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Comparison of some salivary biomarkers between luminal and triple negative subtypes after surgical removal of invasive ductal carcinoma

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Abstract:

Luminal (L) and triple negative (TN) subtypes of breast cancer (BC) are recorded in Iraqi women which have different incidence, treatment, progression, and metastases. This study is aimed to compare some risk factors and salivary biomarkers between them. Only premenopausal Iraqi women with invasive ductal carcinoma (IDC) are involved in this study. Based on histopathologic and immunohistochemistry (IHC) report carried out by hospital itself, the age, Subtype and grade of tumor were recorded, while waist/hip ratio, secretory status, and salivary levels of Ca 15-3, total protein (TP), and PH were determined 2-3 weeks after surgery and before starting therapy. Results revealed that luminal is the predominant subtype of IDC and constitute about 80.5% and the rest (19.5%) is TN subtype, however HER-2 subtype didn't recorded. Also women with TN are presented at age 40.7 year which is significantly ($P < 0.05$) lower than that in (L) subtype (47.1 year). All TN cases are non-secretor and presented at grade 3 and their saliva is more acidic and containing higher levels of Ca 15-3, and TP than those in (L) cases. Our results suggested that saliva can be used as an alternative diagnostic sample in differentiation between various subtypes of IDC, and secretory status of patients may be contribute in determining the subtype of BC.

Key words: *Breast cancer, triple negative, Ca 15-3, saliva, secretory status, luminal subtype.*

Introduction:

Breast cancer (BC) has been classified into three major subtypes namely; luminal, HER2, and triple negative with different incidence, treatment, progression, and metastases (1, 2). The risk of getting BC in women is increased with advanced age and delayed menopause but it is more aggressive in younger ones (3-5). Furthermore, obesity increases risk of BC in post-menopausal women, but reduces its risk pre-menopausal women (6). This heterogeneity in the acting of obesity as BC risk factor may vary based on the menopausal status or ER, and PR status (7). Most case–control studies have found an association between waist/hip ratio (WHR) and BC in postmenopausal patients (8), but not in premenopausal women (9). Recently, it was reported that non-secretors as a non-preventable risk factor significantly increases the risk for getting BC (10). Concerning with biomarkers of BC, Ca 15-3 is still the most important one and can give important information about responsiveness of tumor cells to certain therapy and their biological behavior during disease monitoring (11). Recently, it was found that Ca 15-3 can be detected in the saliva of women with malignant breast cancer in comparison with benign and normal breast (12). Since some of biomarker molecules can pass from blood to saliva (13), about 2,340 salivary protein were identified, 20% of them are derived from plasma (14). Also another 57 salivary metabolites were identified in saliva of patients with oral, breast, and pancreatic cancer and periodontal diseases (15). Recently, about 3,200 - 8,000 gene transcripts were found in human saliva, the majority of them are mRNA (16). More recently, 31 salivary biomarker that diffused from circulation has been described in BC patients (17). Therefore, saliva it become an attractive and non-invasive fluid for assessment disorders in different sites of body rather than oral cavity (18). Since BC is more aggressive in premenopausal women also there are few studies that interested in evaluation of their biomarkers in saliva after surgical removal of tumor mass, thus this study attempt to find an additional risk factors (e.g. secretory status) and biomarkers (e.g. salivary PH and total protein) that may be explain the different behaviour of IDC subtypes.

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Materials & Methods:

More than one hundred BC women in different public and private hospitals in Baghdad after 2-3 weeks

post-operation and before starting therapy were involved in this study. Histopathological investigation was carried out according to the conventional laboratory method of histopathology (19), while measurement of ER, PR, and HER2 were determined semi-quantitatively by using immunohistochemistry assay from (Dako EnVision FLEX system, Denmark) to classify the molecular subtypes of breast carcinoma (20). After obtaining the result of histopathologic and IHC, All cases rather than invasive ductal carcinoma (IDC) as well as postmenopausal cases were excluded. The remainder cases include 41 premenopausal women with IDC. The age and different subtypes of BC and their grade were extracted from the IHC and histopathological report, while waist and hip circumference were measured to calculate W/H ratio. About 3-5 ml of saliva samples were collected from all patients and their PH values were determined by using PH-meter, then saliva samples were centrifuged at 3000 rpm for 10 minutes to eliminate any debris. The supernatant was divided into 2 aliquots; the first was placed in a bath of boiling water for 10-15 minutes and centrifuged the boiled saliva at 3000 rpm for 2 minutes and removed the supernatant fluid which is directly used to determine secretory status by using inhibition of hemagglutination technique (21). While the second aliquot was stored at -20 0C until to be used in determination of Ca 15-3 biomarker by using an automated quantitative Mini VIDAS test from (BioMerieux, France), and total protein biomarker by using the Biuret method provided by (Linear chemicals SL, Spain) (22). Data are statistically analyzed by using one-way ANOVA and Chi-square test, and P values less than 0.05 are considered significant.

Results:

According to the results obtaining from histopathological investigation, only 41 cases of premenopausal patients are recorded as invasive ductal carcinoma (Figure-1).

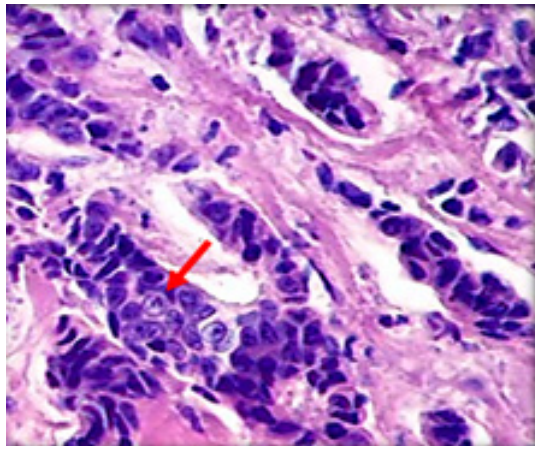

Figure-1: Histopathological section of Ductal Breast Carcinoma with H&E staining at 400X [showing cancer cells (red arrow)].

The cellular staining pattern for ER and PR is nuclear, thus a positive result is defined as nuclear staining in ≥ 1% of tumor cells which is consistent with ASCO/CAP's recommended cut-off of ≥ 1% positive tumor cells for positive assessment (23) as shown in figure-2

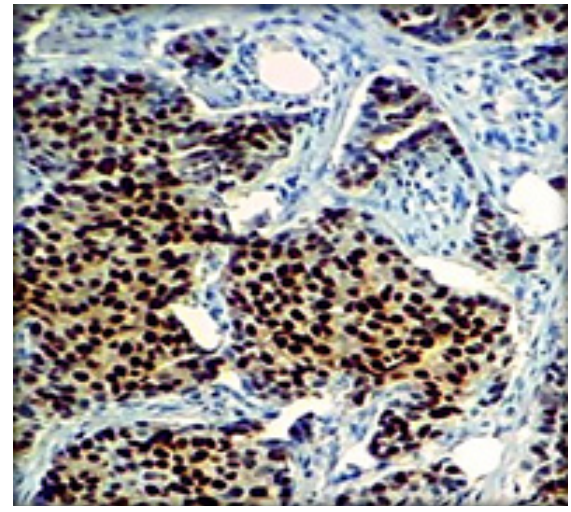

Figure-2: Immunohistochemistry section of luminal subtype of IDC at 200x. [Showing ≥1 of cancer cells positively expressed ER and / or PR with intensive nuclear brown staining].

However, the scoring method for HER2 expression is based on the cell membrane staining pattern and Allred scoring system was used to interpret the staining result based on the proportion and the intensity of staining tumor cell (Figure-3): Positive HER2 expression (+++) with uniform intense membrane staining of more than 30% of invasive tumor cells, Equivocal HER2 expression (++) with complete membrane staining that is either non-uniform or weak in intensity but has circumferential distribution in at least 10% of cells, and finally Negative HER2 expression (0 or +) with non-completely membrane staining in less than 10% of cells (24).

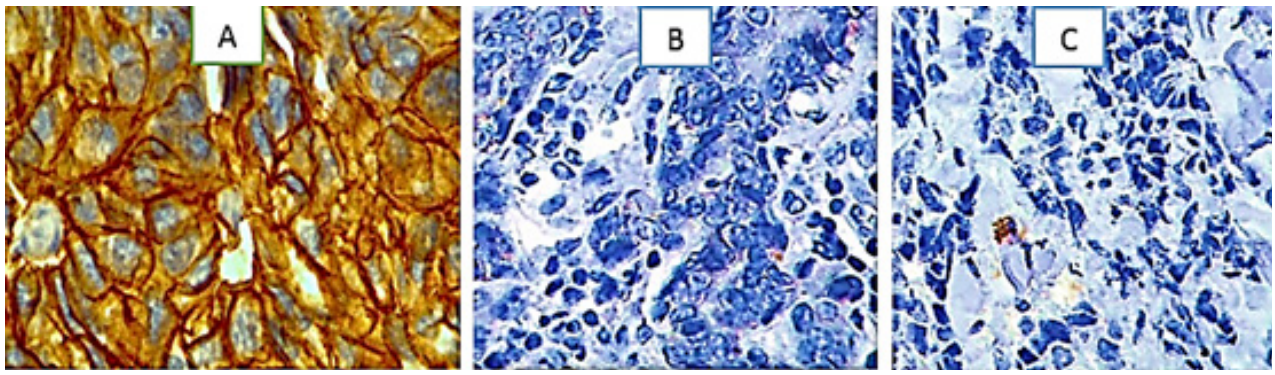

Figure-3: Immunohistochemistry section of triple negative subtype of IDC [showing ≥10 of cancer cells positively expressed HER2 and completely surrounding with brown staining at 400x in control positive sample (A); HER2 negative at 200x(B); ER and / or PR negative at 200x(C)].

Among all premenopausal Patients, 33 (80.5%) of IDC are presented as luminal carcinoma subtype and only 8 (19.5%) of them having triple negative (TN) subtype (Figure-4).

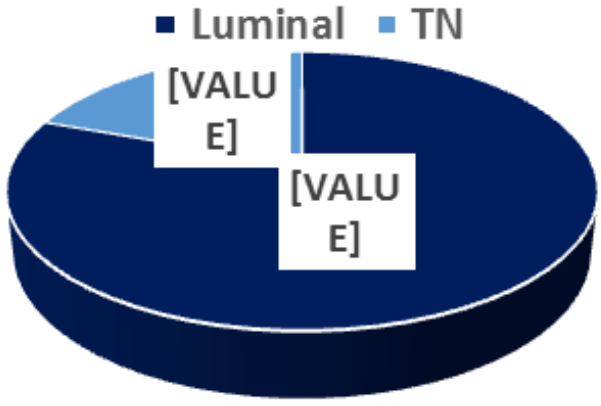

Figure-4: Frequency of Luminal and TN subtypes among IDC premenopausal women

The age of TN women is (40.7 ± 2.3 years) which significantly ($P < 0.05$) lower than that of luminal women (47.1 ± 0.5 years), however, W/H ratio showed non-significant difference between luminal (0.89 ± 0.02) and TN subtype (0.88 ± 0.04) (Table-1).

Table-1: Differences in age and W/H ratio between Luminal and TN of IDC premenopausal women

Character	IDC subtype (N=41)		Significance
	Luminal	TN	
Age (years) (M ± SE)	47.1 ± 0.5	40.7 ± 2.3	[S]
W/H ratio (M ± SE)	0.89 ± 0.02	0.88 ± 0.04	[NS]
[S]: significant difference; [NS]: non-significant difference at $P < 0.05$			

Tumor grade shows significant association ($P < 0.05$) with different subtypes of IDC (Figure-5), in which all TN patients (100%) are presented in grade 3, while only 21.2% of luminal subtype patients are at grade 3 and the remainder are either grade 1 (24.3%) or grade 2 (54.5%).

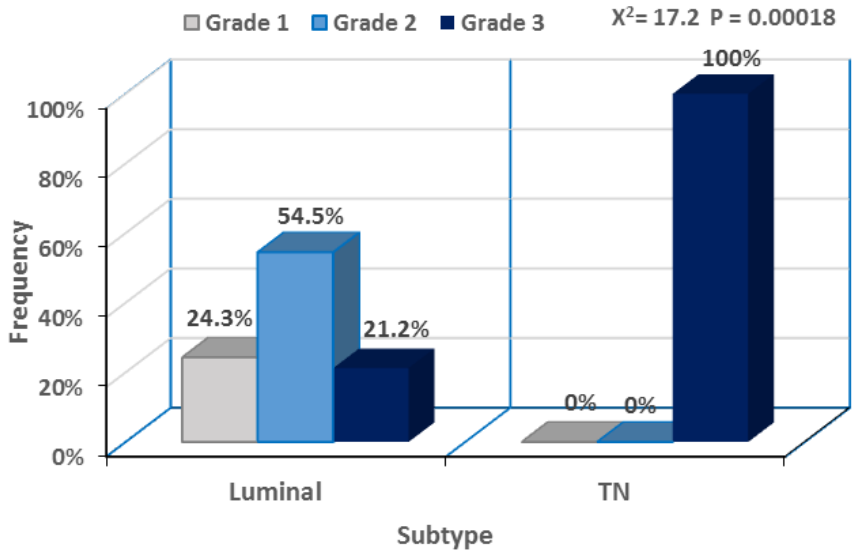

Figure-5: Frequency of cancer cell differentiation grade in Luminal and TN subtypes

Similarly, significant association was shown between secretory status and different subtypes of IDC (Figure-6), in which all patients (100%) of TN subtype are non-secretors in comparison with only 63.6% of luminal subtype.

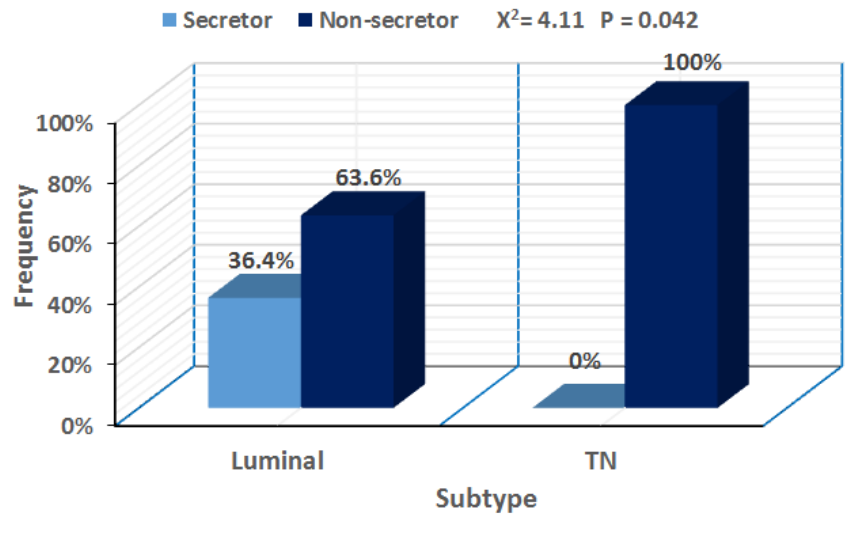

Figure-6: Frequency of secretory status in Luminal and TN subtypes

Concerning with the levels of biomarkers in the saliva of IDC patients, results in Table-2 shows that saliva of TN patients is significantly more acidic (PH = 5.68 ± 0.05) than that in luminal patients (PH = 6.06 ± 0.07). Furthermore, salivary level of Ca 15-3 in TN (12.1 ± 0.32 U/ml) is significantly higher than that in luminal subtype (8.8 ± 0.4 U/ml), also TP level in saliva of TN (1.05 ± 0.05 g/dl) is significantly higher than that in luminal subtype (0.78 ± 0.02 g/dl).

Table-2: Salivary levels of Biomarkers in different subtypes of IDC women

biomarker (M ± SE)	IDC subtype		Significance
	Luminal (n=33)	TN (n=8)	
Ca 15-3 (U/ml)	8.8 ± 0.40	12.1 ± 0.32	[S]
TP (g/dl)	0.78 ± 0.02	1.05 ± 0.05	[S]
Saliva PH	6.06 ± 0.07	5.68 ± 0.05	[S]
[S]: significant difference at P < 0.05			

Discussion:

Results of this study recorded that luminal carcinoma subtype is the most predominant subtype of IDC among premenopausal patients who are presented at age of 47.1 years with different grades of cancer cell differentiation, while the minority is triple negative subtype at average age of 40.7 years and all cases are presented at third grade of differentiation (Figure-4 & 5, and Table-1). Consistent with our results, most of the previous studies stated that IDC is the prominent histopathological type of BC and it is a disease of older women, its incidence increases with age, but rare below 20 years (25-28). Although TN subtype constitute about 15–20% of all BC cases, it is highly frequent among premenopausal women and characterized by poor prognosis, early recurrence, and distant metastasis when compared to other subtypes of BC (29-32).

Concerning with WHR as a measure of central obesity, our result found that premenopausal BC women are presented with high WHR (0.89, and 0.88) whether they have luminal or TN subtype respectively (Table-1). However, previous studies reported that WHR above 0.85 for females increases risk for getting BC only in postmenopausal women (7, 33-35), but not in premenopausal ones (36, 37). Differences in these associations possibly due to different roles of fat and fat distribution among pre- and postmenopausal women as well as across ethnic groups on metabolism particularly insulin signalling on endogenous production of androgen and estrogen (38-41). Furthermore, higher BMI is associated with higher risk for ER+/PR+ tumors in postmenopausal women but has a protective effect in premenopausal women and with no associations in ER−PR− tumors (7). However, recent study suggest that body fat distribution may be associated with an increased risk for ER- tumor among premenopausal women (40). In contrast, elevated BMI in younger women (≤50 years) was associated with the risk of only ER+ or PR+ BC but triple-negative BC may has distinct etiology because it was found that high BMI and high parity have been associated with increased risk for TN, instead of low parity in other subtypes of breast cancer (42-45).

In respect to secretory status as a risk factor, our result showed significant association between secretory status and different subtypes of IDC (Figure-6), in which all patients (100%) of TN subtype are non-secretors in comparison with 63.6% of luminal subtype. Secretor phenotype is defined by the functioning fucosyltransferase FUT2 enzyme that allows for the secretion of ABO antigens into body fluids, however non-functional FUT2 occur in 20% of non-secretor individuals groups (46). Since non-secretor phenotype is associated with metastasis, it can be used as a predictive value for BC susceptibility and lymph metastasis (47). Few data are available about this genetic feature and its relation with the aggressive behaviour in TN subtype of BC and need further investigation.

Concerning with salivary biomarkers, our results shows that saliva of TN patients is significantly more acidic and contain higher levels of Ca 15-3 and TP than those in luminal patients (Table-2). Presence of such markers in saliva facilitate easy detection without even minimal surgical procedure and will also be candidates for population based screening (48). In clinical practice, ER, PR, and HER2, are still the routinely biomarkers for in determination of different subtypes of BC (49), although new markers are needed to more accurately approximate the basal-like subtype (32), thus BC detection and management remains dependent on invasive procedures (50), and CA 15-3 is still the most commonly used serum marker that is helpful in diagnosing and monitoring the breast cancer disease (51, 52). Our results were in accordance with previous studies that found a significant association between tumor size and negative ER/PR status (53-55). Furthermore, it was reported that the level of CA 15-3 is significantly increased in positive hormonal receptor cases and contributes to E-2 mediated growth of cancer cells (56). Also this protein has a high potential for immune intervention via decreasing immunity to MUC 1 and become unable to suppress the growth of tumor which may be responsible for metastasis (57, 58). Several researchers reported that salivary c-erbB-2, VEGF, EGF, and CEA can be used in the initial detection and/or follow-up screening for the recurrence of BC (59-61). Recent study demonstrated important differences in characterizing biomarkers in nipple aspirate fluid (NAF) and found that EGF and TGF-β1 levels in NAF of premenopausal women were significantly higher than postmenopausal women (62). More recent study demonstrated a relationship between salivary levels of estrogen, progesterone, and percent mammographic density in premenopausal women (63).

Since defining molecular abnormalities in BC is an important strategy for early detection, assessment of prognosis, and treatment selection, thus the present findings clearly indicated two facts; the first one is the possibility to use saliva as a good alternative sample for differential diagnosis between the different subtypes of BC; and secondly, salivary biomarkers particularly those with protein nature are detectable and can constitute the backbone of etiology that is often linked in receptor expression status.

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مقارنة بعض المؤشرات الحيوية اللعابية مابين النمط اللمعي والنمط السلبي الثلاثي للسرطان القنوي الأجتياحي بعد الأزالة الجراحية

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الخلاصه:

إن النمطين اللمعي (L) والسلبي الثلاثي (TN) لسرطان الثدي تم تسجيلهما لدى النساء العراقيات ، وأنهما يختلفان من حيث نسبة حدوثهما والعلاج وشدة تطور المرض وإنتشاره. تهدف هذه الدراسة لمقارنة بعض عوامل الخطورة والمؤشرات الحيوية اللعابية ما بين هذين النمطين. شملت الدراسة فقط نساء عراقيات دون سن اليأس ومصابات بسرطان الثدي القنوي الإجتياحي. إستنادا الى تقرير الفحص المرضي النسجي وفحص كيمياء المناعة النسجي المنجز من قبل المستشفى ذاتها ، تم تحديد عمر المصابات ونمط ومرتبة الورم ، أما نسبة الخصر/الورك ، والحالة الإفرازية ، وتركيز كل من المستضد الورمي Ca15-3 والبروتين الكلي (TP) والأس الهيدروجيني فقد تم تحديدها في لعاب المريضات بعد 2-3 أسابيع من عملية إستئصال الورم وقبل البدء بالعلاج. أظهرت النتائج بأنّ النمط L هو الأكثر شيوعا ما بين النساء المصابات بسرطان الثدي القنوي الإجتياحي حيث بلغت نسبته حوالي 80.5% والنسبة المتبقية 19.5% كانت للنمط TN ، في حين لم تسجل أي حالة مصابة بالنمط HER-2 . كما أنّ معدل عمر النساء المصابات بالنمط TN كان 40.7 سنة وهو أقل بشكل معنوي ($P < 0.05$) عن معدل عمر المصابات بالنمط (L) والذي كان حوالي 47.1 سنة. إن جميع حالات النمط TN كانت غير فارزة ومن المرتبة الثالثة وكان اللعاب أكثر حامضية وحاويا على مستويات أعلى لكل من المستضد الورمي Ca15-3 والبروتين الكلي (TP) عما هو عليه في حالات النمط اللمعي . إنّ نتائجنا تقترح بأن اللعاب يمكن إستخدامه كعينة تشخيصية بديلة للتمييز بين الأنماط المختلفة لسرطان الثدي القنوي الإجتياحي ، وأن حالة الافراز عند المرضى قد تكون مساهمة في تحديد النمط الثانوي لسرطان الثدي .