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Assessment of I-CAM1, V-CAM1, and E-selectin Serum Levels in Patients with Breast and Pelvic Cancer: A Case Control Study

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Abstract

Background: Breast and pelvic cancers are the most prevalent cancers among women globally. Several studies have reported on the effect of cell adhesion molecules on the growth, multiplication, invasion, and metastasis of tumor cells as well as inflammatory biomarkers, which are responsible for harmful inflammatory processes.
Objectives: The purpose of the current study was to assess the serum levels of adhesion molecules intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in patients with cancer before and after radiotherapy, compare these with the levels of healthy subjects, and consider the relationship of these levels with the tumor origin.
Methods: The present case-control study investigated 14 patients with breast cancer and 14 patients with pelvic cancer who had been referred to Omid Teaching Hospital's oncology clinic, Mashhad, Iran between 2015 and 2017. Evaluated by the ELISA method for ICAM-1, VCAM-1, and E-selectin were the serum samples of these 28 cancer patients before and after their course of radiotherapy treatment and the serum samples of the 28 healthy subjects who had no history of cancer, radiotherapy or the risk factor of coronary artery disease.
Results: The ICAM-1, VCAM-1, and E-selectin serum levels of all patients with cancer before and after a course of radiotherapy were significantly higher than those of the control group (P-value $\leq$ 0.5). There was no significant difference between the two cancer groups before and after radiotherapy (P-value $\geq$ 0.05).
Conclusions: The current study demonstrated that the serum levels of adhesion molecules in patients with cancer before and after radiotherapy increase significantly regardless of the initial location of the tumor.

Keywords: Breast Cancer, Pelvic Cancer, Cell Adhesion Molecules, ICAM-1, VCAM-1, E-selectin

1. Background

The critical impact of cancer is palpable due to its high mortality rate. Cancer was the second most common cause of death worldwide with 8.8 million victims succumbing to this disease in 2015. In Iran, cancer ranks third in disease-related deaths (1, 2). Despite insightful studies and improvements in treatment, cancer remains a global killer (3). Cancers with the highest mortality rates are those of the lung, liver, colon and rectum, stomach, and breast (2).

Pelvic cancer in females includes the cervix, uterus, vagina, colon, and rectum. Endometrial cancer is the fourth most prevalent cancer among women in developed countries in terms of gynecologic malignancy (4). Also, colorectal cancer is the third most prevalent cancer and the fourth greatest cause of death among all cancers (5).

Nowadays, 12% of women in the world suffer from breast cancer (6). This is the most prevalent cancer with the highest cause of mortality among females worldwide (7, 8).

It should be noted that breast cancer becomes more life-threatening when the lymph nodes and new sites of cancer in the body involve metastasis. As a result, deaths from breast cancer are more likely to occur in the metasta-

sis stage as opposed to the primary stages (9).

There are some approaches for locally treating the primary stages of breast cancer, such as oophorectomy, mastectomy, iron chelation therapy, and hormone therapy (8, 10, 11). However, none are adequate to prevent tumor growth (10). In any case, cancer mortality can be controlled by early diagnosis and treatment. Not only does early diagnosis increase the chances of survival, but also it can also reduce morbidity and expensive treatment (2). It has been shown that cell adhesion molecules (CAMs) contain vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectins. These exert a profound effect on the adhesion of cells to the vascular endothelium and may be related to the metastasis and development of cancer (10, 12). As there are some disorders in the cell expression or structure and a meaningful change in the serum level of CAMs, new strategies in cancer treatment have been suggested based on adjusting the serum level of these molecules by the production of antibodies (13).

Cell adhesion molecules are some surface structures that can bind cells to each other or the extracellular matrix. These molecules take part in biological and physiological processes, such as detachment migration survival and metastases. Despite playing a major role in tumorigenesis, CAMs have recently been considered for possible use in the diagnosis or clinical evaluation of various types of cancer (14, 15). Although there is a measurable number of CAMs in the serum samples of healthy patient groups, any structural disorders or the serum concentration changes of CAMs significantly impact breast cancer, gastrointestinal cancer, melanoma, and hematological malignancies (16, 17). As the main strategy for treating various cancers, especially pelvic and breast cancer, radiotherapy can present patients with some major side effects that call for careful consideration (18).

The interactions between radiotherapy and cell adhesion molecules can be considered as a marker for the evaluation of the response to radiotherapy. In addition, the number of changes in CAM cell expression after radiotherapy can be recognized as a marker for forecasting the primary stages of radiation toxicity (19).

Therefore, when approaching the development of new strategies in cancer treatment, it is beneficial to understand the specific mechanisms of metastasis adjustment, such as the movement of leukocytes in the blood circulation to damaged tissues or infections, just as tumor cells do in the early stages of metastasis (20).

Because of the pressing importance, complications, and high mortality rate of cancer and the matter of early cancer detection, the present work conducted a comparison check of the serum levels of adhesion molecules VCAM-1, ICAM-1, and E-selectin in patients with breast and pelvic cancer undergoing radiotherapy against those of healthy subjects.

2. Objectives

In the current study, we divided the patients with cancer into 2 groups (breast cancer and pelvic cancer) to examine the relationship between the primary site of the tumor and the serum level of adhesive molecules. In fact, we focused on the origin of the tumor rather than the specific type of cancer. But a similar study was not found to investigate cancers in 1 or 2 specific anatomical zones. Most studies have examined serum levels of adhesive molecules in a case-control study of breast cancer or some specific pelvic cancers such as colorectal or bladder. Therefore, differences in the outcomes of patients with pelvic cancers were predictable between our study and similar studies.

3. Methods

The current case-control study was performed between 2015 and 2017 at the oncology clinic of Omid Hospital in Mashhad. The subjects were patients with breast or pelvic cancer who were treated at the clinic by radiotherapy. The tests were carried out at the biotechnology laboratory of the medical faculty affiliated with the Mashhad University of Medical Sciences.

The sample size was determined based on previous studies and the average comparison of 2 independent groups formula of 14 in each group (21). The case group included 14 females with breast cancer and 14 with pelvic cancer (including cancers of the endometrium, ovary, and cervix and all patients were treated with pelvic radiotherapy). These study subjects were randomly chosen among the patients of Omid Hospital's oncology clinic. Immediately after the diagnosis of these cancers, the present research project was presented to the patients and this discussion covered the research's implementation process, benefits, and disadvantages, and freely given testimonials. An initial doctor visit followed, during which the patient's demographic information and risk factors for coronary artery disease were obtained. This patients' history included the type of cancer (breast or pelvic), age, any history of hypertension, diabetes, hyperlipidemia, obesity, tobacco usage, radiation dosages, and radiotherapy sessions.

Twenty-eight healthy subjects were then matched with the case group in terms of age, sex, and having no history of immunosuppression drug consumption, cardiac ischemia, hypertension, diabetes, hyperlipidemia, and radiotherapy. Blood samples were taken twice from the healthy control group and the case group of patients with cancer. Patients with breast cancer received 25 to 30 fractions of three-dimensional conformal radiation therapy

using a 6-Mv linear accelerator machine (5 days per week, in 2 Gy per fraction and the mean total dose of 50 - 60 Gy). Those with pelvic malignancies were treated with 25 to 28 fractions of three-dimensional conformal radiation therapy using a 15-Mv linear accelerator machine (5 days per week, in 1.8 Gy per fraction and the mean total dose of 45 - 50.4 Gy). The first samples were obtained immediately after the definite diagnosis of cancer and before radiotherapy treatment. The second time was several months after the completion of radiotherapy and treatment, which averaged 4 months after the end of the radiotherapy sessions.

Before these blood samples, the current study's patients were checked for the absence of inflammatory and infectious diseases. After centrifugation of the blood samples, serum samples were obtained according to standard procedures and transferred to the Mashhad University of Medical Sciences' Science and Technology Laboratory. The serum level of the adhesion molecules (SE-selectin, ICAM-1, SVCAM-1) was measured by the ELISA method according to the instructions for each kit.

The cardiovascular health of the study subjects was investigated for possible complications arising from radiotherapy. In addition, the case and the control groups were matched in terms of coronary artery disease and atherosclerosis as confounding variables affecting the serum level of the adhesion molecules. For this reason, the control group participants were chosen among candidates without CAD and risk factors of heart disease, such as diabetes, obesity, hyperlipidemia, and hypertension. On the other hand, for the case group, risk factors, symptoms, and a family history of CAD were considered a risk and therefore further investigated by a cardiologist.

3.1. Blood Samples and Assays

One hundred and twelve samples from 14 patients with breast cancer, 14 patients with pelvic cancer, and 28 healthy controls were kept in laboratory pipes in standard conditions with kits from Diaclone SAS (France): An E-selectin ELISA kit (ELISA KIT, Cat. No.: 850.520.096 Human CD62E), an ELISA ICAM-1 Kit (CD54 ELISA KIT Human, Cat. No: 850.540.096), and an ELISA VCAM-1 Kit (Cat. No: 850.580.096 Human CD106 ELISA KIT). Laboratory equipment of the biotechnology laboratory of the Mashhad University of Medical Sciences was utilized to perform tests, according to the kits' instructions, on the main measurable consequences: The serum levels of adhesion molecules ICAM-1, VCAM-1, and E-selectin of the case group before and after radiotherapy and the serum level of the control group.

3.2. Statistical Analysis

The resulting statistics for each of the study groups were recorded in the terms of frequency, mean and standard deviation, and in the form of appropriate tables for general and separate information about each of the study groups.

The relationship between the qualitative variables was studied by the chi-square test. Also, the relationship between the quantitative variables in the case and control groups was analyzed by ANOVA and independent sample *t*-tests. Also, a paired *t*-test was performed to compare the qualitative and quantitative variables before and after. Statistical analyses were performed by the SPSS statistical software package version 24.

4. Results

The present study divided 28 patients with cancer into 2 groups. One consisted of 14 patients with breast cancer and the other of patients with pelvic cancer. The control group was 28 healthy subjects with no history of cancer, radiotherapy, and cardio ischemic disease. All 56 subjects were female of comparable baseline demographics, such as age, sex, body mass index, radiotherapy sessions, diabetes, obesity, hyperlipidemia, and hypertension. There was no statistically significant difference between the groups except for diabetes (P-value = 0.004) and hyperlipidemia (P-value = 0.016). Details are summarized in Tables 1 and 2.

Among the 14 patients with pelvic cancer, there were 6 (42.8%) cases with cervical cancer, 5 (35.7%) with endometrial cancer, 2 (14.2%) with rectal cancer, and 1 (7.1%) with vaginal cancer. Of the 14 patients with breast cancer, there were 6 (42.8%) with cancer in the right breast and, 8 (57.1%) with cancer in the left breast.

Among the 14 cases with breast cancer, 8 were candidates for duodenal stroke echocardiography, 6 (42.8%) had no evidence of ischemic stress in the echocardiography, 2 (14.2%) did not undergo the echocardiographic stress test due to technical limitations, and 6 (42.8%) had their history of cardiovascular disease confirmed in a physical examination with no need for echocardiography. Also, among the 14 pelvic cancer cases, 6 were candidates for duodenal stress echocardiography, 6 (42.8%) had no echocardiographic distress in favor of ischemia, while 8 (57.1%) were considered to be in cardiovascular good health according to their history and physical examination, and did not need for an echocardiography stress test. As a result, none of the patients in the case group had CAD disease, therefore, the case and control groups matched in this sense.

The comparison of the CAM serum levels for both the case (28 subjects) and control (28 subjects) groups revealed that the CAM serum level in patients with cancer before and after radiotherapy, regardless of the type of cancer and cancer origin, was dramatically higher than the level of the control group. Another comparison check of the CAM

Table 1. Quantitative Variable Data [a, b]

Variables	Case 1 (n = 14) [c]	Case 2 (n = 14) [d]	Control (n = 28)	P-Value
Age	44.64 ± 11.43	53.71 ± 13.36	52.10 ± 15.29	0.178
BMI	26.37 ± 5.38	26.42 ± 5.57	25.2 ± 3.8	0.981
Radiotherapy sessions	25.14 ± 3.08	26.50 ± 1.55	-	0.154

Abbreviation: BMI, body mass index.
[a] Data are shown as mean ± SD for age (ANOVA) and for radiotherapy sessions and BMI (independent sample *t*-test).
[b] ANOVA and the independent sample *t*-test were employed to compare the age and BMI/radiotherapy sessions, respectively.
[c] Patients with breast cancer
[d] Patients with pelvic cancer

Table 2. Frequency of Diabetes, Obesity, Hyperlipidemia, and Hypertension Morbidity of Cases 1 and 2 [a, b]

Variables	Case 1 (n = 14) [c]	Case 2 (n = 14) [d]	P-Value
Diabetes	2 (14.3)	5 (35.7)	0.004
Obesity (BMI ≥ 25)	7 (50)	9 (64.3)	0.44
Hyperlipidemia	4 (28.6)	2 (14.3)	0.016
Hypertension	2 (14.3)	2 (14.3)	0.11

Abbreviation: BMI, body mass index.
[a] Data are shown as No. (%).
[b] The chi-square test was used.
[c] Patients with breast cancer
[d] Patients with pelvic cancer

serum level of the breast cancer group before radiotherapy and that of the control group indicated statistically notable differences between the mean serum levels of ICAM-1 (P-value = 0.002), VCAM-1 (P-value = 0.001), and E-selectin (P-value = 0.015) in the two groups. However, the same comparison performed after radiotherapy showed a considerable difference in the serum level of ICAM-1 (P-value = 0.039), VCAM-1 (P-value = 0.002), and E-selectin (P-value = 0.001) of the case and control groups. In addition, when comparing pelvic cancer cases with the controls, there was no meaningful difference in the ICAM-1 serum level, but a significant difference was found between the two groups for VCAM-1 and E-selectin. A comparison before radiotherapy showed the same results as those after radiotherapy.

In addition, a paired *t*-test compared the serum level of cell adhesion molecules of the patients with breast and pelvic cancer before radiotherapy. As Table 3 indicates between these 2 groups, there was no statistically significant difference between the serum levels of any of the adhesive molecules before radiotherapy. After radiotherapy, the results were the same.

In the comparison with the serum level of cell adhesion molecules in patients with breast cancer before and after radiotherapy, there was no statistically significant difference in the level of any of the cell adhesion molecules before and after radiotherapy. However, the ICAM-1 level after radiotherapy was lower than the pre-radiotherapy level, while the VCAM-1 and E-selectin serum levels increased, but these changes were not statistically significant. Similarly, there was no statistically significant difference in the serum level of any of the cell adhesion molecules before and after radiotherapy in the comparison with that of patients with pelvic cancer before and after radiotherapy. However, the E-selectin serum level after radiotherapy was lower when compared with that of pre-radiotherapy, while the VCAM-1 and ICAM-1 serum levels increased; these changes were not statistically significant though.

4. Discussion

The current study demonstrated that the serum level of all cell adhesion molecules (ICAM-1, VCAM-1, and E-selectin) significantly rises in breast and pelvic cancer subjects and that these changes are not related to the type or origin of cancer. Therefore, carcinogenesis can be considered as a factor resulting in elevated CAMs, which pose more risk of complications for patients, including cardiovascular events. With an average of 4 months after the completion of a radiotherapy course, the CAM serum level was not significantly different than that before and after treatment. After remission following radiotherapy (as proven by clinical examination and imaging), the CAM serum level was still higher than that of the healthy control group and did not show any notable changes.

Therefore, even months after treatment, patients demonstrated prolonged complications due to higher CAM levels. However, the results of the present study indicated that an increase of adhesion molecules before treatment and no substantial decrease of adhesion molecules after therapy, regardless of the origin of the tumor (chest or pelvis), can serve as a valuable finding for future studies aiming to employ cell adhesion molecules for providing new diagnostic and therapeutic biomarkers.

Similarly, this finding was also reported in 2002 by O'Hanlon et al. (22) in their case-control study comparing cell adhesion molecule serum levels, such as ICAM-1, VCAM-1, and E-selectin, in 92 patients at different stages of cancer

Table 3. Serum Level of Cell Adhesion Molecules of the Patients with Breast and Pelvic Cancer Before Radiotherapy [a, b]

Variables	Groups				P-Value				
	Case (n = 28) [c]	Case 1 (n = 14) [d]	Case 2 (n = 14) [e]	Control (n = 28)	P1 [f]	P2 [g]	P3 [h]	P4 [i]	P5 [j]
ICAM-1				7.16 ± 1.92				0.618	0.566
Before	10.22 ± 4.06	11.86 ± 3.89	8.59 ± 3.65		0.001	0.002	0.451		
After	10.27 ± 4.47	11.42 ± 5.24	9.12 ± 3.36		0.003	0.032	0.235		
VCAM-1				10.33 ± 2.76				0.918	0.225
Before	18.70 ± 7.70	19.92 ± 6.81	17.47 ± 8.59		0.001	0.001	0.025		
After	19.53 ± 7.57	20.20 ± 8.29	19.47 ± 9.14		0.001	0.01	0.007		
E-selectin				5.12 ± 3.16				0.990	0.811
Before	14.42 ± 11.23	16.54 ± 12.73	12.30 ± 9.50		0.001	0.015	0.044		
After	14.20 ± 7.09	16.57 ± 8.03	11.82 ± 5.27		0.001	0.001	0.001		

Abbreviations: ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.
[a] Data are shown as mean ± SD and the ANOVA, Dunnett T3, and independent sample tests were used.
[b] The data before radiotherapy session and after radiotherapy sessions were shown in all patients and also in special site of cancer (breast or pelvic).
[c] All patients results are shown cancer (pelvic or breast).
[d] Patients with breast cancer
[e] Patients with pelvic cancer
[f] P1 is the P-value of comparing case and the controls.
[g] P2 is the P-value of comparing case 1 and the controls.
[h] P3 is the P-value of comparing case 2 and the controls.
[i] P4 is the P-value of comparing case 1 before and after radiotherapy.
[j] P5 is the P-value of comparing case 2 before and after radiotherapy.

and in 31 patients with benign breast tumors. Although this and the present study are similar in study method, there were differences, namely the selection of the patients with breast cancer as the case group and patients with benign breast disease as the control group, the choice of different types of cell adhesion molecules, the usage of different laboratory techniques, and the consideration of the clinical stages (TNM) of the disease grade and lymph node invasion. However, in the study, the serum levels of all cell adhesion molecules discussed for patients with stage 4 breast cancer were significantly higher than those of the case group.

The present research separated cases into 2 groups: Patients with breast cancer and patients with pelvic cancer. Instead of focusing on the specific type of cancer, the origin of the tumor was significant. To the best of the current work's knowledge, there have not been any other similar studies that investigated cancers of 1 or 2 specific anatomical origins. Most have been case- control studies exploring the serum level of cell adhesion molecules in breast cancer or a specific type of pelvic cancer, such as colorectal or bladder cancer. Therefore, the differences in the pelvic cancer results of the current research in comparison to previous studies are to be expected.

Dymicka-Piekarska et al. (23) explored the relationship between the serum level of sICAM-1, sVCAM-1, and VEGF, and the progression of colorectal cancer, the results of which are similar to the present research. In contrast, there are other studies that have produced different results from the current work as well. One example is Mantur et al. (24) whose findings on the increase in the sVCAM-1 serum level are the same as the present study's findings; on the other hand, their report on the rise in sICAM-1 is contrary.

Coskun et al. (25) conducted another study aiming to check the serum level of cell adhesion molecules in patients suffering from bladder cancer. Their findings indicated that the serum level of sICAM-1 is significantly higher in 51 patients with bladder cancer compared to 8 healthy subjects. The tests were performed by ELISA and showed a rise in the sVCAM-1 and sP-selectin serum levels, as did the current work. However, their results for the serum level of sICAM-1 in patients with bladder cancer differed as a significant rise was observed. This contrast in results, however, can be due to differences in the type of cancer involved.

It is encouraging to compare the results of the present work with those of Prabhakarpandian et al. (26). Utilizing precise methods, such as immunohistochemistry, Northern blot analysis, and flow cytometry, the study examined the effects of acute radiation therapy on the expression of stem cell molecules. However, the present work focused on the rise in the level of cell adhesion molecules after the acute effects of radiotherapy subsided.

Ishii and Kitamura (19) evaluated the level of sICAM-1 in patients with lung cancer before and after radiotherapy. They found that the sICAM-1 serum levels in 30 patients with lung cancer before radiotherapy was higher

than those of 13 healthy control group subjects, a finding which is consistent with that of the present study. Also, the ICAM-1serum level increased in just 12 patients who fell ill with pneumonitis after completing radiotherapy. Therefore, it can be hypothesized that increased serum levels of cell adhesion molecules following radiotherapy are observed only in patients with inflammatory radiotherapy complications and that radiotherapy may not be effective at the adhesive molecule serum level.

As mentioned before, various studies utilizing different scientific methods have investigated the relationship between adhesion molecules and cancer. Most have mentioned the increase of adhesion molecules in the mRNA level, cell expression, and serum level depending on the laboratory method employed.

According to the presented scientific hypothesis and literature review, the current study divided cancer patients into 2 groups: Those suffering from breast cancer (of a thoracic first origin) and the other from pelvic cancer; this division was based on the tumor's initial origin regardless of the cancer type. By this approach, the present work could test both its hypothesis on rising serum levels of adhesion molecules in patients with cancer and also the relationship between the initial tumor origin and adhesion molecules.

The current research found that increasing adhesion molecule serum levels in patients with cancer had no relationship to tumor origin and that both of its cancer case groups were at risk of inflammatory complications due to adhesion molecules.

In contrast, several studies have reported on the acute effects of radiotherapy on increased cellular expression and adhesive molecule serum levels. However, nowadays, considering radiotherapy as an acute stressor on intracellular signals, such as the NF-KB transcription factor, is considered scientifically invalid.

The present study found no significant changes in the adhesion molecule serum levels of patients with cancer in case groups before and after radiotherapy and that serum level values were always higher in the healthy control group. This was at an average of 4 months after the completion of treatment and after any acute inflammatory effects of radiotherapy had subsided.

Therefore, even months after treatment, patients continued to be exposed to long-term complications due to an increase in the expression of adhesion molecules. Of course, it should be noted that patients in the study were referred for second testing at an average of 4 months after radiotherapy and not all patients were referred at a specific time after radiotherapy. In addition, since the current study's patients underwent a variety of treatments after radiotherapy, such as chemotherapy and surgery, the continued increase in adhesion molecule serum levels after the end of treatment cannot be attributed to radiotherapy.

In 2009, a systematic review showed that radiation therapy (RT) increases the likelihood of cerebrovascular events (27). Another study in 2013 found that radiation therapy may increase risk of carotid atherosclerosis (28).

The significant limitation of the present research was not matching the type of treatment after the diagnosis of cancer. Moreover, some patients had contracted infectious diseases, thus preventing them from participating in the second testing and making it necessary to wait for their complete improvement to eliminate the chance of inflammatory effects on the adhesion molecules. According to the current study's data and based on the serum level increase of adhesion molecules in the patients with cancer before treatment, it would be advantageous for a future similar study with a higher sample size to investigate the relationship between the clinical and pathological characteristics of cancer and the serum level of adhesion molecules. This is an important issue for future research.

5.1. Conclusions

The serum levels of adhesion molecules in patients with cancer are higher than those of healthy persons regardless of the cancer's origin, compared to radiotherapy course, and change in treatment.

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Footnotes

Authors' Contribution: S. H. conceived and designed the evaluation and drafted the manuscript. L. J. participated in designing the evaluation, performed parts of the statistical analysis and helped to draft the manuscript H. R. R. re-evaluated the clinical data, revised the manuscript and performed the statistical analysis and revised the manuscript. M. B. K., A. H. B. and S. M. collected the clinical data, interpreted them and revised the manuscript. S. H. and H. R. R. re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript

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