



Original Research Article

Statistical analysis of IDC breast cancer and its representation with Koch fractal curves to prognosis

Ashraf Heidari-pour^{1,*} , Yegane Zamani² 

¹ Department of Chemistry, Khajeh Nasir Toosi University of Technology, Tehran, Iran

² Research Center Karaj Moallem, Karaj, Iran

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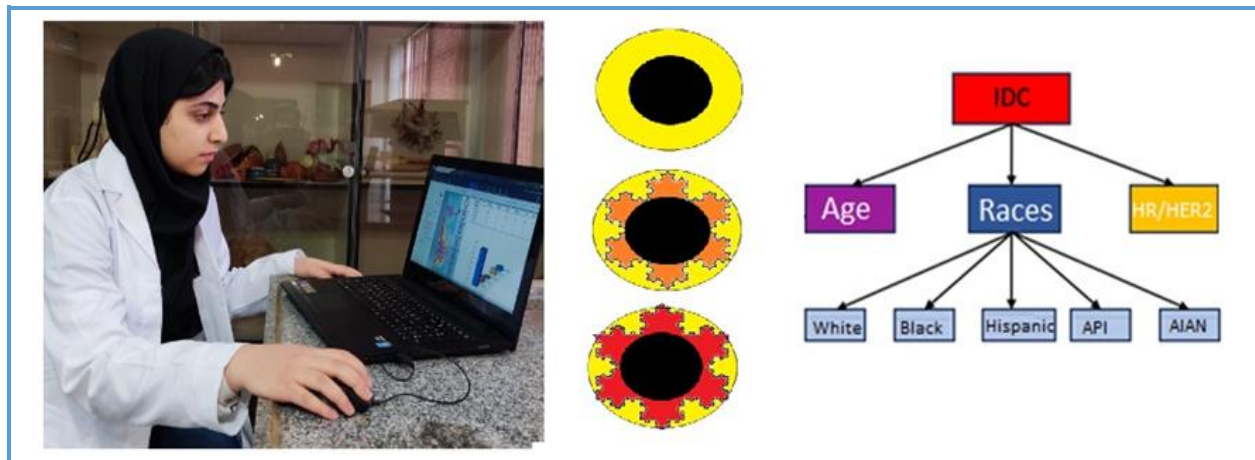
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ABSTRACT

Invasive ductal carcinoma (IDC) breast cancer is one of the most common types of breast cancer among women, with a relatively high mortality rate. Introducing new diagnostic methods to the medical field can lead to a reduction in mortality. One of these methods is statistical monitoring and social screening of people with high risk of IDC cancer. Accordingly, many variables involved in the IDC occurrence should be identified and valued and finally classified. These variables include genetic factors involved in the IDC occurrence, environmental and unknown parameters. Addressing each of the factors requires extensive research. However, in this study, it has been tried to use three effective factors in the IDC occurrence, which include age, HR/HER2 status, and race, to provide a statistical model of the IDC occurrence. This information is reported based on the research of the American Cancer Society for 5 different races, aged 20 to over 79 and with different HR/HER2 status. In this study, a statistical analysis has been done based on the age, HR/HER2 status, and race. To provide a visual presentation of statistical analysis, Koch curve has been used with Python software, which is the best curve to show the progress of IDC disease. The results showed that people in the age group of 60 to 69, with HR+/HER2-status and white race are the people with higher probability of IDC. People in the age group of 20 to 39, with HR-/HER2+ status and with black race are less likely to develop IDC. In the same way, people with characteristics between these two states can be ranked.

Graphical Abstract



Introduction

After skin cancer, breast cancer is the most common cancer in women, which is considered as one of the malignant tumors. According to the latest information published in CA-cancer magazine, the incidence of breast cancer is increasing every year. In 2019, approximately 316,700 new cases of breast cancer were confirmed in US women, with a growth rate of approximately 0.3% per year. Experts predict that by 2050, there will be around 3.2 million new cases of breast cancer worldwide [1-3].

In addition, not only the number of breast cancer patients is increasing in the world, but also the age of affected patients tends to be younger. Many factors are involved in the development of breast cancer, such as: aging, family or genetic history, weight, skin color, number of births, delivery method, race, place of residence, unhealthy sexual relations, environmental factors, and many other things that are still unknown [1-5].

As displayed in Figure 1, the milk duct initially contains several rows of normal and healthy cells. In the initial stage of IDC cancer, an accumulation of abnormal cells with a different appearance from healthy cells is

formed inside the duct, which is called ductal hyperplasia (DH). Ductal hyperplasia is the excessive growth of cells lining the ducts in the breast [4-9].

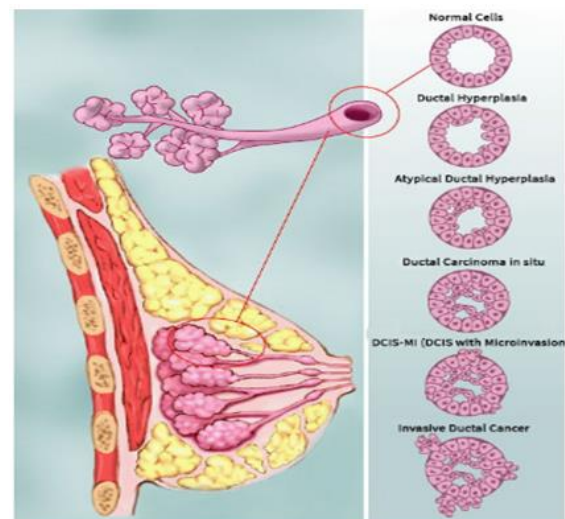


Figure 1. A view of the formation of IDC cancer.

The next stage is atypical ADH hyperplasia, where the cells look more abnormal. With the progress and spread of abnormal cell growth, ductal carcinoma in situ (DCIS) is formed, which means the presence of abnormal cells inside the milk duct in the breast. The next stage is ductal carcinoma in situ micro-invasion (DCIS-MI), which is the spread of

cancer cells beyond the basement membrane into adjacent tissue. With the spread of DCIS-MI, the cancer reaches the advanced stage of invasive ductal carcinoma (IDC) [10-15].

In this way, timely diagnosis of breast cancer in the stage of ADH and DCIS is very important. Even diagnosing breast cancer at the DCIS stage is better than reaching the IDC stage. But often, due to the lack of correct and fast diagnostic methods, breast cancer reaches the advanced stage of IDC [4].

Statement of the problem

IDC cancer is the most common type of breast cancer, which accounts for approximately 70-80% of all breast cancer diagnoses. This cancer is also common in men. Early detection of breast cancer is one of the best ways to prevent cancer progression. Cancer detection methods include mammography (MG), ultrasound (US), magnetic resonance imaging (MRI), positron emission computed tomography (PET), computed tomography (CT), and single photon emission computed tomography (SPECT), which the last three are costly and risky [3-4].

However, with all the wide range of diagnostic methods, most of the IDC cancer cannot be detected in the early stage. Recently, efforts are being made to add new diagnostic methods to the medical field, which is the statistical monitoring and social screening of people with a high risk of IDC cancer. These studies and its achievements require accurate evaluation of patients with IDC cancer and correct evaluation of all the effective factors in breast cancer and finally the selection of the most important ones. For this purpose, a detailed study should be initially done on IDC cancer patients and their personal and social characteristics should be known and classified. In the second stage, a correct evaluation should

be done on each feature [10-15]. This requires drawing related curves and studying the slope of the desired changes. In the third stage, it is necessary to write the appropriate algorithm on the important and effective factors in the IDC occurrence. Finally, the desired codes can be displayed in a 3D visual display. This image can be a measure of the probability of occurrence or progression of IDC cancer.

Significance of the study

A statistical study on IDC sufferers will help in timely and early diagnosis of this disease in others. The results of statistical analysis can be shown in different numerical, graphical, and visual ways. For many years, statistical methods have helped doctors to identify cancer-prone people. However, there is still a long way to go to reach the desired point [5,6]. As an example, presenting an infographic that contains visual and statistical analysis about breast cancer is a good way to establish a mutual relationship between the doctor and the patient. However, this type of images is only an information tool and not enough to be used as a diagnostic and prevention tool [7-9].

In this regard, the necessity of more statistical analysis and integration of statistical methods is felt with two-dimensional and three-dimensional representational methods. If fractal mathematical patterns (with non-Euclidean) that have the same growth as IDC cancer growth are used for statistical analysis, it may open a new way for early IDC cancer detection. Many researchers are studying different dimensions of the IDC cancer and interesting results have been reported [16-19]. The main goal of this study is the statistical analysis of IDC based on a mathematical algorithm and matching the algorithm with Koch fractal curves for the prognosis of IDC cancer. There are few similar studies about

mathematical algorithm and statistical feature in IDC cancer [7-10].

Hypothesis and objectives

In 2005, Delides' research group proposed a hypothesis that fractal dimension (FD) reflects tumor tissue heterogeneity. They studied the analysis of images to calculate the FD of tissue samples from patients with laryngeal carcinoma in order to check its prognostic value. They concluded that in the sample of studied patients, the FD can be used as a prognostic factor [8]. In extensive research conducted on the IDC cancer, its growth pattern has been introduced similar to Koch curve growth (Figure 2). Alan Chan's research group published a study in 2016 that challenged the common methods of cancer diagnosis. He argued that the main way to diagnose breast cancer today is through manual examination of histopathology tissue slides [9].

Such a process is often subjective and error-prone and suffers from inter-observer and intra-observer variability. He proposed the use of an automatic algorithm for the analysis of histopathology slides free of human subjectivity and presented a model whose results were promising in the use of the fractal dimension for the prognosis of tumor malignancy [9]. In the continuation of this research, some people have tried to identify the initial moments of cancer by identifying the growth pattern of cancer cells and matching them with the FD, and by this means, they have proposed a prognosis of the possibility of the formation of the IDC cancer [5]. Others are trying to provide useful infographic images for the initial assessment of people with high risk of the IDC with the help of statistical analysis and matching this information with visual patterns [7]. However, it seems that both

methods of "following the pattern of cancer growth in the IDC" and "statistical analysis of patients with the IDC" are still at the starting point and there is a long way to reach the desired point.

The Koch fractal algorithm is based on the Koch curve and with three complexity variables n , m , and p to create the cross section (A), longitudinal profile (B), and the degree of complexity n . The variable n counts the number of self-similar divisions of the equilateral triangle that produce a Koch snowflake in the limit $n \rightarrow \infty$ (Figure 2). The second complexity variable m controls the number of repetitions of the Koch curve, which is on a fixed part of the longitudinal profile. Finally, the third complexity variable p is the number of copies of such a fragment along the longitudinal span.

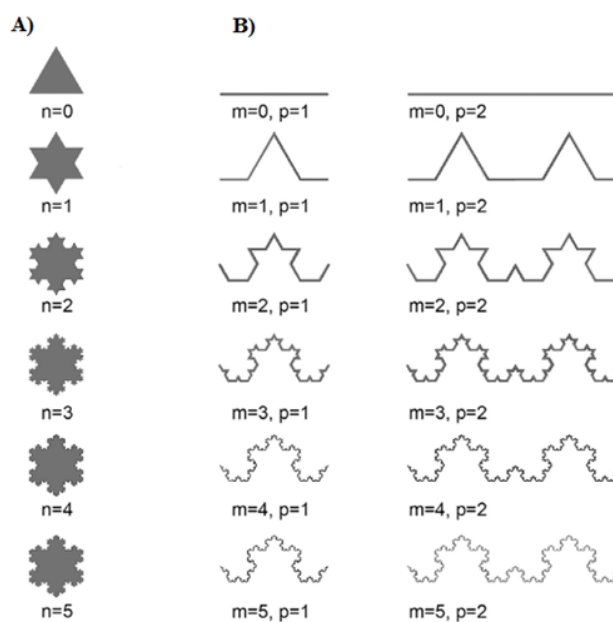


Figure 2. Three variables n , m , and p in Koch curve [6].

Research method

For the practical part of this study, the selection of variables in the Koch curve was done with three complexity variables n , m , and

p. In this way, the necessary statistical analysis was adapted from the article "Breast Cancer Statistics, 2022" published in the journal of the American Cancer Society CA cancer [7]. This information includes research conducted on five different American races. In this article, various factors such as age, hormonal status and race are reported to be effective in the IDC occurrence. The age range is from 20 to over 79 years old.

The hormonal status is ratio of hormone reception (HR), which includes two hormones, estrogen and progesterone, to the human epidermal growth factor receptor 2 (HER2). Five races of women were considered, including white, black, Hispanic, American Indian/Alaska Native (AIAN), and Asian/Pacific Islander (API), and then based on the combination of three variables n, m, and p and the minimum and the maximum states of Koch statistical curve was drawn.

Research tools

Excel software was used to draw a column chart of IDC frequency with three factors: age, HR/HER2 status, and race, and then three variables n, m, and p were selected based on the most and least influential factor in the IDC frequency. Finally, with the help of Python software, the Koch curve was drawn with three variables n, m, and p. To draw the Koch patterns in Python, the turtle library and methods such as left, right, penup, pendown, etc. were used, and finally three different curves related to three statistical patterns were drawn that can match the IDC growth pattern.

Definitions

Information on the molecular subtype of breast cancer is collected by the Cancer

Registry. Epidermal growth factor receptor number 2 (HER2) is a protein found on the surface of breast cancer cells. Its normal function is cell growth and division. Some breast cancers have HER2 more than normal. They are called HER2 positive breast cancers. However, a very small percentage of breast cancers are HER2 positive. Most breast cancers are HER2 negative. According to the National Cancer Institute (NCI), it is estimated that 78% of breast cancers are HER2 negative and do not produce much HER2.

Results and discussion

According to the statistical analysis obtained from the article "Breast Cancer Statistics, 2022", three factors of age, HR/HER2 status and race are the most important influencing factors in the incidence of the IDC.

The first important factor: Age

The most important factor in the occurrence of the IDC cancer is age. Therefore, the n variable in this study is assigned to the age variable. Based on the frequency of age groups, they are classified from n5 (the most frequent) to n0 (the lowest) that contains 6 modes. Table 1 presents the IDC frequency at different ages in ten-year intervals. The visual curve related to Table 1 is drawn as a column in Figure 3. The highest frequency of the IDC in all races corresponds to the ages of 60 to 69 (n5), and then to the ages of 50 to 59 (n4), 70 to 79 (n3), 40 to 49 (n2), over 80 (n1), 30 to 39, and 20 to 29 are jointly (n0). Choosing n0 in the age range of 20 to 39 does not mean the absence of the IDC, but it means the minimum probability of the IDC occurrence, which is considered relatively zero in this study.

Table 1. The relationship between the frequency of the IDC cancer and the age of the patients [7]

Characteristic	All races %	White %	Black %	Hispanic %	API %	AIAN %
Age of diagnosis						
20-29	1	<0.1	1	1	1	1
30-39	4	3	6	7	6	5
40-49	13	11	15	21	22	16
50-59	22	21	25	25	25	24
60-69	29	29	28	25	26	31
70-79	21	23	17	15	14	17
>80	11	12	8	7	6	7

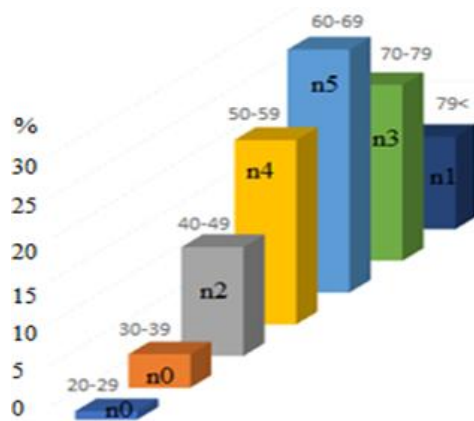


Figure 3. Graph of the IDC % with age and assignment of variable n to each category.

The second important factor: HR/HER2

The next important factor in the occurrence of the IDC is the HR/HER2 status. Therefore in this research variable m is related to the HR/HER2 status (with five statuses HR+/HER2+, HR-/HER2-, HR+/HER2-, HR-

/HER2+, Unknown). The m variables are assigned and classified based on positive or negative status from m5 (most frequent) to m1 (lowest), which includes 5 states in total. Based on Table 2 and Figure 4, for the state (all races), HR+/HER2- status (m5) results in a more severe incidence of the IDC. Furthermore, the status of HR+/HER2+ and HR-/HER2 alone is the cause of 10% of the IDC in all races. More investigation was needed to choose between HR+/HER2+ and HR-/HER2- agents.

For this purpose, these two factors were examined in more detail among races. Due to the higher percentage of the IDC probability for black race with HR-/HER2- status, variables m4 and m3 were included for HR-/HER2- and HR+/HER2- , respectively. Variable m2 was considered for unknown factor and variable m1 was considered for HR-/HER2+ status with the lowest probability of the IDC occurrence.

Table 2. The relationship between the frequency of the IDC cancer and the HR/HER status [7]

Characteristic	All races %	White %	Black %	Hispanic %	API %	AIAN %
Subtype						
HR+/HER2-	68	71	57	63	66	66
HR+/HER2+	10	9	10	11	12	10
HR-/HER2+	4	4	5	5	6	5
HR-/HER2-	10	9	19	11	9	11
Unknown	8	7	8	10	7	9

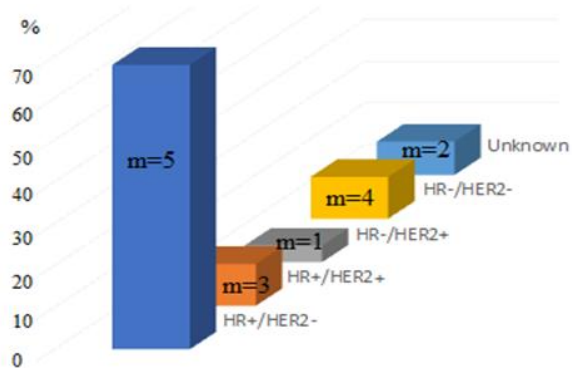


Figure 4. Graph of the IDC % based on HR/HER2 factor and assignment of m variable to each condition.

The third important factor: Race

The third most important factor in the IDC occurrence is the type of race. Variable p is assigned to the race factor in this study. The race factor was investigated based on HR+/HER2- status, which was the most important factor in the IDC occurrence. Variable p is classified from p5 (most frequent) to p1 (lowest) and includes 5 states. Based on Table 2, in the state of (All races), HR+/HER2- (m5) status in all races causes the frequency of the IDC, however, the frequency of the IDC differs from one race to another.

According to the column chart in Figure 5, variable p from the most frequent to the least occurrence of the IDC in all races are: p=5 for white race, p=4 for AIAN race, p=3 for API race, p=2 for Hispanic race, and p=1 for black race.

Relationship between effective factors in IDC with variables n, m, and p

The effective factors in the IDC incidence were valued and coded in section 3.1 to 3.3. The visual results of this work are demonstrated in Figure 6 as a curve. In this way, it is possible to find the position of each person in the graph and provide a measure of the probability of the IDC cancer in them from the sum of n, m, and p variables. For example, for an Asian/Pacific Islander (API), with 45 years of age and with HR-/HER2+ status, the sum of variables is equal to $n2+m1+p3$. This value is far from the most probable case which is equal to $n5+m5+p5$. But it contains a prognosis regarding the possibility of a person suffering from the IDC cancer, because it is far from the least probable of $n0+m1+p1$.

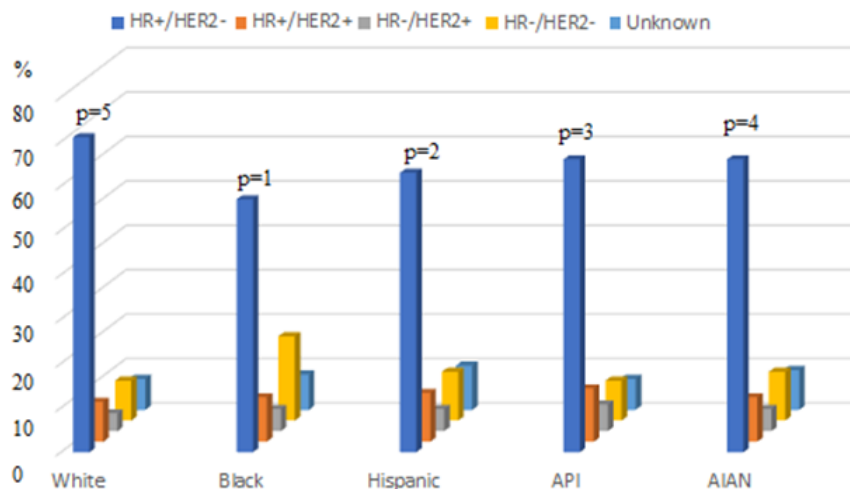


Figure 5. Graph of the IDC% in five different races (based on HR+/HER2- status) assignment of variable p to each race.

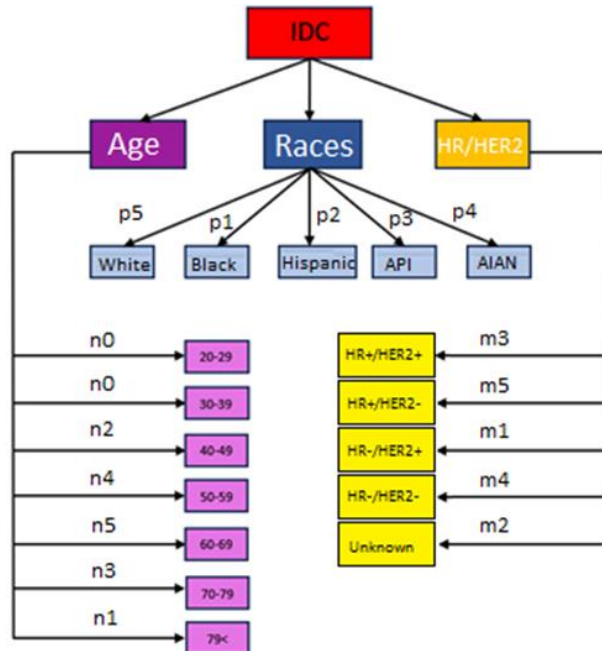


Figure 6. Trend of assigning n , m , and p variables to the influencing factors in the occurrence of the IDC.

Statistical analysis of the IDC with variables n , m , and p in the Koch curve

Providing statistical analysis about the IDC patients in the form of a Koch curves can also be a measure to estimate the growth rate of milk duct cancer cells (IDC incidence). Although Koch curve is actually a representation of statistical analysis, it can also show the index and amount of IDC progression in the milk ducts of sufferers as a clinical aspect. Therefore, combining these two concepts (statistical and clinical) is an innovative and suitable method. In Figure 7, the command related to one state is illustrated with the help of Python software. In this section, statistical analysis on the IDC frequency is displayed as a representation of the growth of milk duct cancer cells.

```
import turtle
wn=turtle.Screen()
wn.title('snowflake fractal drawing')
snowflake_turtle=turtle.Turtle()
snowflake_turtle.penup()
snowflake_turtle.goto(-250,150)
snowflake_turtle.pendown()
def snowflake_side(length, depth):
    if depth==0:
        snowflake_turtle.forward(length)
        return
    length/=3.0
    snowflake_side(length, depth -1)
    snowflake_turtle.left(60)
    snowflake_side(length, depth -1)
    snowflake_turtle.right(120)
    snowflake_side(length, depth -1)
    snowflake_turtle.left(60)
    snowflake_side(length, depth -1)

for _ in range(3):
    snowflake_turtle.pensize(4)
    snowflake_turtle.speed(300)
    snowflake_side(500,4)
    snowflake_turtle.right(120)
```

wn.exitonclick()

Figure 7. Python command for one state.

According to what was mentioned in section 3.1 to 3.5, from the examination of the sum of the three variables n , m , and p in Figures 3, 4 and 5 it can be mentioned:

1. There are six states for n , five states for m and five states for p . With combinations of three of these states, several possibilities for the IDC occurrence can be obtained, for example, $n1+m3+p5$.

2. The minimum probability of the IDC is for $n0+m1+p1$. At this stage, there is no evidence of the onset of the disease; both statistically and clinically.

3. The probability of the IDC occurrence for a large number of states such as $n3+m2+p1$ is moderate (between the minimum and the maximum).

4. The maximum probability of the IDC occurrence can be considered for $n5+m5+p5$ mode.

For visual representation, two concentric circles were drawn as shown in Figure 8(A). The black space is a measure of the inner surface of the milk duct, and the yellow space is a measure of the empty space of the milk duct (ductal). In the state of complete health or no progression of the IDC, the duct is open and there is no blockage.

To show the progression of the disease, a Koch curve was used, which was drawn with Python software. With the development of the Koch curve, the extraneous snowflakes are drawn towards the larger circle, which is a symbol of the growth of cancer cells. With the progress of the disease (Figure 8(B)) and the growth and spread of cancer cells (red color), the duct becomes narrower and the volume of the empty space of the milk duct decreases. In the most advanced state (Figure 8(C)), the growth of cancer cells exceeds the inside of the duct and spreads to the outside of the duct.

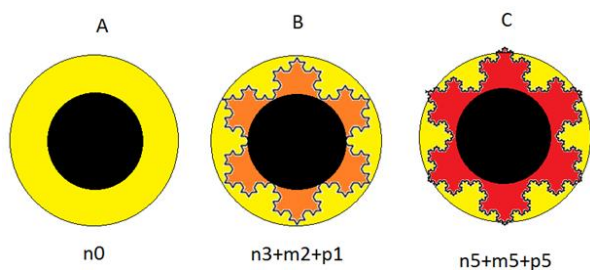


Figure 8. Schematic representation of the IDC cancer spread based on Koch snowflake growth curve.

Accordingly, it can be mentioned that if the patient's conditions (age, HR/HER2 status, and race) are more likely to develop the IDC, in other words, they have higher n , m , and p variables, with high probability of developing the IDC cancer and in case of infection the growth of cancer cells in the breast duct happens at a faster rate. In the same way, if the

patient's conditions are less likely to occur in the IDC, and they have lower n , m , and p variables, the probability of the IDC cancer is lower, and in case of infection, the growth of cancer cells in the breast duct happens at a slower rate. The general results of this study are a suitable answer to some assumptions and preliminary questions. Concerning the disease progression variables that include n , m , and p and assigning them to three factors affecting the IDC incidence, which are age, HR/HER2 status, and race, an algorithm was extracted from these variables and factors.

Visual display is a suitable solution to provide statistical analysis on the incidence rate of the IDC cancer and its progress (clinical) amount, which leads to a prognosis. Therefore, it is possible to write a program that can predict the probability of the IDC occurrence in a healthy person based on information or provide the amount of disease progress. However, more detailed and comprehensive information is needed that are not mentioned in this study.

Conclusion

Breast cancer Invasive ductal carcinoma, IDC, is a cancer with a high incidence and mortality rate in women. The most important factors of the IDC include age, HR/HER2 status, and race. Age is the most important factor in the IDC incidence, which is assigned to variable $n0$ to $n5$. The HR/HER2 status is the second most important factor in the IDC incidence, which is attributed to the variable $m1$ to $m5$. HR+/HER2- status is the most effective status among all HR/HER2 statuses in the IDC occurrence. Race is the third most important factor in the IDC occurrence, which is given from $p1$ to $p5$ according to HR+/HER2- status. Assigning the three variables n , m , and p to the factors of IDC incidence leads to the creation of

a statistical algorithm of the IDC incidence presented as a trend. Drawing the Koch curve based on n , m , and p variables leads to different images of the growth rate of the. The growth rate of the Koch curve is a measure of the probability of the IDC cancer and the rate of cancer growth. In this study, only three factors were considered. It seems that by considering all effective factors in the IDC, better statistical analysis can be achieved in Koch curves.

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Orcid

Ashraf Heidari pour : 0000-0003-0223-5383

Yegane Zamani : 0009-0007-2791-8312

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