中维生素A能降低男女性患病率,而维生素E只对男性明显。目前维生素A及其代谢形式ATRA治疗肿瘤已取得良好效果,但却易引起“维生素A过多综合征”、患者产生耐药性等。为了克服这些问题现已合成并实验了多种类视黄醇衍生物,5-羟基-11-O-水解菲(II F)为其中之一^[24]。不同致癌度下试验II F在CaCo-2、HT-29细胞株内对细胞生长、分化所产生的作用,发现他不仅具有更强的抗增殖效果,并能诱导细胞分化,故而表明II F可作为治疗结肠癌的药物之一。

许多研究资料认为,补充抗氧化剂不仅可以降低消化道肿瘤的发生率,而且可降低其死亡率^[25-27],其效果与患者的基础疾病有关^[28]。对于无烟酒嗜好者而言,类胡萝卜素、维生素A还可降低腺瘤性息肉复发^[29]。但也有研究表明抗氧化剂(维生素A,维生素E,类胡萝卜素等)对胃肠肿瘤无明显预防效果,甚至使死亡率上升^[30-31]。

2 硒

大量资料表明,在肠癌、肝癌高发地区,土壤中微量元素硒较一般地区为低。硒是一种具有较强抗氧化性的微量元素,能防止DNA受损^[32],高血清硒可减低缺硒人群中上消化道肿瘤的发生^[33-35]。在对伊朗四省胃癌发病率与血清硒水平的研究^[36]中发现,胃癌高发区Ardabil人群中血清硒>90 mg/L仅有29%,余省达到了100%。Jacobs *et al*^[37]在调查了1763为受试者后发现血清硒含量高者患大肠腺癌风险较低。在中国同样有资料表明,血清硒浓度与胃贲门癌、食管鳞状细胞癌有关^[38]。

硒降低癌症发生率与细胞溶质中谷胱甘肽过氧化酶(GPX1)有关。GPX1是含硒的抗氧化酶,当其位点上等位基因缺失后会诱发癌症。Hu *et al*^[39]检测出肿瘤组织DNA的GPX1杂合子丢失率达到42%。此外,含硒蛋白质SeIP、胃肠道GPX在正常人群的肠黏膜上表达比患者丰富,有种假设认为是SeIP的下调释放部分Se以结合GI-GPX,抵抗活性氧簇(ROS)对DNA破坏,增强对细胞的保护。硒影响肿瘤形成的机制还包括基因启动子的甲基化、多不饱和脂肪酸代谢等^[40]。肿瘤形成过程中DNMT1表达增强,出现CpG岛的高甲基化,导致甲基化表达紊乱,硒可抑制DNMT1在HCT116、HT29等各种细胞系中的表达,从而抑制细胞生长。研究还发现硒与参

与结直肠癌肿瘤形成的脂肪氧化酶(LOXS)有关。

环氧化酶COX1、COX2是前列腺素合成的主要酶,在近80%的大肠癌(CRC)患者中过度表达。人工合成的无机硒(p-XSC)在蛋白转录后调节COX2活性,显著降低APC小鼠肠道肿瘤形成,并与剂量相关,加用二十二碳六烯酸(DHA)可达协同作用^[41]。COX的脂质产物PGE2通过表皮生长因子受体(EGFR)介导产生诱癌作用。硒蛋氨酸可通过降低HCA-7等细胞中COX-2蛋白、PEG2蛋白水平,抑制HCA-7、HT-29、Caco-pcDNA、Caco-60四个结肠癌细胞系。近几年COX2抑制剂成为防治CRC的新途径。免疫调节剂西妥昔单抗是嵌合体IgG1单克隆抗体,与EGFR高度特异性结合阻断其配位体诱导的磷酸化。当补充硒后可提高西妥昔单抗在CRC患者中的疗效^[42]。Frank *et al*^[43]将含硒酵母(200 mg/d)与塞来考昔(400 mg/d)结合使用,受试者随机分为2组(含硒酵母+塞来考昔;安慰剂+塞来考昔),进行为期6 wk实验研究,检测2, 4, 6 wk受试者的血样和毒性,结果发现两组塞来考昔的血药浓度并无显著差异,试验组也无不适主诉。用含硒复合物处理被HCT-8、HT-29嫁接的无胸腺裸小鼠发现硒不仅具有抗癌作用,还能高度抵抗由化疗因子引起的毒性作用^[44]。

大型随机化临床试验即流行病学研究表明微量元素硒可降低结直肠癌的形成^[45-46],但其防治CRC的最佳剂量、起始时间、持续时间、潜在危害以及性别差异尚无定论^[47-48]。其次,尽管硒的复合物用于临床防治具有广阔前景^[49],但有些也具有一定副作用。如研究发现Na₂SeO₃易使胃黏膜损害、出血,促进肠化生,其机制可能与壁细胞有关^[50]。

3 纤维素

纤维素可简单定义为食物中不被人体消化、吸收的成份^[51],研究认为他能有选择性地促进人体肠道中菌群的生长与活性,并促进肠道蠕动。绝大多数可发酵的碳水化合物及部分寡糖就属于这类物质^[52]。肠道菌群是结肠癌危险因素之一,通过食物纤维素改变其组成与代谢活性,可使大肠癌发病率降低^[53-54],作用效果与性别有关^[55]。Jacobs *et al*^[56]发现男性更受益。有研究证实长期食富含纤维素者患大肠癌比低纤维饮食者降低25%^[57-58]。其机制可能包括调节代谢活性和/或解毒作用,促进丁酸盐等短链脂肪酸生成以改变外源性诱癌因素。

■研发前沿

生物活性食物成份不仅满足人体必需的营养物质,而且可以影响身体健康状况。目前研究已表明,生物活性食物成份中含有的抗氧化维生素、硒、纤维素等对于消化道肿瘤具有有效的防治作用。

应用要点

通过研究生物活性食物成份的作用机制可有效地预防肿瘤,或与传统的抗肿瘤药物合用以加强疗效。

丁酸盐等短链脂肪酸可通过抑制组蛋白去乙酰化来抑制细胞增殖、促进分化与凋亡^[59]。p21诱导的细胞生长抑制是通过组织蛋白高乙酰化发生的:一方面丁酸盐可抑制组蛋白去乙酰化,提高组蛋白乙酰化水平,使稳定高表达的p21基因抑制癌细胞生长;另一方面在p21缺乏的HCT116结肠癌细胞中,丁酸盐无法通过改变组蛋白乙酰化水平抑制细胞生长。因此p21在丁酸盐诱导大肠癌细胞生长过程中起着重要作用^[60-61]。

有些文献认为, p21的过度表达与特定胃癌病理有关, 癌细胞中p21的免疫活性在胃腺癌过程中具有预测作用^[62]。丁酸钠(NaBT)能减低细胞增殖使其在48 h内发生凋亡, Tsai *et al*^[63]发现NaBT诱导胃癌TMK-1细胞的凋亡与c-Myc, c-Jun, Bcl-xs蛋白有关。c-Jun蛋白的诱导先于DNA断裂, NaBT能显著诱导c-Jun, Bcl-xs蛋白水平, 并明显降低c-Myc蛋白水平。此外根据对β2相关基因表达的研究发现, 随着NaBT的增多, Bcl-xs蛋白水平也上升。研究同样表明, 地塞米松可降低NaBT作用。NaBT可诱导凋亡以抑制S II A胃癌细胞增殖, 该过程与细胞周期抑制因子p21 Waf1/Cip1, p27Kip1及调节前体蛋白Bar、Bak和Bik有关, 因而NaBT可作为胃癌诱导的辅助因子^[64-65]。

现代分析技术发现纤维素还具有改变宿主肠黏膜的功能。然而也有些II期、III期实验发现纤维素的补充对癌症的预防没有太大效果^[66-67], 甚至可使腺癌复发率上升。

还有大量文献报道了叶酸、钙等可有效地降低结直肠癌的发生^[68-70]。前者是通过影响DNA甲基化的表达^[71], 后者与患者维生素D的状态有关^[72-73]。此外, 也发现牛乳、人乳中含有的α-乳清蛋白在结肠腺癌细胞株中具有抗细胞增殖作用^[74], 但也影响部分人群的消化功能^[75], 产生乳糖泻等^[76]。

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■同行评价

文章系统综述了生物活性食物成分在消化道肿瘤发生中的作用, 选题新颖, 研究方向独特, 同时在临床工作中有较好的实用性. 文章中各因素的作用机制讲述详细, 有一定深度.

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