



## Comparison of Adenosine Deaminase (ADA) and Antigen 125 (CA-125) Level in Patients with Colon Cancer and Healthy Control

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### Introduction

Colorectal Cancer (CRC) is a very common cancer in many countries [1]. CRC is an asymptomatic disease at the beginning and develops slowly so it can be treated easily but it causes death in most of the patients due to the late diagnosis [2,3]. There are some known agents that are related to the incidence of this cancer that among them family history, age, host microbes and some mutable factors like diet, obesity and low physical activity are important ones that have been studied [4]. Age is the most important factor such that the cancer prevalence is 99% in people older than 40% and 85% in people older than 60 [5]. Most of the patients refer to doctors with pain in abdomen, anaemia, loss of weight and digestive changes but some of them even don't have these manifestations and their disease is known after metastasis [6]. CRC can be prevented if it has been diagnosed on time. Routine screening methods for diagnosing and evaluating CRC are fecal occult blood testing, colonoscopy, computed tomographic colonography and flexible sigmoidoscopy. Most of these tests are expensive and invasive, so finding some other ways for screening CRC seems to be essential. Molecular biomarkers are some potential agents that can be measured as primary screening markers. They can be used for follow up people who have received treatment [7]. They can help physicians to diagnose the cancer and prevent deaths caused by colorectal cancer because of on time treatment, but lack of suitable markers for diagnosing cancer are always felt [8]. Carcinoembryonic Antigen (CEA) is a tumor marker that has been assessed a lot and it is approved as a good marker for screening colorectal cancer specially for follow up because of its high specificity and sensitivity but it is not applicable alone. This issue can be solved by finding some other useful markers [9].

Cancer antigen 125 (CA 125) is a glycoprotein tumor marker which exists in the surface of some tissues including lung, endometrium and fallopian tube [10,11]. It increases in some pathological conditions like ovarian cancer and some other malignancies such as cervix and lung cancer but its elevation can be observed in some normal conditions, too [12]. This marker is mostly used in screening the ovarian cancer but because of low specificity and sensitivity in detection of early stage of the disease, it is better to combine it with other markers [13].

Adenosine Deaminase (ADA) is an important player in purine metabolism [14]. This enzyme converts adenosine to inosine and deoxyadenosine to deoxy inosine by deaminating them [15]. ADA exists in different human tissues and its metabolites contribute in different processes like proliferation and differentiation of various cells including T cells [16]. So the ADA activity in diverse diseases like some cancers has been considered in some researches [17]. The activity of ADA is elevated in some diseases such as leukemia, malignancy, brucellosis, acute pneumonia, rheumatoid arthritis and breast cancer which show the cellular system stimulation [18]. Therefore measuring the level of ADA may be useful in diagnosing of some diseases.

In this study we evaluate the level of ADA and CA-125 in serum of patient who is diagnosed with colorectal cancer.

### Abstract

**Aim:** Colorectal cancer is the third common cancer in the world. This cancer develops slowly and silently so it is usually detected very late. Finding some simple methods for early diagnosis can lead to timely prevention and treatment of the cancer. Molecular biomarkers are factors that assessing their roles in diagnosis, prognosis and follow up different diseases especially cancers have got a lot of attention in recent years. CA-125 and ADA are two proteins that their increases have been observed in various cancers. In this study we want to compare ADA and CA-125 level in colorectal cancer patients and healthy controls.

**Methods:** 50 blood samples from patients and 50 samples from healthy control were obtained and ADA and CA-125 were assessed in both groups. ADA level was assessed using enzymatic method by auto analyzer (BT3000). CA-125 was measured by Eleusis based on chemiluminescence. Data was analyzed by SPSS 16 software.

**Results:** The mean level of ADA in patients group was  $36.57 \pm 1.5$  U/L. Its level was  $12.83 \pm 5.7$  U/L in control group. The average value of CA-125 in patients and healthy control were 63.54 U/ml and 15.67 U/ml, respectively.

**Conclusion:** Based on obtained results, ADA level was increased significantly compared to control group. ( $P < 0.05$ ) Although serum CA-125 level showed no notable differences.

## Materials and Methods

### Patients

In this research, healthy individuals and patients diagnosed with colorectal cancer who were hospitalized in Loghman hospital and different parts of cancer institute of Iran including men cancer, women cancer and intermedical oncology were participated. The study was done from February 2014 to August 2016 with respect to medical ethics and consent of participants [19].

50 specimens were collected from healthy controls and patients separately. The identical factors were measured in both groups. 68% participants were men and 32% were women. Most patients were in age 46 to 55.

### Assays

3 ml of blood sample was obtained from each participants. The specimens stayed at room temperature for 30 minutes and after clotting, they were centrifuged for 5 minutes at 2500 rpm, then the above layer which was serum were collected and kept at -70°C for measuring ADA and CA-125.

ADA was assayed by Zist shimi kit and BT3000 auto analyzer based on photometric method. ADA normal range is less than 40 U/L. Kit calibrator was used to calibrate the apparatus. For setting the considered test on apparatus ADA control which exists in the kit was used. The absorbance was measured in 340 nm.

CA-125 antigen was assayed using chemiluminescence technique and ECL Elecsis immunoanalyser. Its normal range is 0 U/ml to 35 U/ml.

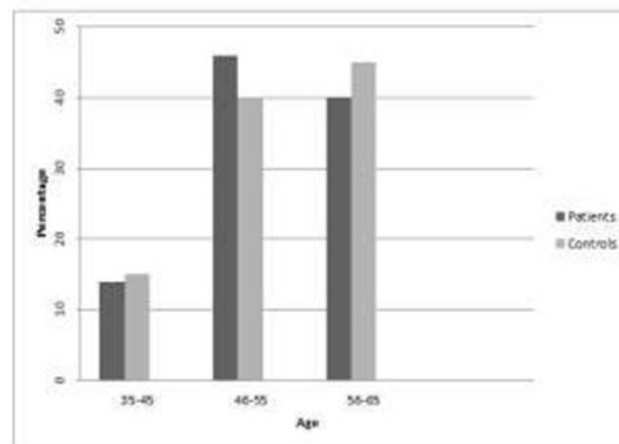
### Statistical analyses

Data was showed as mean ± SD. Analysing data was done by SPSS 16 with student t-test method. The P-value less than 0.05 were considered significant [20].

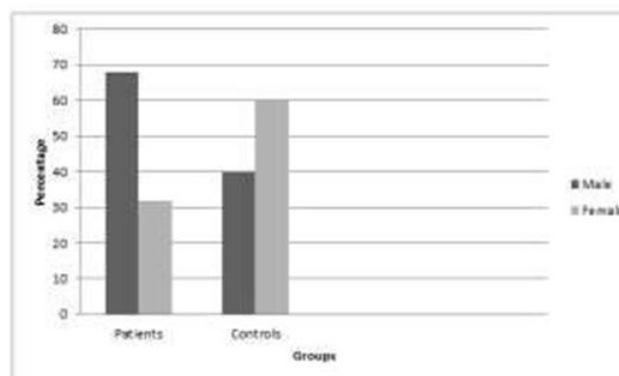
## Results

The patients in this study were in following age range: 14% (35 to 45), 46% (46 to 55) and 40% (56 to 65) years old (Figure 1). 32% of patients were women and 68% were men (Figure 2). 40% of healthy group were male and 60% were female. The percentage of participants

in each age range was: 15% (35-45), 40% (46-55) and 45% (56-65) in healthy controls. The data was obtained by comparing control group with test group.



**Figure 1:** Age range of participants in the study.

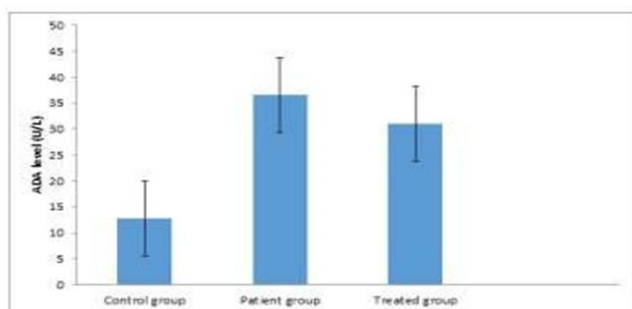


**Figure 2:** Percentage of participants based on gender.

The mean level of ADA in patient group was  $36.57 \pm 1.5$  U/L. It has a mean level of  $12.83 \pm 5.7$  U/L in control group (Table 1 and Figure 3). These findings showed that the ADA level was much higher in patient group compared with reference group, so their difference was statistically significant.

Variable	Control group	Patient group	Treated group	P value
	Mean (SEM)	Mean (SEM)	Mean	
ADA (normal range=<40 U/L)	12.83 (0.8)	36.57 (2.12)	31	<0.05
(P<0.05)				

**Table 1:** The mean and standard error of mean of ADA in controls and patients with colorectal cancer.

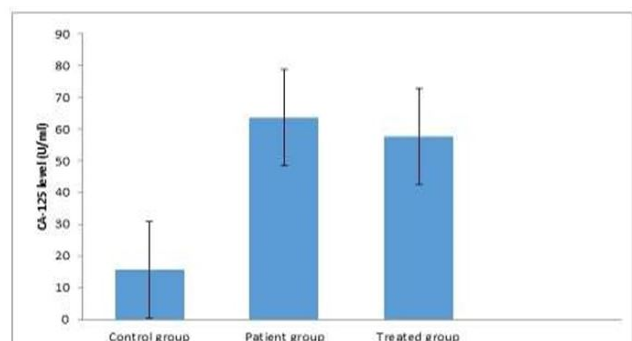


**Figure 3:** Mean serum level of ADA in patients, control and treated group. ADA level in patients group is significantly higher than control group ( $P < 0.05$ ).

The average value of CA-125 in patients and healthy control were 63.54 U/ml and 15.67 U/ml respectively (Table 2 and Figure 4). Although CA-125 value was increased in patient group, the comparison of CA-125 value in these two groups did not show any significant differences.

Variable	Control group	Patient group	Treated group	P value
	Mean (SEM)	Mean (SEM)	Mean	
CA-125 (normal range=0-35 U/ml)	15.67 (1.12)	63.54	57.65	<0.05
(P<0.05)				

**Table 2:** The mean and standard error of mean of CA-125 in controls and patients with colorectal cancer.



**Figure 4:** Mean serum level of CA-125 in patients, control and treated group. CA-125 level in patients group is significantly higher than control group  $P < 0.05$ .

ADA and CA-125 level were also assayed in serum of 12 patients receiving treatment. The mean ADA level was 31 U/L and CA-125 was 57.65 U/ml after treatment. These amounts show a little decrease in ADA and CA-125 level after treatment.

## Discussion

Despite many advances in prevention and diagnosis of colorectal cancer, many people die from this cancer annually. OBT is the primary test for screening colorectal cancer patients but it is not sufficient alone because of low sensitivity. Endoscopy, colonoscopy and biopsy are the gold standard tests for precise diagnosis. Most of the methods available to screen colorectal cancer are either invasive or unpleasant to patients, so this leads to fewer patients being screened for the disease. Discovering the cancer before development or even before appearing at the level of polyps helps physicians to apply useful treatments and prevent the disease occurrence or spreading, so it can cause more survival rate. Finding some markers that can help in early and easy diagnosis has always been in the center of attention. Recently using molecular biomarkers for diagnosis and screening different cancers is becoming more common because of their easy accessibility.

These markers should be sensitive, specific and simply measurable, so they can be reliable to be used for early diagnosis, monitoring the disease and prognosis. Increase in ADA level as a molecular biomarker has been reported in different cancers. We measured ADA level in colorectal cancer patients in our study. A significant elevation in serum ADA activity and a decrease after treatment was observed according to our study. An explanation for this increase is the elevated turnover of DNA in cancerous tissues that causes increment in ADA as a metabolizing enzyme of adenosine. These results are in agreement with other studies. In the primary studies on correlation between ADA and cancers, in 1957, Straub, et al., showed that ADA level was increased in 91% of 527 cancer patients. In a study that was done by Joop ten and colleagues in 1984, an average increase of 40% in ADA was observed in tumors of colorectal adenomatous patients compared to control tissues. In 1972, Dzieza-Lalowicz and Hankiewicz demonstrated that ADA activity in gastric juice of gastric cancer patients is significantly high. Since adenosine, the ADA substrate, seems to be toxic for cells, a hypothesis for ADA elevation in cancers represents that increase in ADA level may be due to neutralizing this toxic effect and helping tumor growth. As a controversial study Kojima, et al., showed a decrease in ADA level in peripheral blood lymphocyte of colorectal cancer patients which might be because of immune suppression in cancer patients.

## Conclusion

We also measured CA-125 in the serum of participants. Although CA-125 level was increased in 40% of patients compared to control group but it was not statically significant. Increase in the serum level of CA-125 has been reported in other studies especially on ovarian cancer but it is not considered as a sensitive and specific maker for early diagnosis. CA-125 value is usually elevated in 85% of ovarian cancer cases. Scientists have combined CA-125 with other markers to improve its sensitivity. In a study which was done by Bashizadeh-Fakhar, et al., determining combination of CA-125 with CEA and ROMA indicated a promising biomarker for ovarian cancer detection. Streppel, et al., showed that CA-125 is also expressed in colorectal cancer patients. It is considered that CA-125 interaction with different

receptors causes cancer cells to escape from apoptosis. Connection of CA-125 to GPI-anchored glycoprotein helps tumors to implant and metastasize. Also a receptor on immune cells has been investigated which inhibits immune responses. These are some of the mechanisms by which CA-125 can promote cancer growth.

In most of the studies that CA-125 level was evaluated in colorectal or other gastrointestinal cancer patients, no significant increase was observed in patients group which is compatible with the result of our study. Although CA-125 status decrease significantly after treatment and could be considered as a treatment monitoring factor beside other markers. For example, in a study with Yamao and colleagues, it was demonstrated that CA-125, CEA and CA-19 decrease after chemotherapy. In 2016, Basu, et al., also determined some tumor markers in colorectal cancer patients before and after treatment and they reported that elevation in CA-125 level in patients group was not significant compared to controls but the decrease in its level was remarkable after therapy. So this marker along with other markers can be used to assess chemotherapy effectiveness. In a study in 2018 which was done by Gao, et al. it was found that among different tumor markers, CA-125 has the lowest sensitivity in colorectal cancer detection and combining that with other markers can improve the sensitivity. So based on the results of these studies and our finding, CA-125 cannot be a useful marker for colorectal cancer on its own.

Although measuring tumor markers can be a useful method for detection and monitoring colorectal cancer but utilizing a panel of appropriate biomarkers can help to achieve more trustworthy results. Further research is needed to clarify the importance of biomarkers in colon cancer and to obtain validated findings.

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