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· 临床研究 ·

不同年龄乳腺癌基因分型的对比研究*

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摘要 目的:对不同年龄乳腺癌患者基因分型的分布特点进行分析,为乳腺癌的治疗和预后判断提供参考依据。**方法:**回顾性分析青年、中年、老年乳腺癌患者的临床资料,对其基因分型分布进行对比分析。**结果:**不同年龄(≤ 40 岁、40岁-60岁、 ≥ 60 岁)乳腺癌的基因分型分布比较有显著性差异,存在统计学意义($P < 0.05$),年轻乳腺癌患者中 ≤ 35 岁与35-40岁患者的基因分型的分布也存在显著性差异($P < 0.05$)。**结论:**不同年龄乳腺癌人群的基因分型不同,需结合其他临床和病理指标综合评估患者病情及预后;老年乳腺癌患者基因分型的分布并不乐观,需强调早期诊断和治疗。

关键词: 乳腺癌;基因分型;年龄

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Comparative Study Of Genetic Typing In Breast Cancer With Different Ages*

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ABSTRACT Objective: To analyze the genetic typing in breast cancer with different ages and guide the treatment and prognosis of breast cancer. **Methods:** The clinical data of young, middle-aged, old patients with breast cancer were analyzed retrospectively. **Results:** The genetic typing distribution of breast cancer with different ages had statistical difference ($P < 0.05$), and the genetic typing distribution in young breast cancer patients (≤ 35 years) with the patients in 35-40 years were also significantly different ($P < 0.05$). **Conclusions:** The genetic typing distribution of breast cancer with different ages were different, comprehensive evaluation of patients' condition and prognosis should be combined with other clinical and pathological information. The genetic typing in elderly patients with breast cancer was not optimistic, which was needed to be emphasized on the early diagnosis and treatment.

Key words: Breast cancer; Genetic typing; Age

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前言

乳腺癌目前已成为威胁女性健康的第二大肿瘤,其在生物学上具有高度异质性,无论分子免疫表型,病理组织形态,生物学行为,还是治疗反应都存在明显的个体差异。随着生物学的发展,2000年,Perou等^[1]最先提出乳腺癌的分子分型,根据肿瘤组织基因谱表达的差异,将乳腺癌分为luminal A型, luminal B型, HER-2过表达型, Basal-like型, Normal-like型五类。不同基因分型的乳腺癌其临床特点和预后不尽相同,为临床医师提供了个体化治疗的参考和依据。本文统计分析了本科收治的612例乳腺癌患者资料,旨在探讨不同年龄段乳腺癌基因分型的分布特点,为乳腺癌的治疗和预后判断提供参考依据。

1 资料与方法

1.1 临床资料

选择2005年1月至2010年12月至本科就诊并获得明确病理诊断的原发性乳腺癌患者612例,其中青年乳腺癌(≤ 40 岁)198例,占32.4%,老年乳腺癌(≥ 60 岁)115例,占18.8%,40岁-60岁乳腺癌299例,占48.9%。所有病例均具有完整的临床资料及病理切片。

1.2 病理资料

复习病理切片,通过免疫组化方法判定ER(estrogen receptor)和PR(progesterone receptor)的表达,以细胞核内出现棕黄色颗粒沉着为肿瘤阳性细胞,当阳性肿瘤细胞数 $>1\%$ 时判定为ER/PR阳性。Her-2(human epidermal receptor-2)状态一般情况下通过免疫组化方法测定,(1+)为阴性,(+++)为阳性,(++)再次通过荧光原位杂交(FISH或CISH)方法测定,比值 >2.2 为基因有扩增(阳性),比值 <1.8 为基因无扩增(阴性),1.8-2.2为可疑

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扩增。

在临床工作中常根据 ER、PR、HER-2 的免疫组化结果将乳腺癌简化分为四种不同的亚型:(1)luminal A 型:ER 阳性和(或)PR 阳性,Her-2 阴性;(2)luminal B 型:ER 和 (或)PR 阳性,Her-2 阳性;(3)Her-2 过表达型:ER 阴性,PR 阴性,Her-2 阳性;(4)三阴性乳腺癌(triple negative breast cancer TNBC):ER 阴性,PR 阴性,Her-2 阴性。

1.3 统计学分析

所有数据均采用 spss13.0 统计软件进行统计学分析,采用卡方检验及 Fisher 确切概率检验比较各组差异,以 $P < 0.05$ 为差异有统计学意义。

表 1 不同年龄乳腺癌基因分型的分布比较

Table 1 Comparison of the genotyping distribution characteristics of breast cancer with different age

Age	luminal A	luminal B	Her-2	TNBC	P value
≤40y	106(53.5%)	40(20.2%)	19(9.6%)	33(16.7%)	
40-60y	140(46.8%)	40(13.4%)	67(22.4%)	52(17.4%)	
≥60y	63(54.8%)	9(7.8%)	12(10.4%)	29(25.2%)	<0.001

表 2 年轻乳腺癌患者不同年龄基因分型分布的比较

Table 2 Comparison of the genotyping distribution characteristics of young breast cancer with different age

Age	luminal A	luminal B	Her-2	TNBC	P value
≤35y	45(57.0%)	19(24.1%)	9(11.4%)	6(7.6%)	
35-40y	61(51.3%)	21(17.6%)	10(8.4%)	27(22.7%)	<0.05

3 讨论

乳腺癌的异质性决定了各亚型特有的临床病理学特点^[1-4]。Luminal A 型是临床上最常见的基因亚型。本研究中,不论在哪个年龄阶段该类型所占比例均为最高,大约 50%左右。此类型乳腺癌特点为内分泌治疗敏感,复发风险低,但一般对化疗不敏感,预后较其他类型好。近年随着对基因分型的深入研究,将评估细胞增殖指数的 Ki67 纳入检测和诊断标准,将 A 型中 Ki-67 LI>14%的这类乳腺癌归为 B 型^[5]。Luminal B 型与 A 型相比,其表达 Her-2 等基因,可应用赫赛汀靶向治疗,预后较 A 型差^[6,7]。本组数据显示随着年龄的增大,Luminal B 型的发病率逐步降低,20.2%>13.4%>7.8%,其原因需待进一步研究探讨。

老年乳腺癌(≥60 岁)中,占第二位比例为三阴性乳腺癌, luminal B 最少。而年轻乳腺癌(≤40 岁)Luminal B 型和三阴性乳腺癌较多,Her-2 过表达型最少,两组不同年龄之间的分布有统计学差异($P < 0.05$)。相关研究^[8,9]认为,老年女性乳腺癌多生长慢,病程长,侵袭性较低,发生淋巴结转移相对较晚,激素受体阳性比例高,HER-2 过表达阳性率低,常合并其他慢性病。国内研究^[10]显示老年乳腺癌中 ER 阳性率低于 70%,而国外的相关研究中^[11,12],老年女性 ER 阳性率高达 81%-95%。本研究中,≥60 岁以上乳腺癌患者 ER 阳性率为 62.6%,与国内的研究数据一致。此外,本年龄组三阴性乳腺癌较其他各年龄组多,提示老年女性乳腺癌基因分型的类型并不完全乐观。相关研究显示,老年乳腺癌的预后并非好于非老年乳腺癌^[9,13,14]。因此,针对这类人群,应强调定时体检,提高就诊意识,及早发现病情,及

2 结果

不同年龄组各基因分型的分布不同。≤40 岁乳腺癌患者 199 例中,分布比率为 luminal A 型>luminal B 型>三阴性>Her-2 过表达型。≥60 岁乳腺癌患者 115 例中,luminal A 型>Her-2 过表达型>三阴性>luminal B 型。40-60 岁乳腺癌患者 299 例中,四种类型分别为 140 例、40 例、67 例、52 例, luminal A 型>Her-2 过表达型>三阴性>luminal B 型(表 1)。不同年龄组之间基因分型的分布差异有统计学意义($P < 0.05$)。将年轻乳腺癌再分为 35 岁以下组和 35-40 岁组,两组患者四种类型乳腺癌的分布具有统计学差异($P < 0.05$)。

早诊断和治疗。

国内一项大型回顾性研究表明^[15],年轻乳腺癌患者孕激素受体(PR)情况与老年乳腺癌比例无明显区别,ER 阳性率均较年轻组低。本研究中结果却不尽相同,可能与选取的年龄界定值不同,本组缺乏远处转移乳腺癌的病例资料且样本量不足。与>40 岁乳腺癌,年轻乳腺癌具有更为侵袭性的临床病理学特点及更差的预后,对化疗及内分泌治疗更不敏感^[16-19]。本组以 35 岁为界,年轻乳腺癌两组基因分型分布的差异具有统计学意义($P < 0.05$)。预后较差的三阴性乳腺癌更多的集中在 35-40 岁年龄组,此结果尚需要更大样本的临床数据证实^[20,21]。因此,单纯的基因分型只能大体上判断预后,但还需结合肿瘤大小、淋巴结转移、分化程度及年龄等病理指标和危险因素才能更全面的个体化评估患者的病情和预后。

对于 40-60 岁的高发人群,除了 Luminal A 型之外,最多见的为 Her-2 过表达型,其余两种类型也有少量分布。不论与哪一年龄组比较,其分布差异均有统计学意义($P < 0.05$),其中能使用赫赛汀靶向治疗的占 35.8%(Luminal B 型及 HER-2 过表达型)。针对这类人群,化疗及内分泌治疗效果不佳时,分子靶向治疗将成为重点,在这一领域的不断探索,将为更多的乳腺癌患者提供希望。

参考文献(References)

- [1] Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours[J]. Nature 2000, 406(6797):747-752
- [2] Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets [J]. Proc Natl

- Acad Sci U S A, 2003, 100(14):8418-8423
- [3] Sorlie T, perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications[J]. Proc Natl Acad Sci USA, 2001, 98(19):10869-10874
- [4] Sotiriou C, Neo SY, McShane LM, et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study[J]. Proc Natl Acad Sci U S A, 2003, 100(18):10393-10398
- [5] Goldhirsch A, Wood W C, Coates A S, et al. Strategies for subtypes-dealing with the diversity of breast cancer:highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011[J]. Ann Oncol, 2011, 22(08): 1736-1747
- [6] Geyer F C, Rodrigues D N, Weigelt B, et al. Molecular classification of estrogen receptor-positive/luminal breast cancers [J]. Advances in Anatomic Pathology, 2012, 15(01): 39-53
- [7] Jianyi Li, Shi Jia, Wenhai Zhang, et al. Survival analysis based on clinicopathological data from a single institution: chemotherapy intensity would be enhanced in patients with positive hormone receptors and positive HER2 in China who cannot afford the target therapy[J]. ISRN Onclo, 2013, (2013):606398
- [8] 李凌,陈立章.老年乳腺癌患者的临床特征, ER, PR 及 CerbB-2 的表达[J]. 中国老年学杂志, 2011,11(30):3265-3267
Li Ling, Chen Li-zhang. The clinical characteristics and the expression of ER, PR, HER-2 in elder patients with breast cancer [J]. Chinese Journal of Gerontology, 2011, 11(30):3265-3267
- [9] 邱梅清, 佟仲生, 贾勇圣, 等. 老年乳腺癌临床特征预后多因素分析[J]. 实用肿瘤杂志, 2013, 28(02):162-166
Qiu Mei-qing, Tong Zhong-sheng, Jia Yong-sheng, et al. Cox multivariate regression analysis on prognosis of elderly patients with breast cancer [J]. Journal of Practical Oncology, 2013, 28(02):162-166
- [10] Chuan-Dong Ma, Qin Zhou, Xiu-Qing Nie, et al. Breast cancer in Chinese elderly women: Pathological and clinical characteristics and factors influencing treatment patterns [J]. Crit Rev Oncol Hematol, 2009, 71 (03): 258-265
- [11] Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials [J]. J Clin Oncol 2005, 23(13): 3112-3124
- [12] Wildiers H, Kunkler I, Biganzoli L, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology [J]. Lancet Oncol, 2007, 8(12):1101-1115
- [13] Van de Water W, Bastiaannet E, De Craen AJ, et al. Worse prognosis for older breast cancer patients[J]. Ned Tijdschr Geneesk, 2012, 156 (33):A5074
- [14] La Vecchia C, Giordano SH, Hortobag yi GN, et al. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle[J]. Oncologist, 2011, 16(6):726-729
- [15] Li-Chen Tang, Wen-Jin Yin, Gen-Hong Di, et al. Unfavourable clinicopathologic features and low response rate to systemic adjuvant therapy: results with regard to poor survival in young Chinese breast cancer patients [J]. Breast Cancer Res Treat, 2010, 122(01):95-104
- [16] Assi HA, Khoury KE, Dbouk H, et al. Epidemiology and prognosis of breast cancer in young women[J]. J Thorac Dis, 2013, 5(suppl1):S2-8
- [17] Canello G, Montagna E, Treatment of breast cancer in young women: do we need more aggressive therapies [J]. J Thorac Dis, 2013, 5 (suppl1):s47-54
- [18] Filleron T, Md FD, Kramar A, et al. Prognostic factors for young women(≤ 35 years)with node positive breast cancer: possible influence on post-therapeutic follow-up [J]. Bull Cancer, 2013,100(7-8): 22-29
- [19] Colleoni M, Rptmsz N, Peruzzotti G, et al. Role of endocrine responsiveness and adjuvant therapy in very young women(below 35years)with operable breast cancer and node negative disease [J]. Ann Oncol, 2006, 16(10):1497-1503
- [20] Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations[J]. Annals of Oncology, 2012, 23(06):7-12
- [21] Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor(ER)-negative, progesterone receptor(PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry[J]. Cancer, 2007,109(09):1721-1728

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- [17] Chen Y, Qian X, Liu B. Advances of drug resistance marker of gemcitabine for non-small cell lung cancer [J]. Journal of Lung Cancer, 2011, 14(5): 421-428
- [18] Lee DS, Kim YS, Kang JH, et al. Clinical Responses and Prognostic Indicators of Concurrent Chemoradiation for Non-small Cell Lung Cancer[J]. Cancer Res Treat, 2011,43(1):32-41
- [19] 王静, 张玉海, 史皆然, 等. Mcl1 对晚期非小细胞肺癌患者预后意义[J]. 现代生物医学进展, 2013, 13(12):2277-2282
Wang Jing, Zhang Yu-hai, Shi Jie-ran, et al. Prognostic Significance of MCL1 in Advanced Non-small Cell Lung Cancer Patients [J]. Progress in Modern Biomedicine, 2013, 32(12):2277-2282
- [20] 张胜利, 张增利, 施敏骅, 等. ERCC1 和 XPD 基因 SNPs 与 NSCLC 含铂类药物化疗敏感相关性分析[J]. 中华肿瘤防治杂志, 2013, 20(10):726-729
Zhang Sheng-li, Zhang Zeng-li, Shi Min-hua, et al. Relationship of ERCC1 and XPD SNPs with sensitivity to platinum-based chemotherapy in advanced non-small cell lung cancer [J]. Chinese Journal of Cancer Prevention and Treatment, 2013, 20 (10):726-729