Kisspeptin 54 as biomarker for breast and ovarian cancer

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Abstract

Cancer disorders are the world's second leading cause of death caused in 90% of cases but the development of metastasis, that are the clinical result of the extremely invasive behavior of cancer, metastasis is the major cause of cancer-related deaths. The Metastatic suppressor activity of Kisspeptin system was identified cancer cells The current study aimed to reveal the relationship between kisspeptin and CA15-3, Ca125 in women with breast and ovarian cancers. The study included 142 women, 61 confirmed breast cancer 41 ovarian cancer, and 40 apparently healthy control whose ages ranging between 40-57 years. CA15-3, CA125, and kisspeptin-54 were determined in serum of all subjects. Depending on breast cancer, BMI level raised significantly in cancer women with non-metastasis compared with metastasis and healthy women, BMI level raised significantly in ovarian cancer women with non-metastasis when compared with metastasis], and healthy women. Kisspeptin level increased significantly in women with non-metastasis breast cancer but it decreases significantly in women with metastasis when compared with healthy women. Kisspeptin level showed increased significantly in women with non-metastasis and metastasis when compared with healthy women. We found a negative correlation between kisspeptin and CA125 in ovarian cancer patients with metastasis. The body mass of women with breast and ovarian cancer increases with non-metastatsis Kisspeptin 54 and CA125 immunoreactivity are substantially linked to ovarian cancer, making them the first independent predictive biomarkers for the disease.

Keywords: *Kisspeptin 54; breast and ovary cancer; metastasis.*

كيسبيبتين 54 كمؤشر بيولوجي لسرطان الثدي والمبيض

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الخلاصة

تعد اضطرابات مرض السرطان السبب الرئيسي الثاني للوفاة في العالم التي تحدث في 90٪ من الحالات ، وكنتيجة لتطور الحالة السريرية يحدث ما يدعى بانشار الخلايا السرطانية وهي السبب الرئيسي للوفيات المرتبطة بمرض السرطان. تم التعرف على نشاط المثبط النقيلي لنظام كيسبيبتين-54 الخلايا السرطانية. هدفت الدراسة الحالية إلى الكشف عن العلاقة بين الكيسبيبتين وCA15-3 ، Ca125 في النساء المصابات بسرطان الثدي والمبيض. اشتملت الدراسة على [142] امرأة ، [61] إصابة مؤكدة بسرطان الثدي

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[41] سرطان المبيض ، و [40] امراة من الاصحاء كمجموعة ضابطة سيطرة تتراوح أعمارهن بين [40-57] سنة. تم تحديد CA15-3و CA125 و kisspeptin-54 في مصل جميع النساء. اعتمادًا على سرطان الثدي ، ارتفع مستوى مؤشر كتلة الجسم بشكل ملحوظ في النساء المصابات بالسرطان المبيض المنتشر مقارنة وتم مقارنتها بمجموعة المصابات بالسرطان غير المنتشر والنساء الأصحاء ، ارتفع مستوى مؤشر كتلة الجسم بشكل ملحوظ في النساء المصابات بسرطان المبيض غير المنتشر عند مقارنته بالنساء المصابات بالسرطان المنتشر والنساء الأصحاء..أظهر مستوى الكيسبيبتين-54 زيادة ملحوظة في النساء المصابات بسرطان الثدي الغير منتشر عند مقارنتهم بالنساء الاصحاء. كما بينت الدراسة وجد علاقة سلبية بين كيسبيبتين-54 و CA125 في مرضى سرطان المبيض المنتشر. تزداد كتلة جسم النساء المصابات بسرطان الثدي والمبيض الغير منتشر يرتبط نشاط كيسبيبتين 54 و CA125المناعي بشكل كبير بسرطان المبيض ، مما يجعلهن أول المؤشرات الحيوية التنبؤية المستقلة لمرض.

الكلمات المفتاحية : *كيسبيبتين 54 ، سرطان الثدي والمبيض ، ورم خبيث.*

Introduction

Cancer is defined as a heterogeneous group of diseases, characterized by uncontrolled cell growth [1]. Cancer disorders are the world's second leading cause of death caused in 90% of cases but the development of metastasis, that are the clinical result of the extremely invasive behavior of cancer [2]. Metastasis is the major cause of cancer-related deaths. After treatment of primary cancer, despite being considered disease free, a substantial cohort of cancer patients' relapse in a type specific manner. The time between the disease-free announcement and relapse is called metastatic latency. Particularly, long metastatic latency [years], or metastatic dormancy, has been clinically observed in breast, cancer [3]. The metastasis of cancer cells hinges upon a series of successive events; hence, interrupting any one step could halt the process [4]. Metastasis suppressors, defined by their abilities to inhibit metastasis without blocking orthotopic tumor growth [5]. The Metastatic suppressor activity of Kisspeptin system was identified breast cancer cells [6]. The kisspeptin (Kisspeptin-54) is a 54 amino acid peptide encoded by the metastasis suppressor gene KiSS-1[7], The expression of the KISS1 gene in human nonmetastatic melanoma cells was first discovered in 1996 [8].

This discovery led to the hypothesis that KISS1 expression in melanoma cells imparted a nonmalignant phenotype [10]. Within a year, it was discovered that KISS1 expression suppressed metastasis in human breast cancer cells [9]. KISS1 encodes a peptide that was initially identified from the human placenta in 2001. One study group termed it metastin to refer to its anti-metastasis capabilities [10]. KISS1 has been found to be responsible for the invasive and migratory features of tumor cells without influencing tumorigenicity [9]. It is found on the short arm of chromosome 1 and has four exons (1q32). Exons 2 and 3 are coding exons among the four exons. Shorter kisspeptins (Kp) with 10, 13, 14, or 54 amino acid residues have also been discovered [11، 12]. The KiSS1 gene codes for a 145 amino acid polypeptide (Kp-145) [13], but shorter kisspeptins (Kp) with 10, 13, 14,

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or 54 amino acid residues have also been reported [11،12]. The current study aimed to reveal the relationship between kisspeptin and CA15-3, Ca125 in women with breast and ovarian cancers.

Material and subjects

The study included 142 women, 61 confirmed breast cancer 23 with metastasis, and 38 non-metastases, 41 ovarian cancer 9with metastasis, and 32 non-metastases, and 40 apparently healthy control whose ages ranging between 40-57 years. BMI estimation BMI = kg/m2, whereby kg represents a human's in kg as well as m2 represents their heights in metres square. Overweight is defined as a BMI of 25.0 or higher, whereas the normal range is 18.5 to 24.9. Most persons between the ages of 18 and 65 have a BMI. The samples were collected during the period from May 2020 – June 2021, they were among outpatients. CA15-3 and CA125 analyzed by using an automated quantitative COBAS e411 test (from Roche, Germany), kisspeptin-54 were determined in serum of all subjects by using a commercially ELISA Micro wells kit.

Statistical analysis

SPSS 20. Software (SPSS, Inc., Chicago, IL, USA) was used to analyze continuous variables, the mean and standard error was calculated, and expressed as the mean ± standard error. The statistical analysis was performed using one-way analysis of variance (ANOVA) test. $P \leq 0.05$ was measured to indicate a statistically significant difference.

Results

Depending on breast cancer, BMI level raised significantly in cancer women with non-metastasis (29.00 ± 0.42) when compared with metastasis (23.92 ± 0.18), and healthy women (24.21 ± 0.50). Based on ovarian cancer, BMI level raised significantly in ovarian cancer women with non-metastasis (30.45 ± 0.42) when compared with metastasis (23.90 ± 0.14), and healthy women (24.21 ± 0.50), There is non-significantly different between healthy women and cancer women Breast and Ovarian with metastasis.

Table (1) :BMI in Women with breast and ovarian cancer patients and healthy Women.

Breast Cancer			
Groups		**Mean ± Std. Error**	**ANOVA P-Value**
BMI	Control	24.21 ± 0.50	Control Vs Metastasis 0.710 Control Vs Non-Metastasis 0.005 Non-Metastasis Vs Metastasis 0.000
	Metastasis	23.92 ± 0.18	
	Non-metastasis	29.00 ± 0.42	
Ovarian Cancer			
BMI	Control	24.21 ± 0.50	Control Vs Metastasis 0.731 Control Vs Non-Metastasis 0.000 Non-Metastasis Vs Metastasis 0.000
	Metastasis	23.90 ± 0.14	
	Non-metastasis	30.45 ± 0.42	

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Table 2 illustrated CA-15 level, and Kisspeptin-54 in women with breast cancer, the CA-15 level showed increased significantly in women with non-metastasis (44.75 ± 1.50) and metastasis (118.26 ± 2.25) when compared with healthy women (11.38 ± 0.49), while it increased significantly in metastasis compared with non-metastasis Figure (1). Kisspeptin level increased significantly in women with non-metastasis breast cancer (562.2 ± 15.31) when compared with metastasis (105.31 ± 2.69), and healthy women (235.57 ± 5.37), but it decreases significantly in women with metastasis when compared with healthy women. Figure (2).

Table (2): CA-15-3 and Kisspeptin-54 in Women with breast cancer patients and healthy Women.

Breast Cancer			
Groups		**Mean ± Std. Error**	**ANOVA P-Value**
CA-15-3 [I.U/ml]	Control	11.38 ± 0.49	Control Vs Metastasis 0.000 Control Vs Non-Metastasis 0.000 Non-Metastasis Vs Metastasis 0.000
	Metastasis	118.26 ± 2.25	
	Non-metastasis	44.75 ± 1.50	
Kisspeptin-54 [pg/ml]	Control	235.57 ± 5.37	Control Vs Metastasis 0.000 Control Vs Non-Metastasis 0.000 Non-Metastasis Vs Metastasis 0.000
	Metastasis	105.31 ± 2.69	
	Non-metastasis	562.2 ± 15.31	

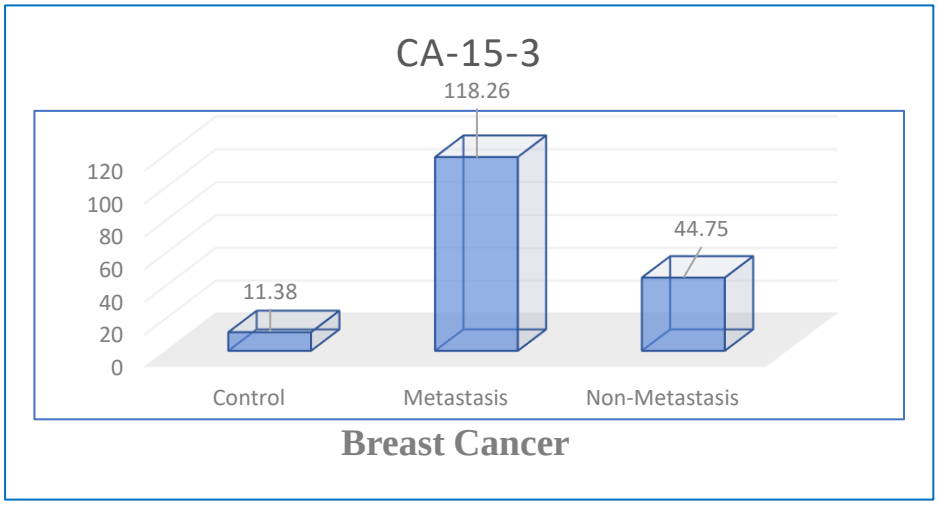

Fig. (1): CA-15 in breast cancer and healthy women.

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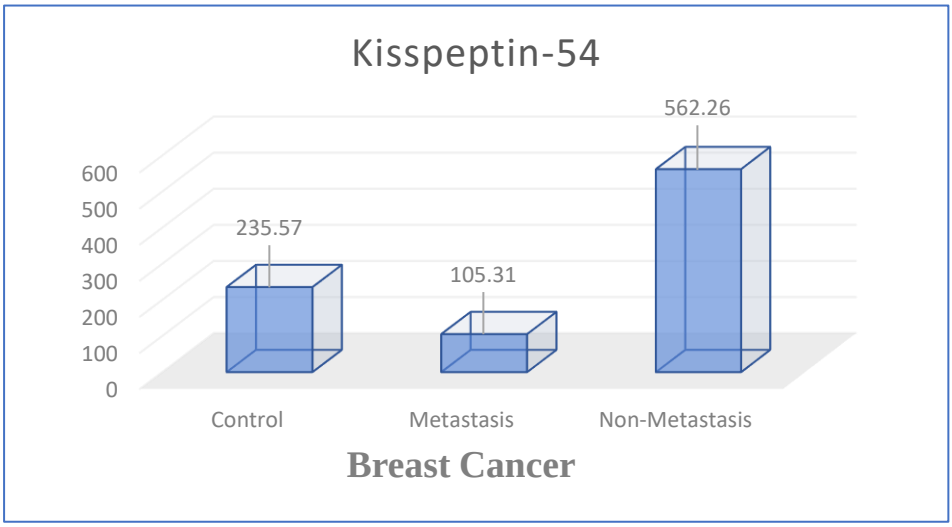

Fig. (2): Kisspeptin-54 in breast cancer and healthy women.

Table 3 illustrated CA-125 level, and Kisspeptin in women with ovarian cancer, the CA-125 level showed increased significantly in women with metastasis (719.00 ± 7.68) when compared with non-metastasis (440.07 ± 10.20) and healthy women (17.65 ± 0.90), as well as it increased significantly in non-metastasis when compared with healthy women Figure [3].

Kisspeptin level showed increased significantly in women with non-metastasis (170.02 ± 7.63) when compared with metastasis (71.20 ± 1.29) and healthy women (33.96 ± 5.37), and also increased significantly in metastasis when compared with healthy women. Figure (4).

Table (3): CA-125 and Kisspeptin in Women with ovarian cancer patients and healthy Women.

Ovarian Cancer			
Groups		**Mean ± Std. Error**	**ANOVA P-Value**
CA-125 [I.U/ml]	Control	17.65 ± 0.90	Control Vs Metastasis 0.000 Control Vs Non-Metastasis 0.000 Non-Metastasis Vs Metastasis 0.000
	Metastasis	719.00 ± 7.68	
	Non-metastasis	440.07 ± 10.20	
Kisspeptin-54 [pg/ml]	Control	33.96 ± 5.37	Control Vs Metastasis 0.000 Control Vs Non-Metastasis 0.000 Non-Metastasis Vs Metastasis 0.000
	Metastasis	71.20 ± 1.29	
	Non-metastasis	170.02 ± 7.63	

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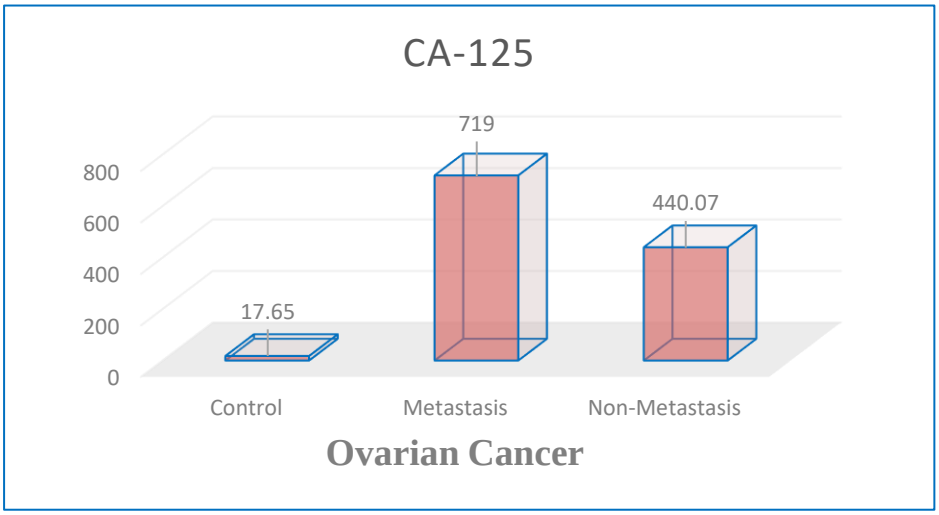

Fig. (3): CA-125 in ovarian cancer and healthy women.

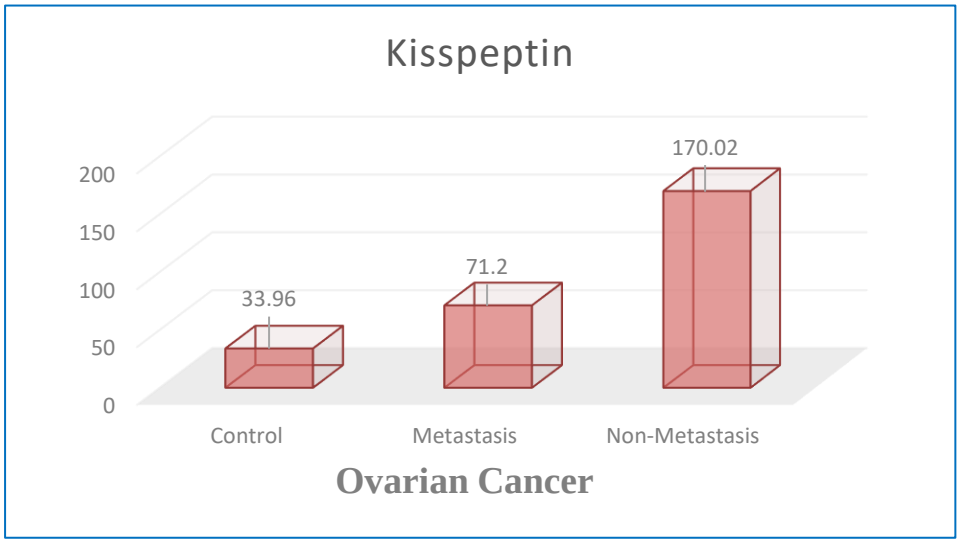

Fig. (4): Kisspeptin in ovarian cancer and healthy women.

Table 4 illustrated no correlation between kisspeptin and CA15 in patients with breast cancer, and showed illustrated negative correlation between kisspeptin and CA125 in ovarian cancer patients with metastasis (r = -0.329) p-value (0.036), but no found correlation between kisspeptin and CA125 in ovarian cancer patients with non-metastasis.

Table (4): correlation between kisspeptin and CA15-3, and CA125 in metastasis and non-metastasis in breast and ovarian cancer.

Brest and Ovarian cancer		**Kisspeptin-54 and CA15**	**Kisspeptin-54 and CA125**
Metastasis	Pearson Correlation Sig. [2-tailed]	0.119 0.458	-0.329* 0.036
Non-Metastasis	Pearson Correlation Sig. [2-tailed]	0.119 0.458	0.119 0.458

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Disscuction

The results of the current study showed that the body mass ratio is high in metasatsis and non-metastasis patients with breast and ovarian cancer, With increasing BMI, there is a statistically meaningful increase in the risk of breast cancer. Given the high rates of overweight and obesity among breast cancer survivors, these results have major public health consequences and highlight necessity effective preventative interventions [14]. Significantly high body fat concentrations were linked to an increased risk of invasive breast cancer and changed levels of circulating metabolic and inflammatory markers in post - menopausal women with a normal BMI. In post - menopausal women, a healthy Bmi classification may be an insufficient predictor of breast cancer risk [15]. Obesity and breast cancer had a positive link in post - menopausal women, but a negative correlation in premenopausal women, according to Park et al., (2020)[16]. Obesity is linked to a variety of malignancies. In obese subjects, Reitman (2021) discovered enhanced creatine production by adipocytes close to breast tumors. Creatine is carried into cancer cells, presumably due to increased energy availability, resulting in bigger tumors. The results suggest that factors influencing breast cancer rates, such as age, menopause, family background of breast cancer, and BMI, may have an effect on clinically meaningful approach proposes, which could have consequences for monitoring, prognosis, and therapy [17،18].In females with metastatic cancer, being overweight or obese is not linked to a worse prognosis, whereas being underweight appeared to be an independent predictor [19]. Mechanical loading appears to be a noninvasive, therapeutic approach for reducing breast cancer-related bone metastases, particularly in obese individuals, according to the findings.Obesity affects the lung milieu prior to tumor development, generating niches permissive to metastatic breast cancer growth, according to the findings [20].

Higher BMI was significantly related with far worse longevity in non-metastatic breast cancer in a huge high dataset, but strangely, higher BMI was significantly associated with better survival in metastatic breast cancer [21]. Patients with non-metastatic breast cancer who had a high BMI had poorer health, which could be understood by the disordered adipose tissue environment and its impact on the immune response [22]. Chemotherapy for non-metastatic breast cancer did not trigger substantial weight alterations in Saudi Arabian women, according to experts. Weight increase was linked to a younger age, post menopausal status, and a huge proportion of taxane-based chemotherapy sessions in this study [23]. Obesity was linked to a slightly worse prognosis of non-metastatic breast cancer, as well as disease-free [DFS] and overall survival [OS] in all breast cancer subtypes, according to Lohmann et al., (2021) [24]. Obesity's affect the development of female-

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specific malignancies varied depending on the malignancy kind and menopausal status, according to a major inhabitants cohort research in Korean women. Females in Korea and Western countries showed similar patterns [25]. Obesity was linked to a higher overall mortality rate in cancer patients. Individuals with lung disease, renal cell carcinoma, and melanoma who were obese had a decreased chance of death than those with the same diseases who were not obese. Weight-loss treatments may be useful in lowering mortality rates in these people [26]. Obesity is becoming more widely recognized as a poorly prognostic marker for a variety of cancers, including those of the breast, prostate, and colon, and numerous lines of data indicate that overweight may also be linked to poor prognosis among females with ovarian cancer [27]. According to Nagle et al., [2015] [28], a higher BMI is linked to a poor prognosis in the majority of women having ovarian cancer. Adult weight growth is a health risk for ovarian cancer in people with BRCA1 [BReast CAncer gene 1] and BRCA2 [BReast CAncer gene 2] mutations, according to Kim et al., (2021) [29]. It is hypothesized that mother post-partum mass maintenance, rather than pregnancy weight growth, may contribute to the risk of epithelial ovarian cancer in normal/underweight women. Whether other investigations meant to directly test this idea back up the theory, then educating women on the need of good weight control after delivery could be another way to help women lower their risks of this often-fatal cancer [30].

Generally, the results backed up earlier findings that overweight elderly patients tolerate complete body-size–based chemotherapy dose just as well as non - obese patients. Less studies that have looked at the dose of targeted treatments and immunotherapeutic in obese patients in terms of safety and effectiveness [31]. Individuals with epithelial ovarian cancer who are obese do not even have a worse lifespan if they get adequate chemotherapy dosages depending on their glomerular filtration rate and their body mass [32].

Obesity has a strong impact on ovarian cancer metastasis recurrence, according to the data, that likely adds to the poor link between obesity and ovarian cancer longevity [33]. Obesity as well as ovarian cancer longevity may vary depending on phase, with lower longevity in those with localized disease and higher longevity in those with delayed disease. Obesity's stage-specific impacts on survival indicate that a personalized approach to improving prognostic may be necessary [34]. Obesity seems to raise the risk of ovarian cancer's fewer common pathological subcategories but not of elevated invasive serous tumors, therefore lowering BMI is uncertain to protect the proportion of ovarian cancer cases [35،36]. The findings show that cellular metabolism adaptability may help women having metastatic ovarian cancer live longer within non-permissive circumstances, and these metabolic adjustments could be candidates for future therapies aimed at improving survival [37]. The

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observations of Al-Wahab et al., (2014) encourage further research into the role of diet modification as an adjuvant to certain other anticancer medications and as a viable customized therapy plan for epithelial ovarian cancer [38]. KiSS1 has been studied in a variety of malignancies, including colon, stomach, prostate, and lung cancers [39، 40]. Kisspeptin is a protein produced by the KISS1 gene that has been shown to decrease the ability of certain cancer cells to spread [6.10], and KISS1 expression levels have been found to be lower in metastatic cancer tissue than in nonmetastatic cancer tissue [41]. In this study Kisspeptin level increased significantly in cancer women with non-metastasis, and but it decreases significantly in women with metastasis when compared with healthy women and A negative correlation between kisspeptin and CA125 in ovarian cancer patients with metastasis were found Dhar *et al.,* (2004) showed gastric tumors with reduced KiSS1 showed distant metastases, according to [39]. Schmid et al., (2007) looked at the expression of the KiSS1 gene in HCC and discovered that it was lower in non-cancerous mucosa than in cancerous mucosa [41]. The findings imply that KiSS-1's distinct mechanism of action is capable of delaying the metastatic cascade by limiting metastatic cell proliferation and colonization in distant locales[42].That KiSS1 has been shown to inhibit metastasis in a variety of malignancies, including gastric cancer, esophageal carcinoma, pancreatic cancer, ovarian cancer, bladder cancer, and prostate cancer [42].

Conclusion

The body mass of women with breast and ovarian cancer increases with non-metastatsis Kisspeptin 54 and CA125 immunoreactivity are substantially linked to ovarian cancer, making them the first independent predictive biomarkers for the disease.

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