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# Serum Annexin A2 Levels in Patients with Colon Cancer in Comparison to Healthy Controls and in Relation to Tumor Pathology

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**Background:** The deregulation and localization of the Annexins is consistently reported to have close relation to tumor cell malignancy, invasion, and metastasis as well as clinical progression of tumors. This study aimed to evaluate serum Annexin A2 (Anx A2) levels in patients with colon cancer in comparison to healthy controls and in relation to demographics and tumor pathology.





**Material/Methods:** A total of 100 patients (mean (SD) age: 58 (5.8) years, 55.0% females) with colon cancer and 70 controls (mean (SD) age: 59 (5.4) years, 50.0% females) were included. Serum levels for Anx A2 were evaluated in relation to study group, demographics, and tumor pathology.

**Results:** Serum levels for Anx A2 were significantly lower in patients with colon cancer than in controls (13.1 (4.5) vs. 22.8 (2.1) ng/mL,  $p < 0.001$ ) and significantly decreased with increase in tumor size ( $p = 0.003$ ), and at higher stages of TNM ( $p = 0.004$ ), tumor invasion ( $p = 0.005$ ), lymph node metastasis ( $p = 0.003$ ), and distant metastasis ( $p = 0.005$ ).

**Conclusions:** Our findings indicate a significant decrease in Anx A2 expression in colon cancer patients compared to healthy controls and in parallel with tumor progression.

**MeSH Keywords:** **Annexin A2 • Colonic Neoplasms • Neoplastic Processes**

**Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/892319>

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## Background

Colorectal cancer (CRC) is the fifth leading cause of cancer-related mortality [1] and is considered to result from a series of genetic changes leading to progressive and irreversible loss of normal control of cell growth and differentiation, in an ordered 3-phase manner including initiation, promotion, and progression. There is consistent and considerable evidence that several biological pathways underlie the transition from normal mucosa to invasive cancer [2].

Given their potential to present specific targets for prevention and cure, well-defined molecular pathways have been investigated in different presentations of CRC, including sporadic CRC (loss of heterozygosity pathway), familial adenomatous polyposis and related polyposis syndromes, hereditary non-polyposis CRC (mutator genes/microsatellite instability pathway), cancer developing in inflammatory bowel diseases, and familial CRC [2].

Indeed, the available evidence on molecular events underlying colorectal cancer has been considered to be far greater as compared with other common solid tumors. Accordingly, specific germ-line mutations for the inherited CRC syndromes and a stepwise accumulation of somatic mutations for most sporadic cases have been considered to be the responsible genetic changes, while the genetic abnormalities underlying “familial” CRC has not yet been completely defined [3].

Patients with metastatic disease have commonly been treated with cytotoxic chemotherapeutic regimens coupled with targeted monoclonal antibodies, but with considerably modest benefits [4]. The risk for overtreatment and related toxic adverse effects has been considered to be inevitable in patients with colon cancer, given the lack of *a priori* knowledge of the likelihood of tumor recurrence [5].

Although prognostic estimation has been performed via colon cancer screening tests, including fecal occult-blood testing and colonoscopy, for years [6] aiming to decrease mortality related to colon cancer [7,8], success with these screening tests has been far from sufficient.

Accordingly, to overcome this limitation, there is growing interest in investigations related to novel biomarkers associated with the occurrence, invasion, metastasis, and progression of the tumor – principally noninvasive biomarkers in serum or plasma, for diagnosis, prognosis, and prediction of response to chemotherapy [9].

Annexin A2 (Anx A2) is a 36 kDa calcium- and phospholipid-binding cytoskeletal protein of the Annexin superfamily [10] localized at the extracellular surface of endothelial cells and various types of tumor cells [11]. It has a bipartite structure

with a conserved C-terminal core carrying the Ca<sup>2+</sup>- and the phospholipid-binding site and a variable N-terminal domain differing between Anx subfamilies [12].

Anx A2 has been considered to participate in a range of physiological processes, including anti-coagulation, anti-inflammatory, endocytosis and exocytosis, signal transduction, cell-proliferation, differentiation, and apoptosis [13–15]. The increased expression of Anx A2 has been reported in cancers of the breast, liver, prostate, and pancreas, while Anx A2 has also been demonstrated to play a role in processes essential for cancer metastasis, such as cancer cell migration, invasion, and adhesion [11]. Accordingly, owing to the consistently reported close relation of deregulation and localization of the Anx to tumor cell malignancy, invasion, metastasis, and clinical progression of tumors, they have been good candidates to study in relation to tumor development and progression [12].

Therefore, the present study was designed to evaluate serum Anx A2 levels in patients with colon cancer in comparison to healthy controls and in relation to tumor pathology.

## Material and Methods

### Study population

A total of 100 patients (mean (SD) age: 58 (5.8) years, 55.0% females) with colon cancer and 70 healthy control subjects (mean (SD) age: 59 (5.4) years, 50.0% females) were included in this study. Consecutive patients admitted to the study sites fulfilling the selection criteria were included in the study. All colon cancer patients who had undergone a surgical resection for colon cancer and received adjuvant chemotherapy were included. Control subjects were healthy volunteers from among patients who underwent colonoscopy for causes other than gastrointestinal cancer. Patients with familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, inflammatory bowel disease, or second primary tumor, as well as patients who received neoadjuvant chemoradiotherapy, were excluded from the study. Lack of any colorectal precancerous disease such as ulcerative colitis or polyps was confirmed in control subjects based on colonoscopy and laboratory findings. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee.

### Study parameters

Data on demographic characteristics (age and sex), tumor pathology (tumor size, tumor location, and the depth of invasion,

status of lymph node metastasis, distant metastasis, and histological differentiation), tumor staging via tumor-node-metastasis (TNM) classification system [16], and serum levels for Anx A2 were collected. Serum levels for Anx 2 were evaluated with respect to demographics, study groups, and tumor pathology. Tumor pathology was evaluated with respect to patient demographics.

### Chemotherapy protocols

Adjuvant CT protocols included modified *FOLFOX6* (*mFOLF-FOX6*) [oxaliplatin (Eloxatin®) 85 mg/m<sup>2</sup> IV over 2 h on day 1 **plus** leucovorin 400 mg/m<sup>2</sup> IV over 2 h on day 1 **plus** 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, **then** 2400 mg/m<sup>2</sup>/day for 2-d continuous infusion; repeated every 2wk for 4 cycles], *mFOLFOX6 plus cetuximab* [cetuximab (Erbix®) 400 mg/m<sup>2</sup> loading dose on day 1, **then** cetuximab 250 mg/m<sup>2</sup> weekly **plus** oxaliplatin (Eloxatin®) 85 mg/m<sup>2</sup> IV over 2 h on day 1 **plus** leucovorin 400 mg/m<sup>2</sup> IV over 2h on day 1 **plus** 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, **then** 2400 mg/m<sup>2</sup>/day for 2-d continuous infusion; repeated every 2wk for 4 cycles], *FOLFIRI plus bevacizumab* [bevacizumab (Altuzan®) 5 mg/kg over 90min on day 1 **plus** irinotecan (Campto®) 180 mg/m<sup>2</sup> over 90min on day 1 **plus** leucovorin 400 mg/m<sup>2</sup> over 2h on day 1 **plus** 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1 followed by 5-FU 2400 mg/m<sup>2</sup> IV continuous infusion over 46 h every 2wk for 4–6 cycles], *FOLFOX4* [oxaliplatin (Eloxatin®) 85 mg/m<sup>2</sup> IV infusion on day 1, **then** leucovorin 200 mg/m<sup>2</sup> (or equivalent) IV infusion, **then** fluorouracil 400 mg/m<sup>2</sup> IV bolus and 600 mg/m<sup>2</sup> 22-h continuous IV infusion on days 1 and 2], *FOLFIRI plus cetuximab* [cetuximab (Erbix®) 400 mg/m<sup>2</sup> loading dose over 2 h on day 1, **then** cetuximab 250 mg/m<sup>2</sup> over 1 h weekly **plus** irinotecan (Campto®) 180 mg/m<sup>2</sup> IV over 90 min on day 1 **plus** leucovorin 400 mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion on day 1 **plus** 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, **then** 2600 mg/m<sup>2</sup>/day for 2-d continuous infusion; repeated every 2 wk for 4 cycles], *FOLFIRINOX* (oxaliplatin (Eloxatin®) 85 mg/m<sup>2</sup> IV over 2 h on day 1 **plus** irinotecan 180 mg/m<sup>2</sup> IV over 90 min on day 1 **plus** leucovorin 400 mg/m<sup>2</sup> IV infusion to match duration of irinotecan (Campto®) infusion on day 1 **plus** 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, **then** 2400 mg/m<sup>2</sup>/day for 2-d continuous infusion; repeated every 2wk for 4 cycles) and *XELOX* [oxaliplatin (Eloxatin®) 135 mg/m<sup>2</sup> over 3 h on day 1 **plus** capecitabine (Xeloda®) 2000 mg/m<sup>2</sup> PO for 14 d every 21d for 4 cycles].

### Analysis for serum Anx A2 levels

In patients with pathologically confirmed colon cancer after colonoscopy, blood samples were collected 1 day before surgery. Blood samples drawn after overnight fasting were centrifuged at 1000 × g (or 3000rpm) for 15 min within the first 2 h of collection at room temperature or overnight at 2–8°C. Isolated serum samples were kept at –80°C until analysis.

Serum levels for Anx A2 was determined using ANXA2 (catalog no: MBS732593, MyBioSource) ELISA kit. The competitive enzyme immunoassay technique utilizes a monoclonal anti-ANXA2 antibody and an ANXA2-HRP conjugate. The assay sample, buffer, and ANXA2-HRP conjugate were incubated for 1 h on a pre-coated plate. After the incubation, decantation and washing 5 times were performed, and then a substrate for HRP enzyme was added to the wells and incubated. A blue complex was formed as the product of the enzyme-substrate reaction. At the end of the incubation, the reaction was stopped by adding a stop solution that turned it to yellow. The intensity of the color was measured spectrophotometrically at 450 nm.

The intensity of the yellow color is inversely proportional to the ANXA2 concentration since ANXA2 from the sample occupies more sites compared the ANXA2-HRP conjugate. A standard curve was plotted relating the intensity of the color to the concentration of standards. The ANXA2 concentration in each sample was interpolated from the standard color intensity-concentration curve. The sensitivity of this assay was 1.0 ng/mL. There was no significant cross-reactivity or interference between ANXA2 and its analogues.

### Statistical analysis

Statistical analysis was made using computer software (SPSS version 21.0, SPSS Inc. Chicago, IL, USA). Chi-square ( $\chi^2$ ) test was used for the analysis of nominal variables. Shapiro-Wilk normality test and Kolmogorov-Smirnov tests were performed and histogram charts were drawn. Independent samples t-test and one-way analysis of variance (ANOVA) were used for the analysis of normally distributed variables, and Kruskal-Wallis test was used for non-normally distributed variables. Binary comparisons (post hoc) for groups with homogeneous variances were performed via Tamhane test, and the Bonferroni-corrected Mann-Whitney U test was used for groups without homogenous variances. Data are expressed as “mean (standard deviation; SD)”, minimum-maximum, and percent (%) as appropriate.  $p < 0.05$  was considered statistically significant.

## Results

### Demographics and serum Anx A2 levels in study groups

Patient and control groups were determined to be homogeneous in terms of age and sex distribution. Serum levels for Anx A2 were significantly lower in patients with colon cancer when compared to control subjects (13.1(4.5) vs. 22.8(2.1) ng/mL,  $p < 0.001$ ), while no significant difference was noted in serum Anx A2 levels with respect to age groups and sex in patient and control groups (Table 1).

**Table 1.** Demographics and serum Anx 2 levels in study groups.

		Patient (n=100)		Control (n=70)	
Age (years)	Mean (SD)	58	(5.8)	59	(5.4)
	Median (min-max)	59	(31-70)	58	(30-70)
Gender, n(%)					
Female		55	(55.0)	35	(50.0)
Male		45	(45.0)	35	(50.0)
Serum Anx 2 level (ng/mL), mean (SD)					
<60 years		18.6	(1.9)	20.6	(2.0)
≥60 years		18.5	(1.6)	21.5	(2.8)
Female		17.5	(2.5)	18.0	(2.4)
Male		18.9	(1.8)	19.5	(3.0)

\* p<0.001 compared to control group.

### Tumor pathology in relation to demographics among patients with colon cancer

In patients, tumor size was >3 cm in 59.0%, tumor was at stage TIII (28.0%) or IV (34.0%) in 62.0%, T3(28.0%) or T4(36.0%) invasion was evident in 64.0%, with N2 level lymph node metastasis in 56.0% of patients and metastasis in 78.0% (Table 2).

No significant difference was noted in tumor size, TNM stage, tumor invasion, lymph node metastasis, or distant metastasis with respect to age groups or sex (Table 2).

### Serum levels for Anx A2 in relation to tumor pathology

Serum levels for Anx A2 were determined to significantly decrease with increase in tumor size ( $p=0.003$ ) and, at higher stages of TNM ( $p=0.004$ ), with tumor invasion ( $p=0.005$ ), lymph node metastasis ( $p=0.003$ ), and distant metastasis ( $p=0.005$ ). Subgroups in each category also significantly differed among themselves ( $p<0.001$ ) (Table 3).

## Discussion

Our findings in patients with colon cancer revealed significantly lower levels of serum AnxA2 compared to control subjects and along with increase in tumor size, at higher stages of TNM, tumor invasion, lymph node metastasis, and distant metastasis. No significant difference was observed in tumor pathology with respect to age or sex among patients. Similar levels for Anx A2 were detected in different age groups both in control and patients.

While over-expression of Anx A2 has been reported in a majority of cancers (e.g., pancreas, breast, and brain [17], Anx

A2 was also shown to be down-regulated in certain types of malignancies, including hormone-refractory prostate cancer [18,19] and carcinomas of the head and neck [20]. Decrease in Anx2 protein levels in patients with colon cancer may emphasize the likelihood of its tumor suppressor function in certain tumor tissues.

Inconsistency of data on AnxA2 expression in tumors, with many studies having validated either an up- or down-regulation of Anx A2 in several tumors types, seems to emphasize the role of empirical techniques used to analyze Anx A2 expression or to reflect differences between primary tumors and metastatic lesions.

In fact, when colon cancer is considered, the expression of Anxa7 protein was also shown to be reduced in neoplastic tissues in comparison with normal counterparts and shown to be down-regulated in benign colon adenoma with mild dysplasia, and dropped further in more invasive colon adenocarcinoma in comparison with normal colon tissue samples [12].

Anx A2 was shown in digestion system-related tumors, such as hepatocellular carcinoma and colorectal carcinoma [21,22]. In colorectal carcinoma, Anx A2 was indicated as a biomarker with diagnostic and prognostic potential because its expression was associated with histological type, tumor size, tumor invasion, and pTNM stage [21], as well as recurrence and survival [23].

While expression of Anx A2 was reported to be positively associated with malignant progression in almost all other cancers [24], our findings indicate a decrease in serum Anx A2 levels with increase in tumor size, at higher stages of TNM, tumor invasion, lymph node metastasis, and distant metastasis in patients with colon cancer.

**Table 2.** Tumor pathology in relation to demographics among patients with colon cancer.

	Overall (n=100)	Gender		Age		p value
		Females (n=45)	Males (n=55)	<60 years	≥60 years	
<b>Tumor size</b>						
≤3 cm	41 (41.0)	12	29	28	13	0.567
>3 cm	59 (59.0)	33	26	34	25	0.614
<b>TNM stage</b>						
T I	20 (20.0)	7	13	11	9	0.521
T II	18 (18.0)	8	10	10	8	0.585
T III	28 (28.0)	15	13	16	12	0.524
T IV	34 (34.0)	15	19	21	13	0.589
<b>Tumor invasion</b>						
T1	18 (18.0)	8	10	9	9	0.712
T2	18 (18.0)	6	12	9	9	0.727
T3	28 (28.0)	12	16	17	11	0.765
T4	36 (36.0)	19	17	23	13	0.529
<b>Lymph node metastasis</b>						
N0	26 (26.0)	14	12	11	7	0.489
N1	18 (18.0)	9	9	10	8	0.543
N2	56 (56.0)	22	34	35	21	0.674
<b>Distant metastasis</b>						
Absent	22 (22.0)	9	13	12	10	0.761
Present	78 (78.0)	36	42	39	39	0.486
M0	30 (30.0)	11	19	10	20	0.549
M1	23 (23.0)	13	10	12	11	0.638
M2	47 (47.0)	21	26	23	24	0.531

In this regard, identification of a consistent decrease in serum Anx A2 levels with tumor progression in our patients seems to be line with the published data from prostate cancer studies, wherein the expression of Ann A2 was reported to be negatively associated with the progression of the metastatic disease [24]. Besides, given the relation between Anx A2 expression and a particular progression in cancer stage, measurement of serum Anx A2 levels seems to have a prognostic value in colon cancer.

The exact mechanism underlying the association between Anx A2 expression and the occurrence, invasion, and metastasis of

malignant tumors (and thereby the diagnostic and prognostic value of Anx A2) is not yet fully understood [13,23].

Anx A2 was demonstrated to interact with HAb18G/CD147, tPA/PLG hexameric extracellular matrix glycoprotein to reinforce the invasion and metastasis of malignant tumors [13], and is either regarded as a tumor suppressor or a tumor promoter, depending on the types of cancers [13]. Additionally, Anx A2 was approved as a high-affinity binding protein required for mediating the growth stimulatory effects of gastrin and progastrin peptides on intestinal epithelial and colon cancer

**Table 3.** Preoperative serum levels for Anx A2 levels in relation to tumor pathology in patients.

	Serum Anx A2 levels (ng/mL)		p value
	Mean (SD), min-max		
Tumor size			
≤3 cm	17.4 (2.1);	15–21	p=0.003
>3 cm	10.0 (2.9);	5–15	
TNM stage*			
T1	18.9 (1.1);	17–21	p=0.004
TII	16.3 (1.8);	13–19	
TIII	13.2 (1.2);	11–16	
TIV	7.9 (1.7);	5–11	
Tumor invasion**			
T1	18.3 (1.1);	17–21	p=0.005
T2	16.1 (2.0);	14–19	
T3	12.9 (1.9);	12–16	
T4	6.8 (2.0);	5–12	
Lymph node metastasis*			
N0	19.1 (1.5);	17–21	p=0.003
N1	15.0 (1.6);	13–17	
N2	7.1 (2.0);	5–15	
Distant metastasis*			
Absent	18.9 (1.0);	14–21	p=0.005
Present	11.4 (3.6);	5–13	
M0	17.1 (2.0);	16–21	p=0.005
M1	13.5 (2.1);	12–16	
M2	7.5 (2.9);	5–14	

Minimum significance of binary comparisons was \*  $p < 0.0167$  and \*\*  $p < 0.0087$  (Bonferroni corrected Mann-Whitney U test). Accordingly, subgroups also significantly differ among themselves ( $p < 0.001$ ).

cells, suggesting the influence of Anx A2 on tumor cell proliferation [24].

Additionally, our findings indicate no significant difference in tumor pathology with respect to age or sex among patients and similar levels for Anx A2 in different age groups, both in control and patients. Accordingly, our findings support the statement that Anx A2 was not correlated with patient sex or age, unlike its association with tumor pathology [25].

Certain limitations to this study should be considered. First, this was a cross-sectional study without a follow-up, which made it impossible to establish any cause-and-effect relationships. Second, although *a priori* sample size calculation was not performed, the power of the study was 99.9%. Finally, while our presented data differs from that in recently published papers, our findings provide diagnostic rather than prognostic or predictive value of Anx A2 expression, based on the single-ELISA assay technique

with lack of data on additional methods such as Western blot analysis or RT-PCR, along with no data on sensitivity/specificity tests with ROC curves and association analyses of survival and/or treatment outcomes, which would confirm our findings and also reinforce the prognostic value of serum Anx A2 levels.

## Conclusions

Our findings revealed significant decrease in serum levels of Anx A2 in patients with colon cancer in comparison to healthy controls and along with advanced tumor pathology. Our findings emphasize the promise of serum levels of Anx A2 as a distinct biomarker with diagnostic value in patients with colon cancer. Further investigation is needed to determine optimal serum Anx A2 levels for precise prognosis and to further explore the interactions between Anx A2 and its binding proteins to promote tumor invasion and metastasis.

## Statement

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## Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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