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17 号染色体不同倍体与乳腺癌临床病理特征的相关性 *

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摘要 目的:探讨 17 号染色体不同倍体与乳腺癌临床病理特征的相关性。**方法:**选取 2018 年 1 月至 2019 年 12 月确诊为乳腺癌的患者 78 例(乳腺癌组)与乳腺良性肿瘤患者 78 例(良性组),采用原位荧光杂交检测所有患者的病灶组织染色体不同倍体情况,分析患者的临床病理特征并进行相关性分析。**结果:**乳腺癌组 17 号染色体的多倍体率为 85.9 %,显著高于良性组(3.8 %,*P*<0.05)。不同年龄、性别、发病位置、病理类型乳腺癌患者的 17 号染色体多倍体率对比差异无统计学意义(*P*>0.05),不同淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性患者的 17 号染色体多倍体率对比差异具有统计学意义(*P*<0.05)。Pearson 分析显示 17 号染色体多倍体率与乳腺癌患者的淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性存在显著相关性(*P*<0.05);多因素 Logistic 回归分析显示淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性都为 17 号染色体多倍体的主要危险影响因素(*P*<0.05)。**结论:**乳腺癌患者多伴随有 17 号染色体多倍体,与其患者的淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性等临床病理特征显著相关。

关键词:乳腺癌;17 号染色体;多倍体;临床病理特征;相关性

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Correlation between Different Ploidy of Chromosome 17 and Clinicopathological Features of Breast Cancer*

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ABSTRACT Objective: To explore the correlation between different ploidy of chromosome 17 and clinicopathological features of breast cancer. **Methods:** 78 patients with breast cancer (breast cancer group) and 78 patients with benign breast tumors (benign group) were selected from January 2018 to December 2019. All patients' tissue samples were collected and in situ fluorescence hybridization was used for detection of different ploidy of chromosomes, and were given investigation of clinicopathological characteristics of patients and correlation analysis. **Results:** The polyploid rate of chromosome 17 in breast cancer group was 85.9 %, which was significantly higher than that in benign group (3.8 %, *P*<0.05). There were no significant difference in the polyploid rate of chromosome 17 in patients of different ages, genders, locations of pathology, and pathological types (*P*>0.05). The difference in polyploid rates of chromosome 17 were statistically significant in lymph node metastasis, histological differentiation, clinical staging, ER positive, PR positive (*P*<0.05). Pearson analysis showed that there were correlation between lymph node metastasis, histological differentiation, clinical staging, ER positive, PR positive, and polyploidy rate of chromosome 17 in patients with breast cancer (*P*<0.05). Multivariate Logistic regression analysis showed that histological differentiation, clinical staging, ER-positive, and PR-positive were the main risk factors for the polyploidy rate of chromosome 17 (*P*<0.05). **Conclusion:** Breast cancer patients was often accompanied by polyploids of chromosome 17, which were significantly related to clinical and pathological features such as lymph node metastasis, histological differentiation, clinical staging, ER positive, and PR positive.

Key words: Breast cancer; Chromosome 17; Polyploid; Clinicopathological features; Correlation

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前言

乳腺癌是女性最常见的恶性肿瘤之一,且近年来的患病率持续升高[1,2]。乳腺癌是在环境因素和基因遗传因素长期作用下,历经 " 炎症 - 腺瘤 - 原位癌 - 浸润癌 " 复杂的变化过程[3,4],每个步骤均涉及一个或多个基因改变。乳腺癌与乳腺良性肿瘤的临床表现、疗效、生存期具有很大差异,其中细胞遗传学异常与患者的预后显著相关[5]。探索诊断治疗乳腺癌的新靶点,寻求更简单、有效的诊疗方式,对改善患者预后具有重要价值[6]。

人类表皮生长因子受体 -2 (epidermal growth factor recep-

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tor-2,HER2)基因扩增的乳腺癌患者是一组独立的类型,约占乳腺癌患者总体的 1/5[7,8]。研究表明 HER2 表达阳性的患者具有较差的临床预后,主要表现为复发率和死亡率[9]。乳腺癌 17 号染色体多倍体是检测 HER2 基因扩增时经常所面临的问题,也关系到患者的临床用药 [10]。荧光原位杂交 (Fluorescence in situ hybridization,FISH)技术是现今常用的分子技术,可检测染色体倍体性与基因扩增状况[11,12]。本研究主要探讨了 17 号染色体不同倍体与乳腺癌临床病理特征的相关性,以进一步明确乳腺癌的发生机制。

1 资料与方法

1.1 研究对象

选取 2018 年 1 月至 2019 年 12 月确诊为乳腺癌患者 78 例(乳腺癌组)与乳腺良性肿瘤患者 78 例(良性组),纳入标准:单侧发病;女性;乳腺癌与乳腺良性肿瘤都经过病理确诊;临床资料完整;年龄在 30~70 岁之间;有相对完整的临床及病理资料;未进行治疗的初诊患者。排除标准:妊娠期及哺乳期妇女;患有淋巴瘤等其他恶性肿瘤及严重免疫缺陷患者;合并糖尿病患者;临床资料缺乏者;不配合调查者;合并精神障碍者;伴有出血性疾病、出血倾向者。两组一般资料对比差异无统计学意义(P>0.05),具有可比性,见表 1。本研究得到了所有患者的知情同意,也取得了本院伦理委员会的批准书。

表 1 两组一般资料的对比

Table 1 Comparison of the general information between two groups

Groups	n	Age (Year)	BMI (kg/m^2)	SPB (mmHg)	DPB (mmHg)
Breast cancer group	78	68.92± 3.10	22.76± 2.14	123.44± 5.60	76.98± 4.11
Benign group	78	68.30± 1.99	23.87± 1.77	125.20± 4.14	77.09± 3.16

1.2 17 号染色体不同倍体检测

取所有患者的病灶组织标本进行荧光原位杂交。标本固定于 4 %中性甲醛液 24~48 h 后石蜡包埋,用经 4~5 μm 厚切片,45 ℃~50 ℃烤片,2× SSC 缓冲液洗片 3 min。纯水洗涤后经 75 %、95 %、100 %乙醇各 1 min。加 10 μL 探针混合液在组织片靶区域放入原位杂交仪,杂交参数:80 ℃变性 10 min,37 ℃过夜。洗涤后将组织片入后洗液 72 ℃ 2 min, 干燥后滴加 10 μL DAPI 显色液,镜下观察。判断标准:计算细胞核内绿色荧光信号为 17 号染色体倍体状况, 每个细胞中 17 号染色体数目在 1.76~2.25 为二体性,≥ 2.26 为多倍体性。

1.3 临床资料与预后调查

调查乳腺癌患者的病理资料(病理类型、临床分期、发病位置、淋巴结转移、PR 阳性、ER 阳性等),随访到 2020 年 1 月 1 日,记录所有患者的生存情况。

1.4 统计学分析

应用 SPSS 20.00 进行统计学分析, 计量资料以 ($\bar{x}$± s)表示,计数资料则以%表示,组间对比分别采用 t 检验与 x^2 分析,多因素分析采用 Logistic 回归分析,以 P<0.05 为差异有统计学意义。

2 结果

2.1 乳腺癌 17 号染色体不同倍体的情况

乳腺癌组 17 号染色体的多倍体率为 85.9 %, 显著高于良性组(3.8 %,P<0.05),见表 2。

表 2 两组乳腺癌 17 号染色体不同倍体对比(例,%)

Table 2 Comparison of different ploidy of chromosome 17 between two groups of breast cancer (n,%)

Groups	n	Polyploid	Polyploidy rate
Breast cancer group	78	67	85.9*
Benign group	78	3	3.8

Note: Compared with the benign group, *P<0.05.

2.2 17 号染色体不同倍体与乳腺癌临床病理特征的相关性

在乳腺癌组 78 例患者中,病理类型:浸润性导管癌 54 例,导管内癌 24 例;临床分期:Ⅰ期 35 例,Ⅱ期 25 例,Ⅲ期 18 例;组织学分化:低分化 22 例,中高分化 56 例;发病位置:左侧 40 例,右侧 38 例;淋巴结转移 22 例;ER 阳性 36 例,PR 阳性 48 例。不同年龄、性别、发病位置、病理类型患者的 17 号染色体多倍体率对比差异无统计学意义(P>0.05),但不同淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性患者的 17 号染色体多倍体率对比有差异(P<0.05),见表 3。

在乳腺癌组患者中,Pearson 分析显示淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性与 17 号染色体多倍体率都存在相关性(P<0.05),见表 4。

2.3 乳腺癌患者 17 号染色体多倍体率的影响因素分析

在乳腺癌组患者中,以 17 号染色体多倍体率作为因变量,以淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性等作为自变量,多因素 Logistic 回归分析显示淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性都为 17 号染色体多倍体率的主要危险影响因素(P<0.05),见表 5。

3 讨论

乳腺癌发病率逐年升高不仅是因为过度诊断,还与一些风险因素相关,如基因突变、表观遗传学、环境致癌物[13-15],这些因素对乳腺癌的发生发展至关重要。目前,临床主要依靠超声、病理学等手段诊断乳腺癌,虽然比较快速与简单,但是存在一定

程度的漏诊及误诊[16]。

乳腺癌的发生发展是多因素、多阶段、多种癌基因相互作用的复杂过程，具体机制还不完全明确。HER-2 定位于 17 号染色体，是一种原癌基因，主要参与肿瘤细胞生长、分化、增殖[17]。HER-2 表达增加常提示肿瘤恶性程度高，容易发生转移，从而导致预后差[18]。已有研究显示 30%左右的浸润性乳腺癌患者可表现为 17 号染色体多倍体，多倍体可能与乳腺癌的预后变化有关。FISH 能定量出 17 号染色体的倍体性，具有很好的诊断稳定性与准确性[19]。本研究显示乳腺癌组 17 号染色体的多倍体率为 85.9 %，显著高于良性组；不同年龄、性别、发病位置、病理类型患者的 17 号染色体多倍体率对比差异无统计学意义，不同淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性患者的 17 号染色体多倍体率对比差异具有统计学意义。从机制上分析，17 号染色体多倍体能够增加 HER-2 基因拷贝数，可导致 HER-2 蛋白过表达，从而影响患者的临床病理特征[20,21]。而发病位置、发病年龄与病理类型与多倍体无关，说明其不是影响肿瘤发展相关因素，与肿瘤发展无明显联系。

表 3 乳腺癌患者不同临床病理特征的 17 号染色体不同倍体对比(例，%)

Table 3 Comparison of different ploidy of chromosome 17 between breast cancer patients with different clinicopathological characteristics (n,%)

Index	The polyploidy rate of chromosome 17 (n=67)	x^2	P
Age		0.077	0.781
≥ 60 (n=12)	10(90.4)		
<60 (n=66)	57(86.4)		
Location of onset		0.055	0.815
Left side(n=40)	34(85.0)		
Right side(n=38)	33(86.8)		
ER		7.078	0.008
Positive (n=36)	35(97.2)		
Negative (n=42)	32(76.2)		
Type of pathology		0.188	0.665
IDC (n=54)	47(87.0)		
Intraductal carcinoma (n=24)	20(83.3)		
Clinical stages		11.110	0.004
Ⅰ Phase (n=35)	25(71.4)		
Ⅱ Phase (n=25)	24(96.0)		
Ⅲ Phase (n=18)	18(100.0)		
Lymphatic metastasis		5.031	0.025
Yes (n=22)	22(100.0)		
No (n=56)	45(80.4)		
PR(n)		14.883	0.000
Positive (n=48)	47(97.9)		
Negative (n=30)	20(66.7)		
Organizational credit		3.997	0.046
Poorly differentiated (n=22)	22(100.0)		
Medium and high differentiation (n=56)	47(83.9)		

表 4 乳腺癌患者 17 号染色体不同倍体与临床病理特征的相关性(n=78)

Table 4 Correlation between different ploidy of chromosome 17 and clinicopathological features in breast cancer patients (n=78)

Index	Lymphatic metastasis	Organizational credit	Clinical stages	ER positive	PR positive
r	0.422	0.571	0.344	0.401	0.443
P	0.023	0.008	0.030	0.026	0.020

表 5 影响乳腺癌患者 17 号染色体多倍体率的多因素分析(n=78)

Table 5 Multivariate analysis affecting the polyploidy rate of chromosome 17 in breast cancer patients (n=78)

Factor	β	SE	Wald	*P*	OR(95%CI)
Lymphatic metastasis	0.323	0.178	34.119	0.000	1.893(1.541-2.386)
Organizational credit	0.627	0.208	34.396	0.000	2.154(1.82-2.737)
Clinical stages	0.525	0.338	23.132	0.000	2.162(1.554-2.771)
ER positive	0.451	0.196	28.175	0.000	2.041(1.885-2.786)
PR positive	0.819	0.344	5.702	0.007	3.298(1.378-8.332)

肿瘤细胞的增殖与侵袭是一个多步骤、多因素相互作用的复杂过程,具体的机制尚不清楚,明确乳腺癌的转移与侵袭机制是当前研究领域的热点[24,25]。肿瘤相关信号通路调节异常、表观遗传学修饰等因素均参与了乳腺癌的发生发展过程,但是疾病进展过程中所包含的分子机制并不明确。本研究分析显示乳腺癌患者的淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性与 17 号染色体多倍体率都存在相关性。目前,也有研究显示约 50%的浸润性乳腺癌癌细胞的染色体为非整倍体,可能与乳腺癌的不良预后有关; 并且多数 17 号染色体多倍体伴有 HER2 基因扩增[26,27]。在肿瘤发生发展中,17 号染色体多倍体或许存在不依赖 Myc 基因而独立存在致癌作用, 预示着患者更易出现淋巴结转移[28-31]。本研究也有一定的不足,实验数据收集存在差异,可能也会影响结果的准确性,存在一定的研究偏倚,将在后续研究中深入分析。

综上所述,乳腺癌患者多伴随有 17 号染色体多倍体,与患者的淋巴结转移、组织学分化、临床分期、ER 阳性、PR 阳性等临床病理特征显著相关。

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