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海南部分地区与省外非转移性浸润性乳腺癌患者 临床病理参数的对比分析*

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摘要 目的:分析海南部分地区(省内)与省外非转移性浸润性乳腺癌患者临床病理参数的异同。**方法:**收集我院自2012年6月-2017年6月经病理和影像学确诊的非转移性浸润性乳腺癌患者214例,筛选有效病例159例,将患者年龄、肿瘤位置、Scarff Bloom and Richardson(SBR)分级、肿瘤标记物(CEA、CA125、CA153)、TNM分期、阳性/活检淋巴结数、luminal分型、初潮年龄、绝经状态、生育子女数、体重指数、体表面积等数据按省内、省外进行统计分析。**结果:**①省内患者确诊年龄明显早于省外(47.48 ± 10.05 vs 51.33 ± 10.03 , $p=0.02$);②省内患者具有生育子女数较多(1.93 ± 0.97 vs 1.38 ± 0.64 , $p=0.00$)和活检淋巴结数较多(20.67 ± 9.56 vs 18.00 ± 6.74 , $p=0.04$)的特征;③省内患者绝经后体重指数(22.66 ± 3.24 vs 25.56 ± 3.67 , $p=0.00$)和体表面积(1.60 ± 0.12 vs 1.68 ± 0.16 , $p=0.00$)较绝经前明显上升,而省外患者此现象不明显。**结论:**海南部分地区非转移性浸润性乳腺癌患者具有发病年龄早等特点,绝经后体质改变可能为该地区乳腺癌的促发因素。

关键词:海南省;乳腺癌;活检淋巴结数;绝经;体重指数

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Comparison of the Clinicopathological Parameters of Non-metastatic Invasive Breast Cancer Patients in and out of Hainan Province*

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ABSTRACT Objective: To analyze the clinicopathological parameters of non-metastatic invasive breast cancer patients in and out of Hainan province. **Methods:** 214 patients were reviewed and 159 validated cases who were diagnosed by pathological and imageological examination in our hospital from Jun 2012 to June 2017 were under estimation, parameters including age, tumor location, Scarff Bloom and Richardson (SBR) stage, tumor markers (CEA, CA125, CA153), TNM stages, positive/resected lymph nodes, luminal style, menarche age, menopausal status, children number, body mass index (BMI), body surface area (BSA) were registered and compared between patients in and out of the province. **Results:** ① patients were much more younger at diagnosis in Hainan province than that from outside (47.48 ± 10.05 vs 51.33 ± 10.03 , $p=0.02$); ② patients in Hainan province were featured by have more children (1.93 ± 0.97 vs 1.38 ± 0.64 , $p=0.00$) and with more resected lymph nodes (20.67 ± 9.56 vs 18.00 ± 6.74 , $p=0.04$), no other significant statistical differences were detected in the rest clinicopathological parameters; ③ the BMI (22.66 ± 3.24 vs 25.56 ± 3.67 , $p=0.00$) and BSA (1.60 ± 0.12 vs 1.68 ± 0.16 , $p=0.00$) displayed a significant increasing in postmenopausal patients in Hainan province, no such differences were detected in cases from outside. **Conclusion:** Non-metastatic invasive breast cancer patients in Hainan province were younger, post-menopausal physical change would have an important role in triggering breast cancer.

Key words: Hainan province; Breast cancer; Resected Lymph Nodes; Menopause; Body Mass Index

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前言

截止至目前,乳腺癌仍然是导致女性死亡的最主要恶性肿瘤^[1]。在我国,仅2015年保守估计新发乳腺癌约27万余例,死

亡近7万余例^[2]。值得注意的是,由于生活方式西化等种种原因,未来我国乳腺癌发病率仍将呈现增加态势^[3]。

我国许多恶性肿瘤的分布具有鲜明的地域特色^[4],海南省作为我国最南端的省份具有独特的地域、气候、人文等特征,但

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目前对该地区乳腺癌患者的临床病理特征尚无报道。本研究拟通过收集海南部分地区(省内)和省外非转移性浸润性乳腺癌患者临床病理参数,分析省内患者临床病理特征,为未来该地区乳腺癌防治提供一定数据支持。

1 材料与方法

1.1 患者筛选

收集我院自 2012 年 6 月 -2017 年 6 月就诊的术前影像学检查(包括 CT、MRI 或 PET-CT 等)未发现明确远处转移的乳腺癌患者,标准如下:①经术后病理证实为浸润性乳腺癌(病理类型符合卫生部《乳腺癌诊疗规范(2011 年版)》),排除非浸润性癌、复发性癌和转移癌;②术前未接受新辅助治疗;③具有较为完整的临床病理资料,无关键数据缺失(包括因标本破碎或其他原因导致病理报告不能详细描述肿瘤大小、淋巴结分期及免疫组化未能提供 Luminal 分型信息、因穿刺明确病理后患者未进一步于我院手术切除等)。

1.2 肿瘤标记物测量和临床病理资料收集

根据患者就诊时登记常住地址分为海南患者(省内)和省外患者,收集年龄、肿瘤位置、肿瘤细胞病理分级(Scarff Bloom and Richardson, SBR)、身高、体重、TNM 分期(根据 AJCC 第 7 版)、肿瘤细胞免疫组化染色结果等。其中肿瘤标记物检测、体重指数(Body Mass Index, BMI)和体表面积(Body Surface Area, BSA)计算方法如前所述^[4];阳性 / 活检淋巴结数根据术后病理报告计算(包括术前前哨淋巴结活检结果)。免疫组化染色方法如下:常规切片,根据我院标准免疫组化流程操作,一抗均购自广州安恺立生物科技有限公司,具体货号如下:ER(SP1)、PR(16)、Her-2 (SP3)、Ki67 (SP6)、EGFR (EP38Y)、CK5/6 (D5&6B4),采用 DAB(20 倍浓缩液)染色法显色,具体操作根据试剂盒进行,阳性结果判定及 luminal 分型根据中国抗癌协会乳腺癌诊疗指南与规范(2015 版)和 2015 年 St Gallen^[5]共识进行。

1.3 统计学分析

所有数据均采用 SPSS20.0 进行分析,所有二分类资料均经方差齐性检验后采用卡方检验(或采用连续校正和 Fisher 确切概率),多分类资料采用 Kruskal-Wallis H(K)检验;计量资料符合正态分布以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,采用独立样本资料 t 检验。资料分类依据如下:术前肿瘤标记物根据我院参考范围分为正常和升高 2 类;Luminal 分型根据中国抗癌协会乳腺癌诊疗指南与规范(2015 版)和 2015 年 St Gallen^[5]会议对应为 A、B、C、D、E 型和不确定(根据患者术后免疫组化结果无法判定为上述具体类型)等 6 类。所有数据均有两位医师独立录入以保证准确,所有数据采取四舍五入法取小数点后两位,双侧 $P < 0.05$ 认为具有统计学意义。

2 结果

2.1 患者数据缺失分析

经回顾共收集有效病例 214 例,除去不符合标准的患者 55 例,有效病例 159 例,其中省内患者 108 例,省外患者 51 例(比例:2.12:1)(图 1)。进一步分析有效病例后发现仍存在部分参数缺失,具体如下:病例报告未提示 SBR 分级 17 例、未提示肿瘤大小 1 例、术前未检测肿瘤标记物(CEA 为 17 例、CA125 为 17 例、CA153 为 19 例)、原始病例未记录生育子女数 24 例。

2.2 省内外患者临床病理参数比较

省内患者平均确诊年龄(47.48 ± 10.05)明显低于省外患者(51.33 ± 10.03)(相对约低 4 岁, $P = 0.02$)。尽管省内外患者活检淋巴结数(20.67 ± 9.56 vs 18.00 ± 6.74)差异具有统计学意义($p = 0.04$),但阳性淋巴结数(3.14 ± 7.93 vs 1.58 ± 2.89)在两组患者中并无明显统计学差异($P = 0.07$)。省内外患者生育子女数(1.93 ± 0.97 vs 1.38 ± 0.64)差异具有统计学意义($P = 0.00$),省内患者生育子女数明显多于省外患者。在其他临床病理参数方面,两组患者均未显示出明显统计学差异(均 $P > 0.05$)。具体见表 1。

表 1 省内外患者部分临床病理参数的对比分析

Table 1 Comparison of the partial clinicopathological parameters of patients in and out of the province

Parameters	No.	In	Out	P
Age		47.48 ± 10.05	51.33 ± 10.03	0.02 [#]
Tumor location				0.25
Left side	78	51	27	
Right side	80	57	23	
Both side	1	0	1	
SBR stages				0.26
Low	29	4	25	
Medium	53	43	10	
High	60	25	35	
CEA status				0.37
Normal	137	95	42	
Elevated	5	2	3	
CA125 status				1.00
Normal	131	89	42	
Elevated	11	8	3	
CA153 status				1.08

Normal	133	91	42	
Elevated	7	5	2	
T stages				0.51
1	80	55	25	
2	67	47	20	
3	5	2	3	
4	7	4	3	
Tumor volume		5.61± 12.18	6.96± 11.92	0.51
N stages				0.11
0	98	71	27	
1	34	18	16	
2	15	9	6	
3	12	10	2	
Positive lymph nodes		3.14± 7.93	1.58± 2.89	0.07
Resected lymph nodes		20.67± 9.56	18.00± 6.74	0.04 [#]
TNM stages				0.52
I	56	37	19	
II	69	50	19	
III	34	21	13	
Luminal style				0.84
A	25	17	8	
B	66	42	24	
C	19	14	5	
D	8	6	2	
E	6	3	3	
Unclear	32	23	9	
Menarche age		14.17± 1.58	14.04± 1.73	0.66
Children number		1.93± 0.97	1.38± 0.64	0.00 [#]
Menopausal status				0.15
Yes	108	72	36	
No	51	28	23	
BMI		23.63± 3.65	23.24± 3.88	0.47
BSA		1.63± 0.14	1.65± 0.11	0.39

Note: # Independent sample t test, significant statistical differences.

2.3 不同年龄和绝经状态分组省内外患者后临床病理参数的对比

年龄和绝经状态是临床上决定非转移性乳腺癌患者后续治疗方案的两个关键参考因素,进一步将省内外患者按年龄因素进行分层(以 35 岁为界^[6]),其中≤ 35 岁的患者共 14 例(省内 12 例,省外 2 例),>35 岁患者共 145 例(省内 96 例,省外 49 例),通过统计分析发现在≤ 35 岁患者中两组在各项临床病理参数上均无明显统计学差异,但在>35 岁患者中 N 分期、活检淋巴结数及生育子女数两组差异具有统计学意义(表 2.1)。同样,以绝经状态将患者进行分层,其中未绝经患者共 100 例(省内 70 例,省外 30 例),已绝经患者共 59 例(省内 36 例,省外 23 例),通过统计分析发现在未绝经患者中,省内患者生育子女数和 BSA 均高于省外患者(差异具有统计学意义),而在已绝经患

者中仅 N 分期在两组患者差异具有统计学意义(表 2.2)。

3 讨论

近年来,我国不同地区乳腺癌相关危险因素研究不断增加,如 Gao 等对通过对江苏地区 669 例患者和 682 例对照进行研究,分析了体重指数、体力活动等因素在该地区乳腺癌发病中的作用,结果显示肥胖、低体力活动和乳腺癌发病增加相关^[7]。Gao 等对通过对上海地区 1459 例患者和 1556 例对照进行研究,分析了初潮年龄、生育、哺乳等因素在该地区乳腺癌发病中的作用,结果表明不论是在已绝经还是未绝经女性中,月经初潮早、未生育、第一胎年龄晚等和乳腺癌发病增加相关,而从未哺乳和绝经晚等因素仅在已绝经妇女中和乳腺癌发病增加相关^[8]。Lin 等通过对广东地区 16314 例乳腺癌患者进行问卷调

查,分析了家族史、射线暴露、良性乳腺疾病、高脂血症等和乳腺癌的关系,结果表明上述因素和乳腺癌发病增加相关^[9]。Qiu等通过对武汉地区 500 例患者和 500 例对照进行研究,分析了高体重指数、长绝经期、人工流产频次、生活环境、家族史等因素和乳腺癌的关系,结果表明上述因素和乳腺癌发病增加相关^[10]。Liu 等对重庆地区 186 例患者和 186 例对照进行研究,探讨了被动吸烟、体重、社会经济状态对乳腺癌发病的影响,结果表明幼年时被动吸烟、低体重指数和社会经济状态差是乳腺癌发病

的危险因素^[11]。Li 等通过对 877 例患者和 890 例对照进行研究进一步证实了被动吸烟和乳腺癌发病的关系^[12]。这些研究对促进地区乳腺癌的防治有一定贡献,然而海南地区乳腺癌类似研究尚较为缺乏。本研究结果显示海南省部分地区非转移性浸润性乳腺癌患者和省外患者在部分临床病理参数上存在一定差异,其中突出表现为省内患者确诊年龄轻,在大于 35 岁和已绝经患者中,省内患者 N 分期明显低于省外患者,其中可能对这些差异有影响的因素包括生育子女数、体重指数和体表面积等。

表 2.1 以 35 岁为界对比分析省内外患者临床病理参数的对比分析

Table 2.1 Comparison of clinicopathological parameters of patients taken 35 years old as a threshold

Parameters	No.	In	Out	P
N stages				0.44
0	8	6	2	
1	5	5	0	
2	1	1	0	
3	0	0	0	
Resected lymph nodes		17.25± 9.24	26.50± 9.19	0.21
Children number		1.33± 1.00	0.50± 0.71	0.30
N stages				0.02*
0	90	65	25	
1	29	13	16	
2	14	8	6	
3	12	10	2	
Resected lymph nodes		21.09± 9.56	17.65± 6.50	0.01#
Children number		2.00± 0.95	1.42± 0.62	0.00#

Note; #Independent sample t test; *Kruskal-Wallis H (K) test, significant statistical differences.

表 2.2 以绝经状态将患者分层后对比分析省内外患者临床病理参数

Table 2.2 Comparison of clinicopathological parameters of patients taken menopause as a threshold

Parameters	No.	In	Out	P
N stage				0.37
0	60	44	16	
1	23	17	6	
2	10	5	5	
3	7	6	1	
Children number		1.82± 0.93	1.19± 0.56	0.00#
BMI		22.66± 3.24	22.89± 2.68	0.73
BSA		1.60± 0.12	1.65± 0.11	0.02#
N stages				0.00*
0	38	27	11	
1	11	1	10	
2	5	4	1	
3	5	4	1	
Children number		2.13± 1.02	1.65± 0.67	0.07
BMI		25.58± 3.67	23.66± 3.12	0.04#
BSA		1.68± 0.16	1.64± 0.12	0.21

Note: #Independent sample t test; *Kruskal-Wallis H (K) test, significant statistical differences.

研究表明乳腺癌的发生和众多因素相关,其中公认的保护性因素包括哺乳、首次生育年龄,不利因素包括肥胖、高龄、家族史(特别是 BRCA1 和 BRCA2 突变)、生育晚、性激素接触、初潮年龄、绝经年龄等等^[13-15]。在本研究中,海南地区非转移性浸润性乳腺癌患者平均确诊年龄比省外患者低 4 岁,提示该地区乳腺癌更年轻化。而就我国目前乳腺癌发病年龄而言,比欧美发达国家整体上要年轻近 10 岁^[16],而既往大量研究已表明年轻乳腺癌患者往往伴有不利的病理因素,如高核分级、高临床分期、激素受体阴性和 Her-2 过表达等,这对于患者控制局部复发和延长总生存极为不利^[6-10]。有鉴于此,我们研究结果提示海南地区早期乳腺癌筛查可能十分必要。同时,我们发现海南地区患者相比省外患者活检淋巴结数明显更多,其中在年龄大于 35 岁的患者中更为明显。众所周知,过多的淋巴结活检是导致术后淋巴水肿的关键因素^[19],严重影响术后患者生活质量,值得注意的是在本研究中更多的淋巴结活检数并未带来阳性淋巴结数和临床分期的差异,这似乎提示未来海南地区此类患者术中活检淋巴结数应适当减少。

在既往的研究中,生育可能是乳腺癌的保护性因素,但生育对于乳腺癌的保护多体现在首次生育年龄,超过 18 岁的后续生育对乳腺癌的保护作用几乎可以忽略^[20]。在本研究中,海南地区乳腺癌患者普遍具有生育子女数较多的特征,特别是对于年龄大于 35 岁或发病时仍未绝经的患者,由于未能获得这些患者首次生育的具体年龄,目前尚无法肯定生育是该地区乳腺癌的保护因素。既往大量研究已充分表明肥胖或高体重指数是乳腺癌发病的危险因素^[21-24],肥胖不仅和女性体内雌激素水平、胆固醇代谢和芳香化酶水平,同时还可影响患者复发、术后疼痛和预后等^[15,25,26],对我国乳腺癌患者研究更是发现肥胖严重影响术前接受新辅助治疗患者的病理缓解率^[27]。类似研究也显示高体重指数不论是在绝经前还是绝经后患者中均和更大的肿瘤体积相关,而绝经后患者高体重指数更是和更多的 ER/PgR 阳性亚型、更短的 DR-FS 相关^[28]。值得注意的是,截止至目前,对于高体重指数在不同绝经状态乳腺癌患者中的作用研究结论并不完全一致,如 Amadou 等通过一项 Meta 分析研究发现绝经前体重指数增加和乳腺癌发病负相关仅在非洲裔和高加索人群中证实,在亚裔妇女中这种负相关变为正相关^[29]。但与此不同的是,我国学者通过对 2800 例汉族女性随访研究发现,绝经前乳腺癌患者似乎具有更高的体重指数,但在绝经后妇女中这种高体重指数似乎并不和乳腺癌相关^[30]。而对于肥胖对绝经后乳腺癌发病的影响,在国外的研究中似乎较为一致,即肥胖和乳腺癌发病正相关^[31],我国研究人员也有类似结论^[32]。我们研究表明海南地区乳腺癌患者绝经后体重指数和体表面积存在明显增加趋势,可能为该地区乳腺癌的促成因素,提示未来对于该地区绝经后妇女应该加强健康教育,适当控制体重有可能起到降低乳腺癌发病的作用。

本研究尚存在以下不足:①研究样本量偏小,对研究结果的解读尚需谨慎,未来需随着样本量的扩大进一步深入研究;②随访资料等不完备,目前尚不能明确不同的病理参数对地区非转移性浸润性乳腺癌患者治疗、预后方面的影响,对地区疾病防治方案尚不能提供有效支持。总之,海南地区非转移性浸润性乳腺癌患者相比省外患者存在部分明显不同临床病理

特征,未来该地区乳腺癌防治工作可针对这些不同特征开展相关研究,可能对于降低该地区乳腺癌发病具有一定帮助。

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