ACTA MEDICA LITUANICA. 2005. VOLUME 12 No. 3. P. 65–70


# The immune and antioxidative state of women with respect to cervical cancer stage

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**Objectives**. To evaluate changes in the parameters of immune and antioxidative systems with reference to cervical cancer stages.

**Materials and methods**. 151 women with cervical cancer comprised the patients' group and 114 healthy women were taken as the control group. The indices of cellular immunity were measured by immunofluorescence methods. In addition, indices of blood neutrophil phagocytosis and humoral immunity parameters (concentrations of immunoglobulins G, A, M) were examined. The parameters of the antioxidative system were determined by the spectrophotometric method in blood serum (the amount of lipid peroxidation product MDA, the activity of antioxidative enzymes CAT and SOD) and by the spectrofluorometric method in hexane extraction of blood serum (the concentration of antioxidant vitamins A and E).

**Results**. The imbalance of immune system parameters was more pronounced in patients with cervical cancer stages II and III comparing than in stage 0 women's group. The percentage of $CD3^+$, $CD19^+$ and $CD16^+$ in patients with cervical cancer stage 0 was lower in comparison with control group indices. Deep immunosuppression was found in women with cervical cancer stages II and III, however, other immune system indices in this group were stimulated (monocytes, neutrophils, PhN, PhI, IgG, IgA, IgM).

The relation of the antioxidative system status and the stage of the disease was found to be ambiguous. SOD activity and vitamin E concentration were risen in later stages of cervical cancer in comparison to earlier stages. The statistically reliable rise of MDA and the reduction of SOD activity in blood serum of cervical cancer patients was determined in comparison to the control group of women. A reliable rise of CAT activity was determined in stage I and stage III, and a drop of vitamin E concentration was noticed in stage 0. The differences of vitamin A concentration were statistically unreliable.

**Conclusions**. The results showed the alterations of the patient's immune state to depend on disease stage. The antioxidative system capacity declines in cervical cancer patients, although the relation between the altered antioxidative system and the stage of the disease was determined to be ambiguous.

**Key words**: stages of cervical cancer, immune system, antioxidative system

## INTRODUCTION

The important role of the immune and antioxidative systems of the organism among the numerous factors determining the progression of tumours should be noted. Experimental studies have shown that regulatory immune mechanisms tend to alter under cancer progression: reduction in the number and function of cytotoxic and regulatory cells were stated (1). Moreover, the activity of the antioxidative system also reduces under tumour progression as could be evident from the rise of the concentration of malondialdehyde – the marker of lipid peroxidation – in the blood plasma of cancer patients (2).

However, data on changes in the immune and antioxidative system status in cervical cancer patients are lacking. Signs of depression of the cellular component of immunity have been determined in stage II and III cervical cancer patients (3). The stage of cervical tumour development also influences the catalytic activity of antioxidative enzymes: the activity of glutathione peroxidase, catalase and superoxide

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dismutase in cancer stage III and IV patients was found to be low (4).

The subject of the research was to investigate alterations in the organism's immune and antioxidative system status depending on cervical cancer stage.

## MATERIALS AND METHODS

In 2001–2004, the immune and antioxidative state of 151 women with cervical cancer and of 114 control group women (without cancer) was studied.

Stage 0 cervical cancer was determined for 22 women, stage I for 71, stage II for 20, stage III for 33 and stage IV for 3 women according to FIGO classification. The stage was not identified in two cases. The age of the women varied from 21 to 66.

The indices of cellular immunity determined for all the women were the following: total leukocyte number, lymphocyte, monocyte and neutrophil percentage and absolute number. The percentage and absolute number of T lymphocyte population ($CD3^+$), immunoregulation index ($CD4^+/CD8^+$), B lymphocyte ($CD19^+$), natural killer (NK) cells ($CD16^+$) were also determined. In addition, to evaluate the immune state of women, two indices of blood neutrophil phagocytosis (phagocytosis index, PhI, and phagocytosis number, PhN) were assessed. To evaluate humoral immunity, IgG, IgA and IgM concentrations in blood serum were examined. The leukocyte formula was determined.

The status of the antioxidative system was examined evaluating the level of lipid peroxidation product malondialdehyde (MDA), the activity of antioxidative enzymes catalase (CAT) and superoxide dismutase (SOD), and the concentration of the endogenous antioxidants vitamins A and E in blood serum. MDA level was determined in a thiobarbituric acid assay, resulting in formation of a coloured complex in MDA and the acid reaction which was tested by the spectrophotometric method. The activity of CAT was defined spectrophotometrically as the development of colour under formation of a hydrogen peroxide and ammonium molibdate complex. The activity of SOD was also examined spectrophotometrically, evaluating the rate of stopping nitro blue tetrazolium reduction reaction. The concentration of vitamins A and E was determined in hexane extraction of blood serum by the spectrofluorometric method.

The differences of comparative quantities were estimated as reliable at $p \leq 0.05$ and as tendencies to differ in the corresponding indices at $0.05 < p < 0.1$.

## RESULTS

**Changes in immune and antioxidative system status of cervical cancer patients depending on disease stage.** The immune state of women with cervical cancer stage I and cervical cancer stage 0 (*Ca in situ*) differed insignificantly.

Comparing the indices of cervical cancer stage II and stage 0 women groups we found that the percentage of lymphocytes and the absolute quantity of $CD4^+$ for stage II were reliably lower, while the percentage of neutrophils and $CD19^+$ lymphocytes, IgA and IgM concentrations in the blood serum were essentially higher. The absolute number of lymphocytes and the PhN index had a tendency to be lower (Table 1).

Cellular immunity indices of cervical cancer stage III patients were lower in comparison with the indices of cervical cancer stage 0 patients. The percentage and absolute quantity of lymphocytes, the absolute number of $CD3^+$ and $CD4^+$ lymphocytes, the

Table 1. **Alterations of immune system status of cervical cancer patients depending on the stage of the disease**

| Parameters | Reduced, % | | | Parameters | Risen, % | | |
|---|---|---|---|---|---|---|---|
| **A** | | | | | | | |
| Lymphocytes (%) | ↓ | 24 | * | Neutrophils (%) | ↑ | 10 | * |
| Lymphocytes ($n \cdot 10^9$/l) | ↓ | 15 | ** | $CD19^+$ (%) | ↑ | 22 | * |
| $CD4^+$ ($n \cdot 10^9$/l) | ↓ | 12 | * | IgA (g/l) | ↑ | 41 | * |
| PhN | ↓ | 1 | ** | IgM (g/l) | ↑ | 20 | * |
| **B** | | | | | | | |
| Lymphocytes (%) | ↓ | 26 | * | Leukocytes ($n \cdot 10^9$/l) | ↑ | 18 | * |
| Lymphocytes ($n \cdot 10^9$/l) | ↓ | 15 | * | Neutrophils (%) | ↑ | 10 | * |
| $CD3^+$ ($n \cdot 10^9$/l) | ↓ | 17 | * | Neutrophils ($n \cdot 10^9$/l) | ↑ | 24 | * |
| $CD4^+$ ($n \cdot 10^9$/l) | ↓ | 12 | * | $CD4^+/CD8^+$ | ↑ | 8 | ** |
| $CD8^+$ (%) | ↓ | 6 | * | | | | |
| $CD8^+$ ($n \cdot 10^9$/l) | ↓ | 14 | * | | | | |
| $CD16^+$ ($n \cdot 10^9$/l) | ↓ | 25 | ** | | | | |

**A** – women with cervical cancer stage II (n = 20) compared with stage 0 (n = 22),
**B** – women with cervical cancer stage III (n = 33) compared with stage 0 (n = 22).
* $p \leq 0.05$ – reliable difference of parameters,
** $0.05 < p < 0.1$ – tendency to difference of parameters.

percentage and absolute quantity $CD8^+$ lymphocytes were reliably lower. The absolute number of $CD16^+$ had a tendency to be lower. Essentially higher were the total number of leukocytes, the percentage and absolute number of neutrophils. The $CD4^+/CD8^+$ index had a tendency to be higher (Table 1).

Thus, the cellular immunity functions and other organism's immunohomeostasis supporting mechanisms were weaker when the cancer was in progress.

Consequently, the functions of cellular immunity and other immune homeostasis supporting mechanisms were found to be weakened under cervical cancer progression (Table 1), while the relation between antioxidative system status and the stage of the disease was ambiguous. The activity of SOD and the concentration of vitamin E were upregulated in the later stages of cervical cancer in comparison to earlier stages (Table 2).

**The status of immune and antioxidative systems of cervical cancer patients group in comparison to control group.** Comparing the indices of cervical cancer stage 0 patients with control group women, the percentage of $CD3^+$ and $CD19^+$, the immunoregulatory $CD4^+/CD8^+$ index were fund to be essentially lower in the former, and the percentage of $CD16^+$ showed a tendency to be lower. The $CD8^+$ index, IgG concentration in blood serum, PhN and PhI were essentially higher (Table 3).

Comparing the immunological indices in cervical cancer stage I and control group women, the percentage and absolute number of lymphocytes and $CD3^+$, absolute $CD4^+$ quantity and the $CD4^+/CD8^+$ index were reliably lower in the patients' group. Reliably higher were the percentage and absolute quantity of monocytes, the percentage of neutrophils and $CD8^+$, IgA and IgM concentration in blood serum, PhN and PhI (Table 3).

Table 2. **Alterations of antioxidative system status of cervical cancer patients depending on the stage of the disease. SOD activity and vitamin E concentration were risen in later stages in all cases**

| Parameters | Comparison of stages | Alterations % |
|---|---|---|
| SOD activity ($U \times 10^4$/ml) | I to 0 | 21 * |
| | II to I | 13 * |
| | III to II | 21 ** |
| Vitamin E concentration (μmol/l) | I to 0 | 15 ** |
| | II to 0 | 29 * |
| | III to II | 25 * |

* $p \leq 0.05$ – reliable difference of parameters;
** $0.05 < p < 0.1$ – tendency to difference of parameters.
Statistically unreliable data are excluded. Patients of stage 0 (n = 22), stage I (n = 71), stage II (n = 20) and stage III (n = 33) were compared.

The percentage and absolute number of lymphocytes and $CD3^+$ cells, $CD4^+/CD8^+$ index were significantly lower in cervical cancer stage II women in comparison with the control group. The absolute quantity of $CD4^+$ and $CD16^+$ had a tendency to be lower. Reliably higher were the total number of leukocytes, the percentage and absolute quantity of neutrophils, the $CD8^+$ index, IgG, IgA and IgM concentration in blood serum, PhN and PhI (Table 3).

A comparison of the data on the cervical cancer stage III women group with the same data on the control women group showed that the percentage and absolute quantity of lymphocytes and $CD3^+$, absolute quantity of $CD4^+$, $CD8^+$ and $CD16^+$ of the former were reliably lower. Reliably higher were the total number of leukocytes, the percentage and absolute quantity of neutrophils, IgG and IgA concentration in blood serum, PhN and PhI. The index of $CD4^+$ had a tendency to be higher (Table 3).

The study results showed that independently of cervical cancer stages some cellular immunity functions of patients were weaker ($CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$), but to maintain bodily homeostasis the other parameters were higher (monocytes, neutrophils, $CD8^+$, IgG, IgA, IgM, PhN, PhI) in comparison with the control women's parameters. It should be emphasized that the number of NK cells ($CD16^+$) and cytotoxic lymphocytes ($CD8^+$) that can destroy cancer cells was decreased in patients with cervical cancer stage III.

Factors indicating the status of the antioxidative system in cervical cancer patients (the amount of lipid peroxidation marker MDA, the antioxidative enzymes CAT and SOD activity, the concentration of antioxidant vitamins A and E) were evaluated in comparison to the control group. A statistically reliable rise of MDA content (44–63%) and a reduction of SOD activity (32–44%) in the blood serum of cervical cancer patients' group should be noted. A reliable rise of CAT activity (13% *versus* 21%) was determined in stage I and stage III, respectively, while the parameter was moderately altered as a tendency both in stage 0 and stage II. A reliable drop of vitamin E concentration (15%) was noted in stage 0 but the parameter was only slightly lower in stages I and II and was even risen in stage III (Table 4). The alteration of vitamin A concentration was determined to be statistically unreliable.

## DISCUSSION

Many studies indicate that the host response to cancer is an important factor in controlling the progression of this disease (5, 6). The results of our study show that the alterations of factors indicating the status of cervical cancer patients' immune system depend on the stage of disease. Cellular immunity suppression was found to be more pronounced in tu-

Table 3. **Alterations of immune system factors of cervical cancer patients in comparison to control group of women**

| Parameters | Reduced, % | | | Parameters | Risen, % | | |
|---|---|---|---|---|---|---|---|
| **A** | | | | | | | |
| $CD3^+$ (%) | ↓ | 3 | * | $CD8^+$ (%) | ↑ | 9 | * |
| $CD4^+/CD8^+$ | ↓ | 8 | * | IgG (g/l) | ↑ | 25 | * |
| $CD19^+$ (%) | ↓ | 10 | * | PhN (%) | ↑ | 2 | * |
| $CD16^+$ (%) | ↓ | 5 | ** | PhI | ↑ | 28 | * |
| **B** | | | | | | | |
| Lymphocytes (%) | ↓ | 11 | * | Monocytes (%) | ↑ | 14 | * |
| Lymphocytes ($n \cdot 10^9/l$) | ↓ | 14 | * | Monocytes ($n \cdot 10^9/l$) | ↑ | 25 | * |
| $CD3^+$ (%) | ↓ | 3 | * | Neutrophils(%) | ↑ | 6 | * |
| $CD3^+$ ($n \cdot 10^9/l$) | ↓ | 15 | * | $CD8^+$ (%) | ↑ | 6 | * |
| $CD4^+$ ($n \cdot 10^9/l$) | ↓ | 12 | * | IgG (g/l) | ↑ | 11 | * |
| $CD4^+/CD8^+$ | ↓ | 8 | * | IgA (g/l) | ↑ | 28 | * |
| | | | | PhN (%) | ↑ | 2 | * |
| | | | | PhI | ↑ | 21 | * |
| **C** | | | | | | | |
| Lymphocytes (%) | ↓ | 26 | * | Leukocytes ($n \cdot 10^9/l$) | ↑ | 15 | * |
| Lymphocytes ($n \cdot 10^9/l$) | ↓ | 19 | * | Neutrophils (%) | ↑ | 18 | * |
| $CD3^+$ (%) | ↓ | 3 | * | Neutrophils ($n \cdot 10^9/l$) | ↑ | 27 | * |
| $CD3^+$ ($n \cdot 10^9/l$) | ↓ | 15 | * | $CD8^+$ (%) | ↑ | 6 | * |
| $CD4^+$ ($n \cdot 10^9/l$) | ↓ | 12 | ** | IgG (g/l) | ↑ | 34 | * |
| $CD4^+/CD8^+$ | ↓ | 8 | * | IgA (g/l) | ↑ | 72 | * |
| $CD16^+$ ($n \cdot 10^9/l$) | ↓ | 25 | ** | IgM (g/l) | ↑ | 33 | * |
| | | | | PhN (%) | ↑ | 1 | * |
| | | | | PhI | ↑ | 33 | * |
| **D** | | | | | | | |
| Lymphocytes (%) | ↓ | 29 | * | Leukocytes ($n \cdot 10^9/l$) | ↑ | 20 | * |
| Lymphocytes ($n \cdot 10^9/l$) | ↓ | 19 | * | Neutrophils (%) | ↑ | 19 | * |
| $CD3^+$ (%) | ↓ | 5 | * | Neutrophils ($n \cdot 10^9/l$) | ↑ | 39 | * |
| $CD3^+$ ($n \cdot 10^9/l$) | ↓ | 23 | * | $CD4^+$ (%) | ↑ | 2 | ** |
| $CD4^+$ ($n \cdot 10^9/l$) | ↓ | 12 | * | IgG (g/l) | ↑ | 18 | * |
| $CD8^+$ ($n \cdot 10^9/l$) | ↓ | 14 | * | IgA (g/l) | ↑ | 28 | * |
| $CD16^+$ ($n \cdot 10^9/l$) | ↓ | 25 | * | PhN (%) | ↑ | 2 | * |
| | | | | PhI | ↑ | 37 | * |

**A** – women with cervical cancer stage 0 (n = 21) compared with control group (n = 114),
**B** – women with cervical cancer stage I (n = 71) compared with control group (n = 114),
**C** – Women with cervical cancer stage II (n = 20) compared with control group (n = 114),
**D** – women with cervical cancer stage III (n = 33) compared with control group (n = 114).
* $p \leq 0.05$ – reliable difference of parameters
** $0.05 < p < 0.1$ – tendency to difference of parameters

mour stages II and III than in stage 0. On the other hand, the capacity of stimulatory mechanisms supporting immune homeostasis fall under cancer progression.

Imbalance of cellular immunity parameters (lowered percentage of $CD3^+$, $CD19^+$, $CD16^+$) was stated in early cervical cancer stage (0) patients in comparison with the control women. Patients with cervical cancer stages II and III had a lower absolute quantity of these parameters, but the other immune system indices were stimulated (monocytes, neutrophils, PhN, PhI, IgG, IgA, IgM) in comparison with those of the control group.

It is evident that certain alterations of the adaptive and regulatory mechanisms of immunity homeostasis occur under cancer development as an immunoreactivity stimulation and suppression. Nevertheless, the multiple functions of the immune system should not be evaluated one-sidedly due to their both protective and stimulant effects on the malignant process (7).

In summary, results of the present research showed a higher concentration of the lipid peroxidation product MDA and the lower activity of the antioxidative enzyme SOD in the blood serum of cervical cancer patients in comparison with women from the control group.

Table 4. **Alterations of antioxidative system status of cervical cancer patients (stage I, n = 71) in comparison to control group of women (n = 114)**

| Parameters | Alterations, % | | | Parameters | Alterations, % | | |
|---|---|---|---|---|---|---|---|
| **A** | | | | **C** | | | |
| Amount of MDA (nmol/ml) | ↑ | 44 | * | Amount of MDA (nmol/ml) | ↑ | 63 | * |
| CAT activity (nmol/l/min) | ↑ | 3 | ** | CAT activity (nmol/l/min) | ↑ | 13 | ** |
| SOD activity (U × $10^4$/ml) | ↓ | 44 | * | SOD activity (U × $10^4$/ml) | ↓ | 44 | * |
| Vitamin E concentration (µmol/l) | ↓ | 15 | * | Vitamin E concentration (µmol/l) | ↓ | 12 | ** |
| **B** | | | | **D** | | | |
| Amount of MDA (nmol/ml) | ↑ | 54 | * | Amount of MDA (nmol/ml) | ↑ | 54 | * |
| CAT activity (nmol/l/min) | ↑ | 13 | * | CAT activity (nmol/l/min) | ↑ | 21 | * |
| SOD activity (U × $10^4$/ml) | ↓ | 40 | * | SOD activity (U × $10^4$/ml) | ↓ | 32 | * |
| Vitamin E concentration (µmol/l) | ↓ | 2 | ** | Vitamin E concentration (µmol/l) | ↑ | 10 | ** |

**A** – women with cervical cancer stage 0 (n = 21) compared with control group (n = 114),
**B** – women with cervical cancer stage I (n = 71) compared with control group (n = 114),
**C** – women with cervical cancer stage II (n = 20) compared with control group (n = 114),
**D** – women with cervical cancer stage III (n = 33) compared with control group (n = 114).
* $p \leq 0.05$ – reliable difference of parameters,
** $0.05 < p < 0.1$ – tendency to difference of parameters.
↓ – reduced parameter, ↑ – risen parameter.

## CONCLUSIONS

1. The status of the immune system of cervical cancer patients depends on the stage of disease. The weakening of cellular immunity and the drop in the stimulant reactions supporting immune homeostasis is revealed under progression of the malignisation process.

2. The capacity of the antioxidative system declines in cervical cancer patients, although the relation between changes in the antioxidative system and the stage of the disease has been found to be ambiguous.

Received 6 May 2005
Accepted 6 June 2005

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## SERGANÈIØ GIMDOS KAKLELIO VËÞIU IMUNINËS IR ANTIOKSIDACINËS SISTEMØ BÛKLË PRIKLAUSOMAI NUO LIGOS STADIJOS

Santrauka

**Darbo tikslas** – ávertinti serganèiø gimdos kaklelio vëþiu moterø imuninës ir antioksidacinës sistemø rodikliø pokyèius priklausomai nuo ligos stadijos.

**Medþiaga ir metodai**. Iðtirta 151 moteris, serganti gimdos kaklelio vëþiu, ir 114 kontrolinës grupës moterø.

Nustatyti šie làstelinio imuniteto rodikliai: bendras leukocitø skaièius, limfocitø, monocitø, neutrofilø procentiniø rodikliø reikðmës ir jø absoliutus kiekis, bendra T limfocitø populiacija ($CD3^+$), T helperiai/induktoriai ($CD4^+$), T supresoriai/citotoksiniai limfocitai ($CD8^+$), imunoreguliacinis rodiklis ($CD4^+/CD8^+$), B limfocitai ($CD19^+$), NK (natûralieji kileriai) ($CD16^+$). Apskaièiuotos limfocitø populiacijø ir subpopuliacijø procentinës reikðmës ir absoliutûs kiekiai. Be to, tiriamøjø imuninei bûklei ávertinti panaudoti du kraujo neutrofilø fagocitozës rodikliai (fagocitozës indeksas – FI ir fagocitozës skaièius – FS%). Imuniteto humoralinë funkcija vertinta pagal IgG, IgA, IgM koncentracijà kraujo serume. Apskaièiuota leukocitø formulë. Antioksidacinë bûklë vertinta pagal lipidø peroksidacijos produkto – malono dialdehido (MDA) – kieká, antioksidaciniø fermentø katalazës (CAT) ir superoksido dismutazës (SOD) aktyvumà bei endogeniniø antioksidantø – vitaminø A ir E – kieká kraujo serume.

**Rezultatai**. Gauti rezultatai rodo, kad progresuojant ligai maþëja làstelinio imuniteto rodikliai (limfocitai, $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD19^+$) ir silpnëja kiti organizmo imunohomeostazæ palaikantys mechanizmai (monocitai, neutrofilai, FI, FS, IgG, IgA, IgM). Taip pat nustatyta, kad vëlesnëse piktybinio proceso stadijose padidëja SOD aktyvumas ir vitamino E koncentracija pacienèiø kraujo serume. Lyginant su kontroline moterø grupe, gimdos kaklelio vëþiu serganèiø moterø serume nustatyta didesnë MDA koncentracija ir maþesnis SOD aktyvumas.

**Išvados**. Vystantis piktybiniam procesui, pacienèiø imunitetas silpnëja, o antioksidacinës sistemos rodikliai priklausomai nuo ligos stadijos kinta nevienareikðmiðkai.

**Raktaþodþiai**: gimdos kaklelio vëþys, ligos stadijos, imuninë sistema, antioksidacinë sistema