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Original Research Article

Evaluation of the ultrastructure and expression of desmoglein 2 in breast cancer: A novel biomarker

MARYAM MOHAMMADHOSSEINI[1]
HAMIDREZA MIRZAEI[2]*
AHMAD MAJD[1]
MONA FARHADI[3]
NASRIN SHAYANFAR[4]

[1] Department of Biology, North Tehran Branch, Islamic Azad University, Tehran, Iran

[2] Cancer Research Center (CRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Department of Microbiology, Karaj Branch, Islamic Azad University, Karaj, Iran

[4] Iran University of Medical Sciences, Tehran, Iran

***Correspondence:**
Hamid Reza Mirzaei
E-mail address: mirzaei.hr@gmail.com

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Abstract

Background and purpose: *Breast cancer is the most common malignancy among Iranian women. In recent years, the study of dysfunction in the expression of cell-cell junction genes and the related proteins in the malignant process has been at the center of attention.*

Materials and methods: *In this study, 50 patients were selected who had both cancerous tissue and adjacent healthy tissue. The expression of the desmoglein 2 gene was evaluated. Healthy and cancerous tissue were compared using routine hematoxylin and eosin staining. The total protein was also compared between these two groups. The ultrastructural examination was performed.*

Results: *The real-time polymerase chain reaction results showed a decrease in the expression of the desmoglein 2 gene in all tumor samples compared to the healthy samples ($p<0.0001$). Besides, receiver operating characteristic curve analysis showed that the area under the curve was equal to 0.98. Transmission electron microscopy microscopic studies revealed a change in the status of desmosomal junctions.*

Conclusions: *Overall, the findings showed that the association between desmoglein 2 gene expression and alterations in cellular connections leads to impaired cellular connections, which is an important risk factor for breast cancer. This result proposed the understudy gene as a new biomarker in the development of breast cancer.*

INTRODUCTION

A total of 12.5% of all cancers are breast cancer in Iran, making it the 6th leading cause of death in this nation *(1,2)*. In light of the reports enrolled in the National Cancer Registry of Iran (INCR), the yearly ASIR for malignant breast growth is 27.4 (Per 100,000) with a crude rate of 22.6 (per 100,000) *(2,3)*. In recent years, breast carcinoma growth in Iran has had an expanding pattern in rate and mortality *(4,5)*.

Conventional diagnosis and treatment of breast cancer are based on prognostic estimates using the anatomical features of cancer (TNM system) and clinical findings *(6)*. However, studies have shown that individuals respond differently to these treatments, and some patients, after the treatment, experience recurrent problems. This indicates that molecular changes occur before any phenotypic, clinical, or pathological changes and that molecular evaluations, along with clinical and pathological findings, are of paramount importance *(7)*. One of the most important of these assessments is the study of functional defects in cell junction genes and the related proteins *(8)*; studies show that disorders

in the regulation of their components play an important role in the process of malignancy and metastasis *(9)*.

Breast cancer is regulated in part by various adhesion molecules known as cadherin *(10,11)*. These molecules are responsible for key cell functions such as programmed cell death, growth, migration, and differentiation *(9)*. Cadherin is also known as tumor suppressor genes that play a unique role in tissue development and differentiation. If any dysfunction occurs due to various genetic processes, epigenetics, and mutations, it can lead to tumor growth, invasion, and metastasis *(12-14)*.

Desmosomes are intercellular junctions that mechanically connect cells in combination with intermediate filaments and stabilize tissue structure *(15)*. Desmosome structure was first observed in 1864 by the Italian pathologist Bizzozero. The structure has since been analyzed using techniques such as electron microscopy (EM) to reveal complex structures and structures. Desmosome components include three major protein families: transmembrane cadherin family (desmoglein [DSG] and desmocollin [DSC]), armadillo (ARM) protein family (plakoglobin [PKG], placophylline [PKP], and β-catenin), and the Plakin protein family (desmoplakin [DSP]). The genes encoding desmosome components are known to be mutated and can affect tissue integrity. However, they are not just static adhesive structures, but evidence that desmosomes also function as tumor suppressors or oncogenes of various cancers by regulating cell proliferation, differentiation, migration, apoptosis, and therapeutic susceptibility, is increasing *(16)*. Among the various components of desmosomes, the role of desmoglein 2 (DSG2) in cancer has not been definitively determined. According to the recent research, the expression of this gene can be used as a cancer suppressor in malignancies such as gastric, prostate, melanoma, pancreas, and colon cancers. On the other hand, research shows that this gene is overexpressed in skin cancer, stem cells carcinoma, and lung cancer *(17)*.

Desmoglein 2 (DSG2) is one of the desmosomal cadherins identified in the mammary gland. However, it is unclear how this cadherin is involved in breast cancer development and progression *(12,18)*.

In the present study, given the high prevalence of breast cancer in Iran, in addition to the special and ambiguous role of desmoglein 2 in the development of cancer, we aimed to compare the expression of desmoglein 2 in cancer tissue and healthy tissue of patients and analyzed the location of desmosomal cadherin.

MATERIAL AND METHODS

Patients and tissue samples

After obtaining the necessary permits and obtaining the code of ethics from the Ethics Committee of the Islamic Azad University, Tehran North Branch to maintain patient confidentiality in accordance with the Helsinki Agreement, patients' information was considered confidential and used only for research purposes. The patients were individuals referred to Rasoul Akram Hospital from the beginning of June 2018 to July 2019 with a breast cancer pathology diagnosis. The written informed consent was obtained from all the patients (code of ethic: IR.IUMS.REC.1399.1210). One hundred pairs of formalin-fixed, paraffin-embedded (FFPE) ductal carcinoma breast tumor tissues and adjacent normal tissues were collected. The patients' clinicopathological variables, including age, tumor size, histological grade, involvement/non-involvement of lymph nodes, and involvement/non-involvement of vascular node are summarized in Table 1.

Total RNA extraction and cDNA synthesis

Total RNA was extracted from the FFPE using TRIzol reagent (Geneall, South Korea) according to the manufacturer's instructions. RNA concentration was quantified by NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). A hundred ng RNA was used to synthesize the first-strand cDNA using the BeyoRT™ II First Strand cDNA Synthesis Kit (*SMOBIO*, Taiwan) following the manufacturer's instructions.

RT-PCR assay

RT-PCR was performed to measure the mRNA expression level of Dsg2 using the 5x Hot FIREPOL Eva Green qPCR Mix No ROX (Solis BioDyne, Estonia) at an ABI 7300 Real Time-PCR System (Applied Biosystems, Life Technologies GmbH, Darmstadt, Germany). The following PCR reaction was used: step 1: 95°C for 15 min, 1 cycle; step 2: 95°C for 15 sec, 60°C for 45 sec, 40 cycles. The primers used in this study were the same as the previous one 21 and listed as follows: Dsg2: forward 5'-TGGACACCCAAACAGTGGCCCT-3', reverse 5'-CTCACTTTGTTGCAGCAGCACAC-3'; β-actin: forward 5'-GGCACCACACCTTCTACAATGA-3', reverse 5'-TCTCCTTAATGTCACGCACGAT-3'. All samples were run in triplicates, and samples were normalized against an endogenous internal control, β-actin. Levels of Dsg2 mRNA were quantified using the $2^{-\Delta\Delta Cq}$ method.

Data analysis

All data are presented as the means ± standard deviation (SD). Statistical analyses (student's -test and one-way analysis of variance (ANOVA)) were performed using GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA, USA). Also, in these studies, the 95% confidence level (CI) was determined. To evaluate the biomarker potential of the desmoglein 2 gene, software GraphPad Prism 5 was used to draw a ROC diagram. A value of * was considered to indicate a statistically significant difference. All results presented in the study figures were obtained from at least three independent experiments.

Haemotoxylin and eosin staining

First, the tissues were recovered with the Harris' hematoxylin arrangement for 6h at a temperature of 60–

70°C and then washed in tap water until the water was colorless. Then, 10% acetic acidic and 85% ethanol in water was utilized to distinguish the tissue two times for 2 h and 10 h, and the tissues were rinsed with tap water. Within the bluing step, the tissue was doused in a saturated lithium carbonate arrangement for 12 h and after that washed with tap water. At long last, recoloring was performed with eosin Y ethanol arrangement for 48 h.

Electron microscopy

The examples were minced into 1–2 mm3 pieces, hatched for 2 h in fixative, and 1 h in 1% OsO_4 in a 0.2 M phosphate cushion (pH 7.3). The tissue was then treated with 0.5% uranyl acetic acid derivation in 0.05 M sodium maleate cushion (pH 5.2) for 2 h in obscurity. The tissue was dried out and implanted in Araldite utilizing $(CH_3)_2CO$ as intermedium. At 60°C for 48 h, functionalization was performed. Semithin areas of 0.35 µm were acquired utilizing glass cuts and stained with toluidine blue. Ultrathin areas of 50 nm were then set up with an ultramicrotome (Reichert Ultracut S, Leica, Wetzlar, Germany) utilizing precious stone blades. To upgrade contrast, the segments on copper frameworks were first treated with 3% uranyl acetic acid derivation for 5 min and afterward with lead citrate arrangement (as indicated by Reynolds 1963) for 4 min. Pictures were taken on an EM 10 (Zeiss) with a computerized camera (Olympus, Münster, Germany) utilizing the iTEM programming (Olympus). Transmission electron microscopy was utilized to describe the ultrastructure and desmosomes.

RESULTS

DSG2 expression in ductal carcinoma tissues

The results showed that the mRNA expression level of *DSG2* was significantly decreased in cancer tissues compared to the matched noncancerous tissues (p<0.01, Figure 1a). The status of differentially expressed *DSG2* gene in the breast cancer tissues was calculated as the ratio of *DSG2* mRNA expression in tumor tissue to the matched normal tissue (T/N ratio).

Correlation between DSG2 expression and clinicopathological variables

To better understand the clinical significance of *DSG2* expression in breast cancer, we analyzed the correlation between *DSG2* expression and clinicopathological variables, including involvement/non-involvement lymph node, age, histological grade, vascular non-vascular involvement and tumor size (all p>0.05). However, *DSG2* expression was not associated with the clinicopathological variables (Table 1). ROC curve analysis was performed to evaluate the biomarker potential of desmoglein 2.

This rate is at a very acceptable level, indicating the expression of this biomarker gene is suitable for diagnosing breast cancer in tissue samples. The sensitivity was 98, specificity 70, and the cutoff value 0.47 (Figure 1b).

Table 1. *The correlations between clinicopathological variables and DSG2 expression.*

variables	N	p-value
Age (years)		
≥45	18	0.1692
<45	32	
Tumor size		
> 2 cm	9	
2–5 cm	39	0.3102
<5 cm	2	
Lymph node involvement		
Yes	21	0.1604
NO	29	
Tumor grade		
I-II	35	0.3876
III	15	
Vascular involvement		
Yes	10	0.3406
NO	40	

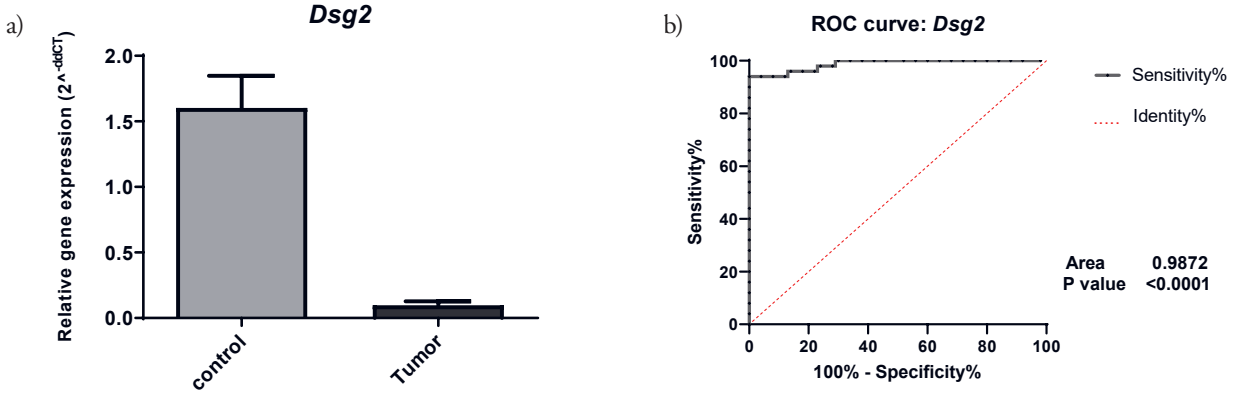

Figure 1. *a) Significant decrease in the expression level of desmoglein 2 gene in tumor cells compared to adjacent healthy tissue. b) ROC curve for desmoglein2. The area under the curve shows the biomarker potential of desmoglein 2 in breast cancer tumor tissues.*

Increased number of inflammatory nuclei and cells

In this regard, after general hematoxylin and eosin (H&E) staining, the difference between healthy tissues and tumors was observed with a light microscope. An increase in the number of nuclei was seen in tumor tissue compared to adjacent healthy tissue (Figure 2a and 2b).

In many patients, the ductal incidence was observed in cancer specimens, while in healthy specimens, none was observed (Figure 2d). The observation of ductal formation is consistent with lymph node involvement and metastasis in these patients.

Inflammatory cells were observed in the tumor tissue. However, no inflammatory cells were found in healthy tissue (Figure 2c). The presence of these cells indicates that the tissue is cancerous.

Ultrastructure disruption and desmosome junctions

In the study of normal tissue, cell cohesion, an appropriate number of nuclei, heterochromatin state, appropriate collagen fibers, interconnected cell membranes, and milk proteins are well observed, which is consistent with the definition of a normal cell (Figure 3a). In contrast, in

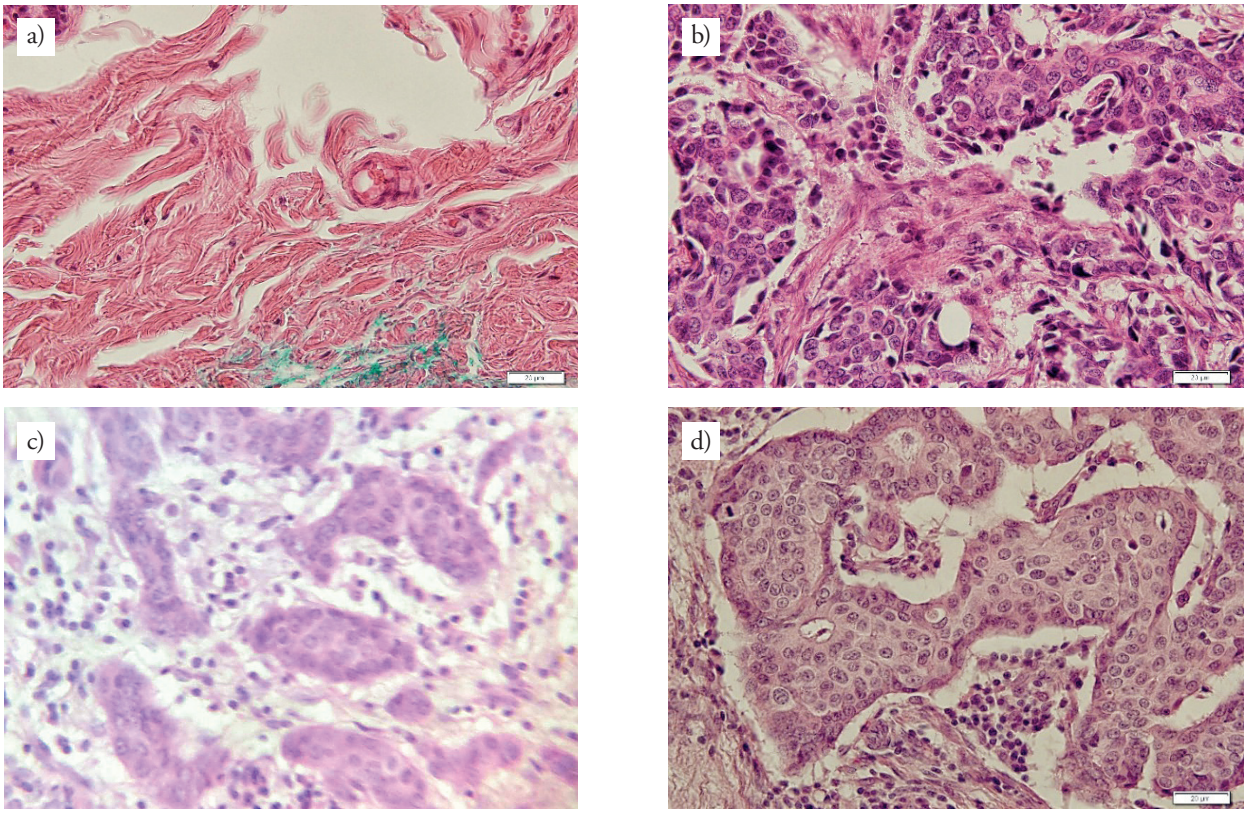

Figure 2. *Increase in the number of nuclei in the cancer cell (b) compared to the same type in a healthy sample (a) 40X. Inflammatory cells in the cancer cell (c) 40X. Ductal formation in the cancer cell (d) 40X.*

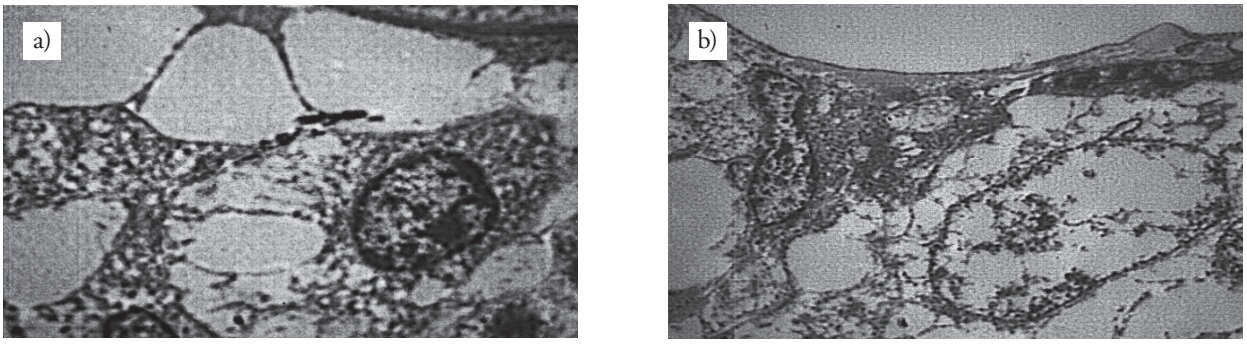

Figure 3. *Comparison of typical desmosomes in the healthy cell and cancerous cell. In a) the desmosomes (D) and nucleus (N) in heterochromatin state can be seen. In b) the desmosomes (D) rupture and nucleus (N) is in the euchromatin state are shown. Scale bar 200 nm.*

cancer cells, an increase in the number of nuclei is observed in the euchromatin state, cell membrane rupture, cell vacuolation, and a decrease in milk proteins, which is consistent with the definition of a cancer cell (Figure 3b).

Desmosome integrity was also observed in normal cells, but desmosome lack of integration was observed in tumor tissue (Figure 3).

DISCUSSION

Breast cancer is one of the most common cancer *(19)*. In recent years, several studies have been performed to identify and evaluate the genetic markers involved in cancer, which has led to identifying several predisposing genes. Among the genes, those related to cell junctions are of particular importance. Studies have recently shown that desmosomal proteins play a special role in tumor progression and inhibitory functions in different cancer types *(8,20)*.

Desmogleins are a collection of adhesion cadherins and membrane proteins that bind to other cadherins to provide the ability to bind as desmosomes between cells. Desmosomal cadherins and classical cadherins are critical for the stabilization of tissue integrity *(21)*. The main function of DSG2 is to form desmosomal adhesion structures in the epithelium, myocardium, and cardiomyocytes. However, emerging reports have suggested that DSG2 also has essential tumorigenic functions, yet its specific role is unclear *(22)*. Kai et al. showed that DSG2 expression is increased in lung cancer, and decreased regulation could suppress tumor growth *(23)*. Similarly, Barber et al., Abulrob et al., Plus Kamekura et al. found that DSG2 deficiency leads to inhibition of cell proliferation and tumor growth in colon epithelial cancer *(24-26)*. Shuhang showed that desmoglein 2 is a biomarker that causes tumor proliferation and metastasis and is associated with a poor prognosis in the early stages of cervical cancer *(27)*. In 1997, Davies and colleagues studied DSG2 (although they did not study the expression of the desmoglein 2 gene) and found a negative role in breast cancer onset and motility. They stated that the cause of this phenomenon was still unknown but reported that it was undeniable that DSG2 does not have a significant effect on cancer. Besides, DSG2 can cause angiogenesis *(28)*. Therefore, in the present study, we investigated the expression of the *DSG2* gene in breast cancer because the expression of this important desmosome binding molecule, which has a special role in the progression and metastasis of other cancers, has not been investigated. In our breast cancer studies, we found that the expression of the desmoglein 2 gene in tumor cells was decreased compared to healthy breast cells. Also, we revealed that DSG2 could be a potential biomarker. The precise and dependable estimations of the particular changes in protein biomarkers for cancer location and treatment are critical challenges *(29)*. In the following, for the importance of the subject, we examined this cadherin in more detail.

A prominent and unique feature of the structure of desmosomes is the existence of a dense electron midline between the plasma membranes in the intercellular space, which was observed by electron microscopy. Desmosomes are button-like spots. The plate desmosome connection is known as the sticky button structure. The distance between the two membranes is 200 Å, and it is located just below the strong junction, which acts as an intercellular bridge to connect two adjacent cells *(30)*. Rayns et al. described the regular structure of a desmosome *(31)*. Waschke observed that removing the DSG2 gene with the help of an electron microscope leads to the rupture of desmosomes *(32)*. With the help of the study findings, Burke and colleagues showed that decrease of desmoglein 2 leads to a noticeable change in the ultrastructural level and, to a significant extent, in the desmosomes, which is directly related to pathogenicity *(33)*. COTRUTZ, by studying E-cadherin, showed that changes in desmosomal structures promote metastatic and aggressive behavior in ductal carcinoma. He considered these changes as prognostic markers *(34)*. The COTRUTZ studies were consistent with our findings. We also showed in our study that in healthy breast tissue, desmosomal junctions are cohesive and integrated, while in cancerous tissue, this type of junction is disrupted. Our findings were also consistent with the pathological descriptions of patients who presented metastatic behavior and lymph node invasion.

CONCLUSIONS

In this study, the expression of the desmoglein 2 was examined in breast cancer. We found in our studies that the decrease of expression can alter the status of cell connections. Therefore, with the obtained results, the desmoglein 2 gene can be introduced as an effective biomarker in cancer progression and malignancy in breast cancer. Further research with longer follow-ups and a larger study population is required to study the importance of the biomarker and examine OS.

REFERENCES

1. BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA, JEMAL A 2018 Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 68(6): 394–424. https://doi.org/10.3322/caac.21492
2. ROSHANDEL G, GHANBARI-MOTLAGH A, PARTOVIPOUR E, SALAVATI F, HASANPOUR-HEIDARI S, MOHAMMADI G, KHOSHAABI M, SADJADI A, DAVANLOU M, TAVANGAR SM, ABADI H, ASGARI A, BEHROOZ M, CHERAGHI M, DANECHIN L, DOLATKHAH R, ENFERADI F, ESSHAGHI S, FARAHANI M, FARROKHZAD S, FATEH M, VAHEDI S, GOLPAZIR A, HASANZADEH M, HAZAR N, HOSEINI-HOSHYAR H, IZADI M, JAFARNIA A, JAHANTIGH M, JALILVAND A, JAZAYERI M, JOOLA P, KAZEMZADEH Y,

KHALEDNEJAD M, KOOSHKI M, MADANI A, MALEKPOUR-AFSHAR R, BAYAT AH, MOINFAR Z, MOHAMADIFAR H, MOHAMADZADEH G, MOTIDOST-KOMLEH R, NAROOEI M, NIKSIAR S, PIRNEJAD H, POORNAJAF A, POURSHAHI G, RAHNAMA A, RASHIDPOUR B, RAVANKHAH Z, REZAEI K, REZAEIANZADEH A, SADEGHI G, SHAHDADI A, SHAHI M, SHARAFI Z, SHARIFI-MOGHADAM F, SOLEIMANI A, SOLTANY-HOJATABAD M, TAHMASEBI Z, YADOLAHI S, YAGHOUBI-ASHRAFI M, ZANDIAN H, ZAREIYAN A, POUSTCHI H, ZENDEHDEL K, OSTOVAR A, JANBABAEI G, REISI A, MALEKZADEH R 2019 Cancer incidence in Iran in 2014: results of the Iranian National Population-based Cancer Registry. Cancer epidemiology 61: 50–8. https://doi.org/10.1016/j.canep.2019.05.009

3. JAZAYERI SB, SAADAT S, RAMEZANI R, KAVIANI A 2015 Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer epidemiology 39(4): 519–27. https://doi.org/10.1016/j.canep.2015.04.016
4. SHARIFIAN A, POURHOSEINGHOLI MA, EMADEDIN M, ROSTAMI NEJAD M, ASHTARI S, HAJIZADEH N, FIROUZEI SA, HOSSEINI SJ 2015 Burden of breast cancer in Iranian women is increasing. Asian Pacific Journal of Cancer Prevention 16(12): 5049–52. https://doi.org/10.7314/apjcp.2015.16.12.5049
5. ZAHMATKESH B, KERAMAT A, ALAVI N, KHOSRAVI A, KOUSHA A, MOTLAGH AG, DARMAN M, PARTOVIPOUR E, CHAMAN R 2016 Breast cancer trend in Iran from 2000 to 2009 and prediction till 2020 using a trend analysis method. Asian Pacific Journal of Cancer Prevention 17(3): 1493–8. https://doi.org/10.7314/apjcp.2016.17.3.1493
6. CSERNI G, CHMIELIK E, CSERNI B, TOT T 2018 The new TNM-based staging of breast cancer. Virchows Archiv 472(5): 697–703. https://doi.org/10.1007/s00428-018-2301-9
7. HAYES DF, SCHOTT AF 2015 Personalized medicine: genomics trials in oncology. Trans Am Clin Climatol Assoc 126: 133–43.
8. ZHOU G, YANG L, GRAY A, SRIVASTAVA AK, LI C, ZHANG G, CUI T 2017 The role of desmosomes in carcinogenesis. OncoTargets and therapy 10: 4059. https://doi.org/10.2147/OTT.S136367
9. JOHNSON JL, NAJOR NA, GREEN KJ 2014 Desmosomes: regulators of cellular signaling and adhesion in epidermal health and disease. Cold Spring Harbor perspectives in medicine 4(11): a015297. https://doi.org/10.1101/cshperspect.a015297
10. AFZAL ASHAIE M, HOQUE CHOWDHURY E 2016 Cadherins: the superfamily critically involved in breast cancer. Current pharmaceutical design 22(5): 616–38. https://doi.org/10.2174/1381612822051601270953338
11. LI D-M, FENG Y-M 2011 Signaling mechanism of cell adhesion molecules in breast cancer metastasis: potential therapeutic targets. Breast cancer research and treatment 128(1): 7–21. https://doi.org/10.1007/s10549-011-1499-x
12. ANDREWS JL, KIM AC, HENS JR 2012 The role and function of cadherins in the mammary gland. Breast cancer research 14(1): 1–10. https://doi.org/10.1186/bcr3065
13. HALBLEIB JM, NELSON WJ 2006 Cadherins in development: cell adhesion, sorting, and tissue morphogenesis. Genes & development 20(23): 3199–214. https://doi.org/10.1101/gad.1486806
14. JEANES A, GOTTARDI C, YAP A 2008 Cadherins and cancer: how does cadherin dysfunction promote tumor progression? Oncogene 27(55): 6920–9. https://doi.org/10.1038/onc.2008.343
15. HOLTHÖFER B, WINDOFFER R, TROYANOVSKY S, LEUBE RE 2007 Structure and function of desmosomes. International review of cytology 264: 65–163. https://doi.org/10.1016/S0074-7696(07)64003-0
16. DUSEK RL, ATTARDI LD 2011 Desmosomes: new perpetrators in tumour suppression. Nature Reviews Cancer 11(5): 317–23. https://doi.org/10.1038/nrc3051
17. HAN CP, YU YH, WANG AG, TIAN Y, ZHANG HT, ZHENG ZM, LIU YS 2018 Desmoglein-2 overexpression predicts poor prognosis in hepatocellular carcinoma patients. European review for medical and pharmacological sciences 22(17): 5481–9. https://doi.org/10.26355/eurrev_201809_15808
18. HUBER O, PETERSEN I 2015 150th anniversary series: desmosomes and the hallmarks of cancer. Cell communication & adhesion 22(1): 15–28. https://doi.org/10.3109/15419061.2015.1039642
19. SUNG H, FERLAY J, SIEGEL RL, LAVERSANNE M, SOERJOMATARAM I, JEMAL A, BRAY F 2021 Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 71(3): 209–49. https://doi.org/10.3322/caac.21660
20. MOHAMMADHOSSEINI M, MIRZAEI H, MAJD A, FARHADI M, SHAYANFAR N 2021 Evaluation of the Ultrastructure and Expression of Desmoglein 2 in Breast Cancer: A Novel Biomarker https://doi.org/10.21203/rs.3.rs-506346/v1 [preprint]
21. SHAFRAZ O, RÜBSAM M, STAHLEY SN, CALDARA AL, KOWALCZYK AP, NIESSEN CM, SIVASANKAR S 2018 E-cadherin binds to desmoglein to facilitate desmosome assembly. Elife 7: e37629. https://doi.org/10.7554/eLife.37629
22. BROUSSARD JA, GETSIOS S, GREEN KJ 2015 Desmosome regulation and signaling in disease. Cell and tissue research 360(3): 501–12. https://doi.org/10.1007/s00441-015-2136-5
23. CAI F, ZHU Q, MIAO Y, SHEN S, SU X, SHI Y 2017 Desmoglein-2 is overexpressed in non-small cell lung cancer tissues and its knockdown suppresses NSCLC growth by regulation of p27 and CDK2. Journal of cancer research and clinical oncology 143(1): 59–69. https://doi.org/10.1007/s00432-016-2250-0
24. KAMEKURA R, KOLEGRAFF KN, NAVA P, HILGARTH RS, FENG M, PARKOS CA, NUSRAT A 2014 Loss of the desmosomal cadherin desmoglein-2 suppresses colon cancer cell proliferation through EGFR signaling. Oncogene 33(36): 4531–6. https://doi.org/10.1038/onc.2013.442
25. BARBER AG, CASTILLO-MARTIN M, BONAL DM, RYBICKI BA, CHRISTIANO AM, CORDON-CARDO C 2014 Characterization of desmoglein expression in the normal prostatic gland. Desmoglein 2 is an independent prognostic factor for aggressive prostate cancer. PLoS One 9(6): e98786. https://doi.org/10.1371/journal.pone.0098786
26. FLEMMING JP, HILL BL, HAQUE MW, RAAD J, BONDER CS, HARSHYNE LA, RODECK U, LUGINBUHL A, WAHL JK 3RD, TSAI KY, WERMUTH PJ, OVERMILLER AM, MAHONEY MG 2020 Journal of Extracellular Vesicles 9(1): 1790159. https://doi.org/10.1080/20013078.2020.1790159
27. ZHOU BX, LI Y 2020 Significance of desmoglein-2 on cell malignant behaviors via mediating MAPK signaling in cervical cancer. The Kaohsiung journal of medical sciences 36(5): 336–43. https://doi.org/10.1002/kjm2.12182
28. DAVIES E, COCHRANE R, HISCOX S, JIANG W, SWEETLAND H, MANSEL R 1997 The role of desmoglein 2 and E-cadherin in the invasion and motility of human breast cancer cells. International journal of oncology 11(2): 415–9. https://doi.org/10.3892/ijo.11.2.415
29. COLE KD, HE HJ, WANG L 2013 Breast cancer biomarker measurements and standards. PROTEOMICS – Clinical Applications 7(1–2): 17–29. https://doi.org/10.1002/prca.201200075
30. GARROD D 2010 Desmosomes in vivo. Dermatology research and practice. 2010: 212439. https://doi.org/10.1155/2010/212439
31. BORYSENKO JZ, REVEL JP 1973 Experimental manipulation of desmosome structure. American Journal of Anatomy 137(4): 403–21. https://doi.org/10.1002/aja.1001370404
32. WASCHKE J, SPINDLER V 2014 Desmosomes and extradesmosomal adhesive signaling contacts in pemphigus. Medicinal

research reviews 34(6): 1127–45. https://doi.org/10.1002/med.21310

33. YEUNG KT, YANG J 2017 Epithelial-mesenchymal transition in tumor metastasis. Molecular oncology 11(1): 28–39. https://doi.org/10.1002/1878-0261.12017

34. ZHAO Q, SUN X, WU B, SHANG Y, HUANG X, DONG H, LIU H, CHEN W, GUI R, LI J 2021 Construction of homologous cancer cell membrane camouflage in a nano-drug delivery system for the treatment of lymphoma. Journal of Nanobiotechnology 19(1): 1–19. https://doi.org/10.1186/s12951-020-00738-8