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## 人附睾蛋白 4 在上皮性卵巢癌中的应用价值

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**[摘要]** 近年来卵巢恶性肿瘤的发病率逐年升高并趋于年轻化。上皮性卵巢癌因早期常无明显症状, 亦无有效监测手段, 故多于晚期发现, 预后较差。即使通过规范的手术及化疗, 晚期上皮性卵巢癌的5年生存率为20%~30%, 而早期上皮性卵巢癌(I~II期)患者5年生存率可达90%。上皮性卵巢癌患者的生存率与其分期及治疗效果相关。临床上一直在探索一种有效的监测手段, 以期早期诊断并准确评估晚期上皮性卵巢癌的治疗效果, 从而提高患者的生存率。人附睾蛋白4(human epididymis protein 4, HE4)作为近年来新发现的肿瘤标志物, 在正常组织中呈限制性表达, 在良性肿瘤组织中表达水平较低, 在上皮性卵巢癌组织及血清中呈高水平表达。多项研究表明, HE4在早期上皮性卵巢癌的诊断、卵巢癌治疗效果及预后中有一定的应用价值。

**[关键词]** 人附睾蛋白4; 上皮性卵巢癌; 应用价值

## Application value of human epididymis protein 4 in epithelial ovarian cancer

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**Abstract** In recent years, the incidence of ovarian malignant tumor is increasing year by year and the patients tend to be younger. Typically, epithelial ovarian cancer often has no obvious symptoms and no effective monitoring means in the early stage, and is usually diagnosed in the late stage with poor prognosis. Even with standard surgery and chemotherapy, the 5-year survival rate of advanced epithelial ovarian cancer is 20%–30%, while the 5-year survival rate of early epithelial ovarian cancer (I–II) patients is 90%. The survival rate of epithelial ovarian cancer is related with its stage and treatment effect. Clinically, an effective monitoring method has been explored for early diagnose and accurate evaluation of the treatment effect of advanced epithelial ovarian cancer, so as to improve the survival rate of patients. As a new tumor marker in recent years, human epididymis protein 4 (HE4) has a limited expression in normal tissues, a low expression level in benign tumors, and a high expression level in epithelial ovarian cancer tissues and serum. Many studies have shown that HE4 has a certain value in the diagnosis, treatment, and prognosis of early epithelial ovarian cancer.

**Keywords** human epididymal protein 4; epithelial ovarian cancer; application value

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宫颈癌、子宫内膜癌及卵巢癌为妇科三大恶性肿瘤, 严重危害女性生殖健康。宫颈癌可通过宫颈细胞学检查、HPV检测、阴道镜检查、子宫颈组织活检的“三阶梯”手段进行早期诊断。子宫内膜癌通过诊断性刮宫或宫腔镜检查在早期或癌前病变作出诊断, 并给予有效治疗, 从而提高生存率。上皮性卵巢癌(epithelial ovarian cancer, EOC)占卵巢癌的85%~90%, 是妇科恶性肿瘤死亡的首位。早期EOC(I~II期)常无明显症状, 缺乏有效的监测手段, 晚期因出现腹胀、腹部肿块、腹腔积液及其他消化道症状就诊, 70%以上的卵巢癌患者发现时均为晚期(III~IV期), 即使通过规范的手术及化疗, 晚期EOC患者的5年生存率也仅为20%~30%<sup>[1]</sup>, 5年复发率达80%<sup>[2]</sup>, 而早期EOC患者5年生存率可达90%<sup>[3]</sup>。

EOC通过病史、体征及辅助检查进行初步诊断, 但确诊需依靠病理学方法, 可选择腹腔镜探查术或剖腹探查术获得病理组织诊断, 但这种手段是有创伤性的, 并不是常规检查手段。超声诊断易受超声诊断医师的经验及超声诊断仪的影响, 主观性较强, 具有一定的局限性。血清肿瘤标志物的检测具有简便、无创伤性的特点, 在目前EOC的诊断与治疗过程中, 肿瘤标志物血清糖类抗原125(CA125)、CA199及CA153等得到普遍应用, 但其特异性及敏感性有限, 无法在EOC早期辅助诊断。CA125是目前最常用于EOC诊断的肿瘤标志物, 但许多研究证明CA125可在许多良性疾病中出现升高, 包括妊娠、子宫内膜异位症、子宫肌瘤、胰腺炎、月经期、盆腔炎症性疾病和肝脏疾病<sup>[4]</sup>, CA125的阳性率与EOC的国际妇产科联盟(International Federation of Gynecology and Obstetrics, FIGO)分期有关, 分别为I期50%, II期70%, III期91%, IV期98%, 不能单独用于早期诊断<sup>[5]</sup>。寻找一种能对早期EOC具有预测价值的肿瘤标志物对提高卵巢癌患者的预后具有重要的意义。人附睾蛋白4(human epididymal protein 4, HE4)作为近年来新发现的肿瘤标志物, 多项研究发现在EOC诊断过程中, HE4与CA125具有相似的敏感性, 但HE4具有更高的特异性。本研究通过阐述HE4在早期卵巢癌的诊断价值及对卵巢癌治疗效果及预后的价值, 旨在进一步指导HE4在妇科临床工作中的使用。

## 1 HE4 的结构与表达

HE4是一种分泌糖基化蛋白, 是附睾分泌蛋

白E4的前体物质, 主要是由Whey酸性蛋白家族产生, 又名核心表位蛋白(WFDC2), 属于抑蛋白酶家族<sup>[6]</sup>, 与细胞外蛋白酶抑制剂有非常高的相似性, 分子质量相对较小。HE4编码基因定位于染色体20q2-q13.1位置上14个同源基因之一, 其长度约为12 kb, 由4个内含子和5个外显子组成。HE4的主要构成为WFDC即二硫键核心, 相对分子质量为25 kD, 其包含的一个单肽链中含有2个乳清酸性蛋白4-二硫键核心结构域(WFDC结构域)<sup>[7]</sup>。由于其分子质量远小于CA125, 更容易分泌到血清中, 故较CA125更易从血清中检测到。

1991年Kirchhoff等<sup>[8]</sup>在附睾远端上皮首次发现HE4, 起初认为是男性附睾特有的与精子成熟有关的蛋白质, 能够抑制精子成熟, 而后随着对HE4的研究发现, HE4可表达于女性呼吸道上皮、乳腺上皮、生殖道上皮、肾远曲小管、结肠黏膜等处, 但其在正常组织和良性肿瘤组织中含量极低<sup>[9-10]</sup>。研究<sup>[11]</sup>表明: 在EOC组织及患者血清中, HE4呈高表达状态, 但在癌旁组织中不表达, 在卵巢良性肿瘤或非EOC中, HE4呈低表达或不表达。Moore等<sup>[12]</sup>和Hallamaa等<sup>[13]</sup>研究发现血清HE4水平不受月经周期及雌孕激素变化的影响, 无确定证据证明血清HE4水平与绝经状态相关, 但与年龄呈正相关。多数研究认为HE4水平在绝经前后预测EOC的敏感性不同。Al Musalhi等<sup>[14]</sup>研究发现HE4在绝经前后的EOC早期预测中的特异性分别为93%和75%。在目前普遍接受的HE4的正常范围: 绝经前妇女血清HE4<70 pmol/L, 绝经后妇女血清HE4<140 pmol/L。2003年, HE4被FDA批准为血清肿瘤标志物, 并用于EOC的诊断、监测治疗效果及肿瘤复发。

## 2 HE4 对 EOC 的诊断与鉴别诊断价值

### 2.1 HE4 对早期 EOC 的诊断价值

根据国际癌症研究机构的统计, EOC患者的5年生存率为46%, 其中早期卵巢癌患者生存率可达94%<sup>[15-16]</sup>, 如果EOC能在早期确诊, 可提高患者的生存率。Moore等<sup>[15]</sup>研究发现: HE4在EOC的诊断中具有高灵敏度和特异性。Havrilesky等<sup>[17]</sup>在2008年收集大量卵巢癌患者与正常对照组的血清, 通过对10种肿瘤标志物水平的检测(其中包括HE4和CA125), 发现敏感性最好的是HE4, 灵敏度为62.4%~82.7%, 特异性为96%。Zheng等<sup>[18]</sup>的研究表明当血清中HE4水平为58.66 pmol/L时, 则HE4诊断EOC的敏感性和特异性分别为82.35%和96.03%。

2009年Montagnana等<sup>[19]</sup>观察到血清中HE4的释放似乎早于CA125, 在早期卵巢癌(I~II期)诊断中HE4的敏感性为82.7%, CA125的敏感性为45.9%。李静等<sup>[20]</sup>研究发现在确诊EOC前1年可检测出血清HE4升高, 从而表明血清HE4可作为早期诊断卵巢癌的肿瘤标志物。Dewan等<sup>[21]</sup>研究表明: 当血清HE4的临界值为69.8 pmol/L, 预测EOC的敏感性为83.6%, 特异性为100%。与CA125相比, HE4对I/II期卵巢癌的灵敏度为62.4%, 特异性为96%, 对III期卵巢癌诊断的灵敏度为74.6%, 特异性为96%, 而HE4和CA125联合检测卵巢癌的敏感性可达92.54%。Yu等<sup>[22]</sup>对2 607例患者的Meta分析结果显示: 血清HE4在EOC诊断中的灵敏度为80%, 特异度达90%以上。综上, 血清HE4对早期EOC具有预测价值, 从而提高早期卵巢癌的诊断率, 提高卵巢癌患者生存率。

## 2.2 鉴别原发性卵巢上皮癌与转移性卵巢癌

HE4有助于鉴别原发性卵巢上皮癌与转移性卵巢癌。Stiekema等<sup>[23]</sup>检测147例原发性卵巢上皮癌和40例转移性卵巢癌患者血清HE4水平发现: 原发性卵巢上皮癌HE4中位数为431 pmol/L, 而转移癌HE4中位数为68 pmol/L, 处于正常范围内, 两组血清CA125均明显增高且差异无统计学意义。

## 3 术前预测肿瘤细胞减灭术的效果

EOC首次手术能否获得满意的肿瘤细胞减灭术对卵巢癌的预后具有重要意义。满意的肿瘤细胞减灭术的标准为术中尽可能切除肿瘤病灶, 使盆腔残留瘤灶最大直径不超过1 cm。术前评估肿瘤细胞减灭术是否满意, 不仅有助于术前充分准备, 而且与患者充分沟通手术方式及手术目的, 能尽可能指导选择获益最大的治疗方案。目前对术前能否获得满意的肿瘤细胞减灭术建立了相关评估系统, 其中CT评价系统将术前CA125值纳入为预测因子之一, 腹腔镜探查术中通过Fagotti评分系统决定是否进行满意的肿瘤细胞减灭术<sup>[24]</sup>。相关研究<sup>[25-28]</sup>表明: 术前血清HE4水平对EOC患者是否可获得满意的肿瘤细胞减灭术有一定的预测价值, 并发现血清HE4水平对初次肿瘤细胞减灭术的满意度预测优于CA125, 但具体界值尚存争议。Angioli等<sup>[26]</sup>研究发现: EOC患者初次肿瘤细胞减灭术前血清HE4为262 pmol/L时, 预测获得满意的肿瘤细胞减灭术的灵敏度为86.1%, 特异度为89.5%。蒋清秀等<sup>[29]</sup>通过分析获得满意的肿瘤细

胞减灭术组与不满意的肿瘤细胞减灭术组间临床病理资料的差异, 发现术前血清HE4>274 pmol/L及病理级别为高级别时, 不满意的肿瘤细胞减灭术的可能性更大; 并进一步对临床病理资料行多因素分析, 仅HE4值>274 pmol/L为不满意的肿瘤细胞减灭术的独立影响因素(OR=4.580,  $P<0.001$ ), 其ROC AUC为0.676, 预测灵敏度为71.0%, 特异度为64.3%。综合以上研究, 虽然单一术前血清HE4的预测的灵敏度和特异度有限, 但HE4水平对肿瘤细胞减灭术结局的预测作用提示其有联合其他临床资料建立有效的评价系统的潜力。

## 4 评价化疗效果

EOC对化疗敏感, 即使已有广泛转移也能取得一定疗效, 化疗效果与卵巢癌患者术后生存率相关。约20%的患者开始治疗时对铂类治疗有抵抗力, 在化疗期间出现疾病进展或在化疗结束后6个月内出现复发。目前研究认为乳腺癌易感基因1(breast cancer susceptibility gene 1, BRCA1)与BRCA2基因突变型卵巢癌对含铂类化疗药物敏感, 但血清HE4水平与BRCA1与BRCA2基因突变无相关性<sup>[30]</sup>。Angioli等<sup>[31]</sup>认为在一线化疗期间评估血清HE4的变化可以预测患者的化疗反应。Hynninen等<sup>[32]</sup>研究表明: 与CA125相比, 血清HE4可以提高EOC化疗效果评估的可靠性。Chudecka-Głaz等<sup>[33]</sup>研究90例卵巢癌患者, 发现术前HE4水平是铂敏感性(AUC=0.644;  $P=0.035$ )的预测因子, 并发现化疗结束后HE4标志物水平的正常化和新辅助化疗中HE4浓度降低50%是进展时间和总生存时间的有力预测因素, 能够有效地评价化疗效果。Ribeiro等<sup>[34]</sup>认为术前血清HE4高表达者较正常范围内的EOC患者, 术后更易对铂类联合紫杉醇一线化疗发生耐药, 降低化疗效果。通过对卵巢癌患者新辅助化疗期间血清HE4的变化研究, 发现血清HE4水平变化分别在>80%与<80%时中位生存期分别为3.3与1.6年, 表明血清HE4可作为评估患者新辅助化疗效果的指标<sup>[35]</sup>。Pelissier等<sup>[36]</sup>通过对117例新辅助化疗的卵巢癌患者血清HE4与CA125研究发现: 当血清HE $\leq$ 115 pmol/L, 评估晚期EOC的化疗效果的灵敏度为92.9%, 特异度为68.7%。

此外, Lee等<sup>[37]</sup>研究发现HE4的过度表达则导致细胞生长增强, 激活磷酸化(Akt)和磷酸化细胞外信号调节蛋白激酶(ERK)通路, 抑制紫杉醇的抗肿瘤活性, 降低了对化疗药物的敏感性, 增加对

化疗药物的耐药性。Moore等<sup>[38]</sup>分析HE4对化疗耐药的影响,发现HE4过度表达促进的卵巢腺癌细胞(SKOV3)、人卵巢癌细胞(OVCAR8)对顺铂和紫杉醇的耐药性增加。一些报道指出,卵巢癌晚期患者腹水中也可检测出HE4,且腹水HE4的变化与治疗反应和复发的关系密切。研究<sup>[39]</sup>发现:一些卵巢癌患者在化疗过程中腹水持续增加,腹水HE4表达增加,表明这些患者可能对化疗产生了耐药性,从而得出卵巢癌腹水中HE4水平可反映卵巢癌患者的治疗效果的结论。

## 5 评估复发

晚期EOC患者在经过规范手术及化疗后中位生存期为18~24个月,5年内复发率可达80%<sup>[40]</sup>。EOC患者术后血清肿瘤标志物水平的监测对于尽早发现复发具有重要意义。CA125是目前最常用的用于监测治疗结束后疾病复发的肿瘤标志物,多项研究<sup>[41-42]</sup>证明在评估EOC复发中血清HE4比CA125的作用更大。Nassir等<sup>[42]</sup>发现HE4和CA125的AUC分别为0.658(95%CI: 0.535~0.781,  $P=0.016$ )和0.62(95%CI: 0.506~0.74,  $P=0.046$ ),且血清HE4的最佳截断值为165 pmol/L时,灵敏度为86.1%,特异性为34.9%。Sölétormos等<sup>[43]</sup>研究表明术前血清HE4水平与卵巢癌的分级、亚型、腹膜种植、淋巴转移、肿瘤分期及术后肿瘤残留大小显著相关,这些因素均与卵巢癌术后复发相关,这可能与HE4参与了卵巢癌的生长,并且在细胞凋亡过程中也有一定的调控作用有关。Steffensen等<sup>[44]</sup>对卵巢癌患者术后3个月和6个月随访发现:HE4升高是EOC复发的危险因素,在卵巢癌复发预测中具有高度特异性,且复发的患者中HE4较CA125可更早出现升高;与术后3个月相比,术后6个月血清HE4值对卵巢癌复发的预测价值更大。2010年Anastasi等<sup>[39]</sup>的研究显示:血清HE4评估卵巢癌患者复发的灵敏度高于CA125(96.9%vs85.7%),且术前高水平的HE4预测卵巢癌的复发比CA125提早5~8个月。Innao等<sup>[45]</sup>对经手术或化疗的47例晚期卵巢癌患者持续随访22个月,发现HE4预测卵巢癌复发的灵敏度高于CA125(91.3%vs52.2%,  $P=0.022$ ),且术前高水平的HE4可比CA125提前3~6个月预测卵巢癌的复发,但对预测卵巢癌复发的价值,两者的效果相同( $P=0.8314$ ),该结果与Anastasi等<sup>[40]</sup>的结果大致相同。Lakshmanan等<sup>[46]</sup>随访149例卵巢癌

(III期71例、IV期31例,II期28例,I期19例)患者发现:共102例发生复发,血清HE4和CA125检测复发的敏感度分别为85.3%和84.3%,特异度为91.4%和70.2%,血清HE4较血清CA125检测复发的时间平均早2.76个月,中位为3个月。综上所述,HE4较CA125检测卵巢癌复发更敏感,尽早发现卵巢癌复发。

## 6 HE4 与 CA125 联合检测的现状

HE4作为新发现的用于EOC诊断与治疗的血清肿瘤标志物,具有较CA125更高的敏感性与特异性。Dewan等<sup>[21]</sup>的研究表明:HE4和CA125联合检测的敏感性和特异性分别为92.54%和100%,较单独使用HE4预测EOC的特异性增高,同时发现HE4和CA-125联合检测有助于鉴别盆腔肿块的良恶性。2009年,Moore等<sup>[47]</sup>提出将血清CA125,HE4和绝经状态相结合的卵巢癌风险预测模型(risk of ovarian malignancy algorithm, ROMA)来预测卵巢癌发病风险,用于鉴别盆腔肿块的良恶性,从而提高早期卵巢癌的诊断。Terlikowska等<sup>[48]</sup>通过超声检测出附件区包块的120例未绝经患者和104例绝经患者,分别检测其血清CA125,HE4水平,并通过ROMA模型预测附件区包块良恶性风险,结果发现ROMA指数预测患者患卵巢癌的效果最佳(AUC=0.918, 95%CI: 0.853~0.938)的CA125,HE4和ROMA指数最佳截断值分别为62.0 U/mL, 72.3 pmol/L和21.0%。Teh等<sup>[49]</sup>测定129例怀疑起源于卵巢的盆腔肿块患者的血清HE4,CA125,发现对于绝经前妇女,HE4的特异性优于CA125(97.7% vs 54.5%,  $P<0.001$ ),ROMA较CA125更敏感(100.0% vs 92.3%,  $P=1.000$ ),但两者对绝经后妇女的特异性相同(71.4%),并认为血清HE4对于排除绝经前卵巢癌具有较高的特异性,由血清CA125和HE4结合而成的ROMA指数在绝经后卵巢癌预测中具有高于HE4与CA125的敏感性和特异性。

## 7 结语

卵巢癌的早期诊断与疾病预后密切相关。HE4在早期诊断EOC、提前预测是否可行满意的肿瘤细胞减灭术、评价化疗效果及评估复发有很大的应用价值,但HE4在临床上并没有广泛应用,期待未来能普遍应用于临床。此外,需进一步研究HE4在EOC与其他部位恶性肿瘤中的区别。

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