性激素与胃癌发病风险的研究进展

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摘　要：胃癌在发病率上存在明显的性别差异，男性高于女性。既往研究指出，这一差异不能完全归因于吸烟、饮酒、幽门螺杆菌感染等已知危险因素，性激素也可能是导致这一差异的重要原因。本文从基础学与流行病学研究等角度，综述了内源性雌激素、雄激素、环境激素与胃癌发病风险关系的相关研究，以期为胃癌的发病机制探索和危险因素防控提供科学依据。

关键词：雌激素；雄激素；环境激素；胃癌
中图分类号：R73-31；R735.2　　**文献标识码**：A　　**文章编号**：1004-0242(2020)10-0768-09
doi：10.11735/j.issn.1004-0242.2020.10.A009

Progress in Research on Relationship Between Sex Hormones and Gastric Cancer

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Abstract：The morbidity of gastric cancer is higher in men than that in women. Previous studies have revealed that this gender difference cannot be attributed solely to known risk factors such as smoking，alcohol consumption，and Helicobacter pylori infection. It has been speculated that sex hormonal factors may play a role in the development of gastric cancer. This article summarizes the progress in the research on the relationship of endogenous sex hormones and environmental hormones with gastric cancer from the perspective of basic science and epidemiological studies in order to provide scientific evidence for the pathogenesis of gastric cancer as well as the prevention and control of risk factors.

Key words：estrogen；androgen；environmental hormone；gastric cancer

胃癌是严重威胁人类生命健康的消化道恶性肿瘤。根据国际癌症研究机构统计数据，2018 年全球胃癌新增病例数为 103.4 万例，居恶性肿瘤发病顺位第 5 位，死亡病例数 78.3 万例，居恶性肿瘤死因顺位第3 位，发病与死亡分别占全球总数的 5.7%和 8.2%[1]。超过 70%的胃癌新发病例发生在发展中国家，约 50%的病例发生在亚洲东部，主要集中在中国[1]。流行病学研究表明，胃癌发病存在明显的性别差异，男、女性发病率之比约 2:1[2]。相关数据表明，胃癌的男女发病比在 60 岁左右达到高峰，约 2.5:1，而在 60 岁后逐渐下降至 1.5:1[1-2]。既往研究发现，胃癌发病的性别差异不能完全归因于吸烟、饮酒及幽门螺杆菌感染等已知的环境危险因素[3]。鉴于胃癌患者发病率存在明显的性别差异，考虑性激素可能是导致这一差异的重要原因。本研究综述了近年来性激素与胃癌相关性研究进展。

收稿日期：2020-06-02；修回日期：2020-07-10
基金项目：国家重点研发计划(2016YFC0901400，404)；中国医学科学院医学与健康科技创新工程(2019-I2M-2-004)
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1　人体性激素与环境激素

人体性激素来源可分为两类，一类是内源性性激素，包括主要由卵巢分泌雌激素与孕激素，以及由睾丸分泌的雄激素。其进入细胞后与性激素受体蛋白结合，形成激素-受体复合物，随后作用于细胞

核染色质，通过调控 DNA 转录影响相应蛋白质合成，进而发挥其生理功能，包括促进生殖器官和骨骼的发育，参与心血管系统和内分泌系统的稳态调节，并在恶性肿瘤(如乳腺癌、胃癌、结肠癌、子宫内膜癌等)的发病中发挥一定的作用[4]。另一类是外源性性激素，也称为环境激素。此类化合物的分子结构与内源性性激素相似，当其进入机体后，与机体正常分泌的激素竞争性地结合细胞中的激素受体，产生激素样作用，干扰机体正常应答反应，造成内分泌紊乱[5]。近些年来，大量的环境激素在工农业生产过程中被释放到环境，并通过食物链富集于人类体内，严重威胁着人类健康与全球环境。

2 人体性激素与胃癌发病之间的关系

2.1 雌激素与胃癌

2.1.1 雌激素与胃癌关系的流行病学研究

胃癌发病呈现明显的性别差异，男女发病比在 60 岁左右达到高峰，约 2.5:1，而在 60 岁后逐渐下降至 1.5:1。多项国外流行病学究结果表明，绝经时间晚的女性罹患胃癌的风险低[6-10]。一项欧洲大型前瞻性队列研究结果表明，月经周期累积年数与胃癌风险呈负相关，最高组与最低组相比，发病风险降低了 45%(HR=0.55，95%CI：0.31~0.98，P_{trend}=0.06)，行卵巢切除术女性的胃癌发病风险增加了 79%(HR=1.79，95%CI：1.15~2.78)[11]。这提示我们，女性绝经或切除卵巢后，体内雌激素水平可能与胃癌男女发病性别比的改变有关。另一方面，使用激素替代治疗(hormone replacement therapy，HRT)可对卵巢功能不全及绝经期妇女内分泌功能进行调节，从而影响其体内雌激素水平。为了进一步分析 HRT 与胃癌发病风险之间的关联，本研究利用 Meta 分析方法，系统检索了 PubMed、CNKI 等数据库文献，对 2000—2019 年 HRT 与胃癌发病风险的相关研究进行了筛选归纳。入选标准：①2000—2019 年国内外发表的有关 HRT 与胃癌发病风险的病例对照研究、队列研究；②能获得全文；③文章中统计了 HRT 使用与否，各组胃癌的发生情况，以及相应的效应值(OR：病例对照研究，RR：队列研究)。排除标准：①同一人群样本的重复研究；②综述或 Meta 分析等二次数据分析文献。根据上述排除纳入标准，最终共纳入 11 篇文献[6,8-9,11-18]，提取其相应效应值(OR/RR)进行 Meta 分析，计算合并 OR 值及 95%置信区间(Figure 1)。根据固定效应模型结果，HRT 与胃癌发病之间的合并效应值 OR 为 0.69(95%CI：0.62~0.77)，提示通过 HRT 调节体内雌激素水平与胃癌发病之间存在负关联。除此之外，有研究还指出，使用抗雌激素药物，如他莫昔芬等会增加胃腺癌发病风险[19]。

综合上述研究来看，体内雌激素水平可能与胃癌男女发病性别比的改变有关，但大多研究多以绝经期、卵巢切除、HRT 及抗雌激素治疗作为暴露指标，缺乏定量衡量雌激素的指标。Petrick 等[20]采用巢式病例对照研究设计，通过气相色谱—质谱分析法，对比男性胃癌患者与对照组血清中雌激素水平，

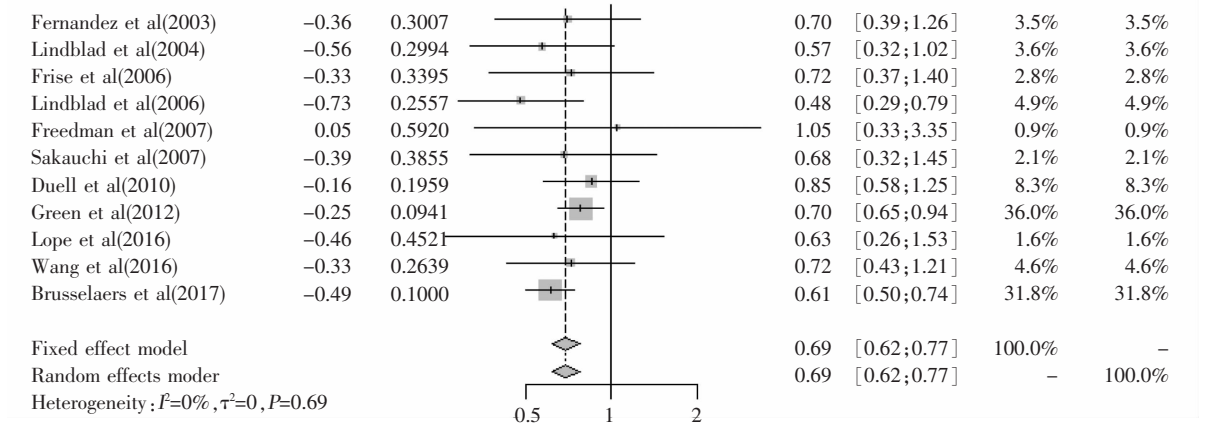

Figure 1 Meta-analysis of the relationship between HRT and gastric cancer in 11 studies

发现体内高水平雌激素及游离雌激素与较低的胃癌风险有关(OR=0.66,95%CI:0.45~0.98),但其研究对象仅局限于男性患者。与上述传统流行病学研究相比，利用质谱法直接对血清中激素组分及含量进行测定,可更为准确地评价雌激素暴露水平,为胃癌男女发病率差异提供更为客观的证据。

2.1.2 雌激素与胃癌关系的动物实验和体外实验研究

研究发现,经致癌物诱导后,雌性小鼠细胞增殖标志物及胃癌发病率均低于雄性组[21-22]。而经雌二醇处理后，患有重症胃炎并感染幽门螺杆菌的小鼠其胃上皮萎缩、增生、异型增生等不良病变得到有效改善[23]。目前在细胞水平上,关于雌激素对胃癌组织的作用机制尚未得到明确证实。有研究指出,雌二醇能直接降低胃癌细胞的活力,诱导癌细胞凋亡[24],并可抑制免疫因子白介素 6 相关信号通路，来抑制间充质干细胞诱导的胃癌细胞迁移[25]。此外,还一种观点认为，雌激素对胃癌的作用机制是通过调节胃黏膜细胞内三叶因子(trefoil factor family,TFF)肽的含量来实现的[9]。正常生理状态下,TFF 在受损的黏膜组织中表达增加,具有保护胃肠黏膜、促进胃肠黏膜再生的作用[26-27]。而 TFF1 基因表达下调,会使 ER 与雌激素反应元件(estrogen response element,ERE)结合的亲和力减小,继而导致胃癌患病风险增加[28-29]。综上,动物实验与细胞实验结果均提示,内源性雌激素具有抗胃癌细胞增殖的作用,但其作用机制尚未得到明确证实。因此,进一步探讨两者之间的作用机制,可为胃癌辅助治疗药物的选择上提供新的思路。

2.1.3 雌激素受体在胃癌患者中的表达

雌激素受体(estrogen receptor,ER)的表达与包括癌症在内的多种疾病密切相关。为进一步探讨 ER 表达与胃癌的关系，我们将近些年来相关研究进行了汇总(Table 1)。ERα 和 ERβ 在胃癌及胃部正常组织中均有表达[30-32];在癌组织中,低分化腺癌患者 ERα 表达量高于高分化腺癌[33-35];ERα 阳性率与胃癌淋巴转移和浸润深度有关,抑制 ERα 表达可降低胃癌细胞扩散与侵袭[35-37];且 ERα 阳性常提示不良预后[30,33,36,38]。有研究指出,ERα 通过相应信号通路调控肿瘤细胞葡萄糖调节蛋白表达，影响胃癌的发生[39];但体外实验也证实,ERα 在细胞内过表达对肿瘤细胞增殖有一定抑制作用[40]。对于 ERβ,目前研究普遍认为雌激素在胃癌组织中的生理作用主要是由 ERβ 介导实现的[32,41],ERβ 能抑制胃肿瘤细胞增殖[35],对胃癌的侵袭性有保护作用[42]。然而,并非所有相关研究都支持 ER 亚型的表达与胃癌发病之间存在关联。Jukic 等[43]的研究指出,虽然肿瘤上皮中 ERα 阳性率低于对照组,但其差异并无统计学意义;Gan 等[31]对 866 例胃癌病理组织进行检测,结果发现 ERα、ERβ 在胃癌及正常组织中虽然都有表达,但其表达水平较低,部分受体可能参与胃癌的发生,但其在胃癌中的临床病理和预后意义有限。

整体来看，虽然诸多研究均支持 ERα 与 ERβ 在胃肿瘤细胞恶性增殖与侵袭中，分别发挥着促进和抑制作用。但由于各研究在实验方法、阳性标准、样本大小和患者种族等方面存在差异，对于 ER 亚型与胃癌发病之间的联系仍存在争议。进一步探索不同亚型与胃癌作用机制，通过雌激素类药物激活或抑制 ER 的表达,可对胃肿瘤细胞增殖与侵袭,以及胃癌病情进展与控制提供新的思路。

2.2 雄激素与胃癌

目前有关雄激素和胃癌关系的流行病学研究较少，但动物实验发现高水平雄激素与胃癌发病风险升高有关。早在 20 世纪八九十年代,日本学者通过动物实验证实,经化学致癌物诱导后,阉割后的雄性大鼠胃癌发病率为 29%，而正常雄性大鼠高达 81%[44];经 X 线照射处理后,睾酮处理后的大鼠,其肠上皮化生发生率明显升高[45]。人体内雄激素大多通过与雄激素受体(androgen receptor,AR)结合,发挥其生理作用，而 AR 过度表达已证实与多种恶性肿瘤的发病密切相关[46-48],我们将近些年来相关研究进行了汇总(Table 2)。AR 的表达与胃癌发生、分化程度以及淋巴结转移密切相关，且 AR 阳性的患者常提示不良预后[43,49-54]。除此之外,越来越多的研究证据表明,AR 不仅可以充当雄激素在胃部的应答原件,还可以作为一种“癌蛋白”与胃癌组织内相关因子相互作用,进而调控癌细胞增殖、扩散和转移[55-58]。总体来看,无论是在动物实验、体外实验或是流行病研究中,体内高水平游离雄激素及 AR 的过度表达,均与较高的胃癌发病风险有关。当下,对于雄激素与胃癌的分子机制尚未明确，相应流行病学研究尚待进一步探索。此外,随着肿瘤标志物检测技术的发展,在雄激素应答代谢通路水平上整合转录组学和代谢组学的结果,可以为探讨胃癌病因线索提供新思路。

Table 1 Summary of the association between estrogen receptors and gastric cancer

Studies	Detection method	N	Outcome
Yokozaki et al(1988) [33]	Immunohistochemical	108	ERα(+): 30/108, the ER-positive rate of poorly differentiated adenocarcinoma was significantly higher than that of highly differentiated adenocarcinoma, and ER-positive patients had a poor prognosis.
Matsui et al(1992) [34]	Immunohistochemical	107	The ER-positive rate was 27.7% for males and 31.0% for females. The ER-positive rate was slightly higher in young women and patients with poorly differentiated gastric cancer.
Yi et al(2014) [36]	Immunohistochemical	932	ERα(+): 40/932, ER α(+) expression was associated with diffuse gastric cancer and indicating poor prognosis.
Deng et al(2010) [37]	Immunohistochemical	22	ERα-36 mRNA was detected in 17 tumor samples, the content was higher than normal tissue. The expression of ERα-36 is closely related to lymph node metastasis of gastric cancer.
Xu et al(2010) [30]	Immunohistochemical	211	ERα(+): 48/211, ERβ(+): 104/211, ERα(+) and ERβ(−) indicate poor prognosis.
Wang et al(2007) [35]	Immunohistochemical	39	ERα(+) was correlated with the depth of tumor invasion and only detected in poorly differentiated adenocarcinomas. ERβ expression was reduced in tumor tissues compared to non-cancer tissues. It is speculated that ERβ has an anti-tumor cell proliferation effect.
Matsuyama et al(2002) [41]	Immunohistochemical	29	ERβ(+) and ERα(−) are present in all gastric cancer tissue. It is speculated that the role of estrogen in gastric cancer is mediated by ERβ
Ryu et al(2012) [42]	Immunohistochemical/ tissue chip	148	ERβ(+): 67 cases(45.3%), ERβ-positive group was associated with lower tumor stage, negative perineural invasion, Lauren's intestinal type, and free of recurrence.
Tang et al(2017) [47]	Immunohistochemical	155	ERα positive is related to poor prognosis in Chinese patients with GC.
Jukic et al(2017) [43]	Immunohistochemical	60	The incidence of ERα (+) in the tumor epithelium was lower than that in the control group, but the difference was not statistically significant.
Fu et al(2018) [39]	Immunohistochemical	86	ERα promotes the pathogenesis of gastric cancer by regulating the expression of glucose-regulating protein in tumor cells through corresponding signaling pathways.
Gan et al(2012) [31]	Immunohistochemical/ tissue chip	866	Although the positive expressions of ERα and ERβ can be detected in both gastric cancer and normal tissues, the positive rate is at a low level which have limited clinical pathological and prognostic significance in gastric cancer.
Zhou et al(2013) [40]	Western blotting	Culture in vitro	Overexpression of ERα inhibits tumor cell growth and progression by inhibiting β-catenin in gastric cancer tissue.
Kim et al(2013) [32]	Immunohistochemical	Culture in vitro	Five gastric cancer cell lines were ERβ(+) and three were ERα(+). ERβ-plays a more important role than ERα in tumorigenesis.

3 环境激素与胃癌发病之间的关系

近些年来，环境激素被广泛应用于农业生产和人们的日常生活中，包括农药、激素类药品、添加剂和塑料制品的生产及使用和垃圾处理等。目前列入环境激素的化合物约有 70 种，按照其作用类型，可分为环境雌激素、环境雄激素和环境甲状腺激素，其中具有雌激素效应的环境雌激素类化合物种类最多，包括植物雌激素、二噁英类化合物、双酚类化合物、重金属化合物和部分含氯农用化学品。我们将常见环境激素与胃癌发病之间的分子机制进行了汇总(Table 3)。植物雌激素，如大豆异黄酮、木酚素等，是植物体内具有类似雌激素样作用的一类化合物，多存在于豆类、葛根等植物及其种籽中，其与受体的亲和度要远低于内源性雌激素。大豆异黄酮是豆类食物中具有类似雌激素样作用的一类化合物，血清中高浓度大豆异黄酮与胃癌风险降低有关[59]，且有研究指出其可抑制幽门螺杆菌生长[60]，降低胃癌细胞耐药性[61]，但豆制品摄入与胃癌风险的流行病研究结果存在争议。Kweon 等[62]在上海市开展的一项队列研究表明，吃豆腐可降低男性远端胃癌发病风险(饮食最高组 *vs* 饮食最低组，HR=0.64，95%CI：

Table 2 Summary of the association between AR and gastric cancer

Studies	Detections	N	Outcomes
Kominea et al (2004) [54]	Immunohistochemical	86	The positive rate of AR is related to lymph node metastasis, and the prognosis of AR positive patients is poor.
Zhang et al(2014) [53]	Immunohistochemical	40	Overexpression of AR can induce migration, invasion and proliferation of gastric cancer cells.
Nakamura et al(2006) [52]	Immunohistochemical	117	AR and androgen synthase and metabolic enzymes were detected in tumor tissues.
Jukic et al(2017) [43]	Immunohistochemical	60	In women, AR positive cells were not found in T1 and T2 tumor tissues. In men, the positive rate of AR at T3 and T4 was significantly higher than that at T1 and T2. The AR positive rate of male is higher than that of female.
Liu et al(2003) [51]	Immunohistochemical	59	AR, RB and CyclinD1 have high positive expression rates in gastric cancer and participate in the regulation of the occurrence and development of gastric cancer.
Li et al(2014) [50]	Immunohistochemical	40	AR positive expression is closely related to the occurrence, differentiation degree and lymph node metastasis of gastric cancer in Hui nationality.
Sun et al(2009) [49]	Immunohistochemical	42	The positive rate of cancer tissues was lower than that of adjacent tissues, and the positive rate of AR was related to tumor tissue type, degree of differentiation, lymph node metastasis and TNM stage.
Gan et al(2012) [31]	Immunohistochemical/ tissue chip	866	The AR-positive expression is related to tumor grade and pathological classification. However, the low expression level of AR makes its clinicopathological and prognostic significance limited in gastric cancer.

Table 3 Relationship between environmental hormones and gastric cancer

Environmental hormone	Source	Access to the body	Molecular mechanism
Isoflavones	Phytoestrogens, derived from legumes	Ingestion	(1)Associated with a lower risk of gastric cancer [59]; (2) Inhibit the growth of helicobacter pylori[60]; (3) Reduce drug resistance in gastric cancer cells[61]. However, the epidemiological studies on soy intake and gastric cancer risk are controversial [62-65].
Agrochemical	Some pesticides, herbicides, plant and animal growth regulators	Inhalation, ingestion, percutaneous absorption	Disrupting the physiological effects of estrogen, the organochlorine pesticides(DDT) can produce chronic teratogenic and carcinogenic effects, especially in breast cancer and cancers of the reproductive system [66-68]. The relationship between agrochemicals and gastric cancer remains controversial due to the lack of studies[69-71].
Dioxin	Metal smelting, garbage incineration, chemical and automobile exhaust	Food chain concentration	Dioxins can bind to aromatic hydrocarbon receptors in the body and produce highly carcinogenic intermediate metabolites, leading to biological toxicity reaction[72-73]. The positive rate of aromatic hydrocarbon receptor increased with the aggravation of gastric mucosal lesion[74].
Bisphenol A	Plastic products, food and beverage packaging materials	Ingestion	Bisphenol A can bind to estrogen´s nuclear receptor[75] and membrane receptor[76], producing an endocrine disrupting effect. With the increase of BPA concentration, the growth of gastric cancer cells was abnormal and the invasion ability was enhanced[77], and the biological flora in the gastrointestinal tract was changed[78].
Phthalates	Plastic products, food and beverage packaging materials, cosmetics	Inhalation, ingestion, percutaneous absorption	(1) Enhance the cytotoxicity of helicobacter pylori and induce apoptosis of gastric epithelial cells[79]; (2) Promote the expression of genes related to gastric inflammation[80].
Cadmium compound	Industrial emissions, waste incineration and fossil fuels	Water and diet	(1) Damage to the barrier of gastric mucosa[81]; (2) Inducing DNA damage and inhibiting DNA damage repair mechanisms to induce mutations[82]. However, epidemiological studies on the relationship between the intake of cadmium-containing food (rice) and the risk of gastric cancer are controversial[83-84].

0.42~0.99)，而干豆类可以降低绝经后妇女患胃癌的风险（饮食最低组 *vs* 饮食最高组，HR=0.63，95% CI：0.43~0.91）；另一项韩国的队列研究则发现大豆/豆腐的摄入量与女性患胃癌的风险呈显著负相关(RR=0.41，95%CI：0.22~0.78)，但在男性中，效果并不显著(RR=0.77，95%CI：0.52~1.13) [63]。然而，Kim 等[64]的一项 Meta 分析结果表明，发酵类的豆制品与较高的胃癌风险相关 (OR=1.22，95%CI：1.02~1.44)，而未发酵类的大豆食品则相反 (OR=0.64，95%CI：0.54~0.77)。除植物雌激素外，其余多数环境雌激素多存在不同程度的毒性作用，虽然其相应分子机制均提示与胃癌风险升高有关，然而缺乏相应的流行病学研究证据支持。考虑到环境激素暴露与否及暴露剂量难以准确测量，且多需要大样本人群的监测信息，而个体水平上的暴露较难调查。因此，有关环境激素与胃癌发病风险之间的真实关系，还需开展进一步的前瞻性队列研究加以验证。

4 小结与展望

综上所述，我们发现①动物实验、体外实验以及流行病学研究结果均提示，高雌激素水平可能与胃癌低风险有关，ERα 可促进胃肿瘤细胞在癌变过程中的增殖，而 ERβ 对细胞恶性增殖与侵袭具有抑制作用；②雄激素及其受体过度表达与胃癌发病风险升高可能有关；③虽然部分环境激素相应分子机制均提示与胃癌风险升高有关，但缺乏相应的流行病学研究证据支持。性激素水平差异可能是导致胃癌发病性别差异的原因之一，但两者之间实际关联需要进行进一步的分子机制探索并通过前瞻性队列研究加以验证。

虽然性激素与胃癌相关研究起源较早，但在两者在分子水平上作用机制尚未完全阐明；而流行病研究多以绝经期及 HRT 等作为性激素暴露评估的替代指标，缺乏定量的检测指标。随着分析化学技术发展与多学科领域之间交叉融合，生物质谱技术为主的代谢组及蛋白组学等新兴测量分析方法在肿瘤标志物检测领域具有广泛的应用前景，可为探索性激素与胃癌发病关系提供新的思路。因此，探索性激素在胃癌发病机制中的作用，可为胃癌的病因学防控以及其他激素相关癌症防控提供新思路。

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