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ASSOCIATION OF NATURAL KILLER CELLS ACTIVITY WITH THE INCIDENCE OF COLORECTAL NEOPLASIA AT SCREENING

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ABSTRACT

Relevance: *Increased natural killer cell (NK cells) activity reduces colorectal cancer (CRC) risk. Previously published studies examined the association of NK cells and CRC prevalence in individuals at high cancer risk.*

The study aimed to *study the relationship between NK cell activity and the incidence of advanced adenomas (AA) and CRC in a population with average cancer risk.*

Methods: *The activity of NK cells was assessed by enzyme immunoassay (ELISA) of blood in participants of average risk with a measurement range of 25-2500 pg/mL. The level of NK cells below 200 pg/mL was defined as pathological. The informativeness of the diagnostic test for determining NK cell activity was assessed using indicators such as sensitivity, specificity, negative and positive predictive value, and clinical utility index. The probability coefficient for the development of colorectal cancer was calculated using logistic regression.*

Results: *NK cell activity was assessed in 354 persons of average risk (mean age – 59 years; 36% men). The diagnostic accuracy of NK cells determination for CRC and AA was 76% and 72%, respectively, and the negative predictive value was 96%. The NK cell test demonstrated a good negative clinical utility index for CRC and AA (0.66 and 0.74, respectively). Individuals with low NK cell levels were seven times more likely to be diagnosed with CRC (95% CI 2.3-20.3; p<0.001). NK cell levels were higher in men compared to women (549 pg/mL vs 500 pg/mL) and lower in smokers (412 pg/mL versus 544 pg/mL), non-athletic participants (413 pg/mL versus 654 pg/mL), in people who abuse alcohol (389 pg/ml versus 476 pg/ml).*

Conclusion: *Our study shows that a high level of NK cells can potentially exclude CRC and AA in individuals with average cancer risk.*

Keywords: *colorectal cancer, screening, adenoma, natural killer.*

Introduction: Natural killer cells (NK cells) are a distinct group of innate immune lymphocytes known for their cytolytic function and protect the human body against infection and malignant cells [1]. Inhibitory receptors expressed on the surface of NK cells allow them to differentiate healthy cells from affected ones [2] and increase the cytotoxicity of NK cells against target cells [3, 4], which allows them to fight the growth and spread of tumor cells effectively.

A low level of NK cells leads to an increased risk of cancer development [5], while a high level of NK cells in the blood is associated with a decreased risk of cancer development. Earlier studies have shown that NK cells can be used as a prognostic marker in various malignant processes. Thus, as benign colorectal adenoma transforms into colorectal cancer, there is a gradual decrease in the level of NK cells [6]. A 10-fold increase in the risk of detecting CRC has been observed at NK cell levels below 200 pg/mL [7].

The authors have been unable to find data on using the NK cell activity test in a population at intermediate risk of developing CRC.

The study aimed to study the relationship between NK cell activity and the incidence of advanced adenomas (AA) and CRC in a population with average cancer risk.

Materials and methods:

Study object

The study included persons aged 45-75 years at intermediate risk of developing cancer. The participants underwent CRC screening using CT colonography as the primary screening modality in our previous scientific study [8]. The intermediate-risk group included those without risk factors, such as personal/family history of colorectal neoplasia and inflammatory bowel disease, hereditary syndromes associated with CRC, type II diabetes, etc.

Exclusion criteria: (1) a history of acute inflammation within four weeks or chronic diseases such as human immunodeficiency virus, hepatitis B or C viruses, (2) a history of malignancy, (3) use of drugs that may affect NK cell function, such as immunosuppressive drugs, therapeutic immunoglobulins, methylprednisolone, anticoagulants, etc. [9-11].

Study design

A prospective cross-sectional observational study was conducted. The Local Ethical Committee approved the study at the Kazakh Research Institute of Oncology and Radiology (Almaty, Kazakhstan). All participants signed voluntary informed consent.

On the day of CT colonography, 1 mL of venous blood was sampled into an NK Vue tube (ATGen, South Korea) using a standard antecubital approach. The NK cell activity was determined according to the previously established method [12]. During the test, a blood sample was stimulated with a cytokine. As a result, NK cells released interferon-gamma, which was subsequently quantified by enzyme-linked immunosorbent assay (ELISA) (Figure 1). A 24.5-2,500 pg/mL range was established; NK cell levels below 200 pg/mL were considered abnormal.

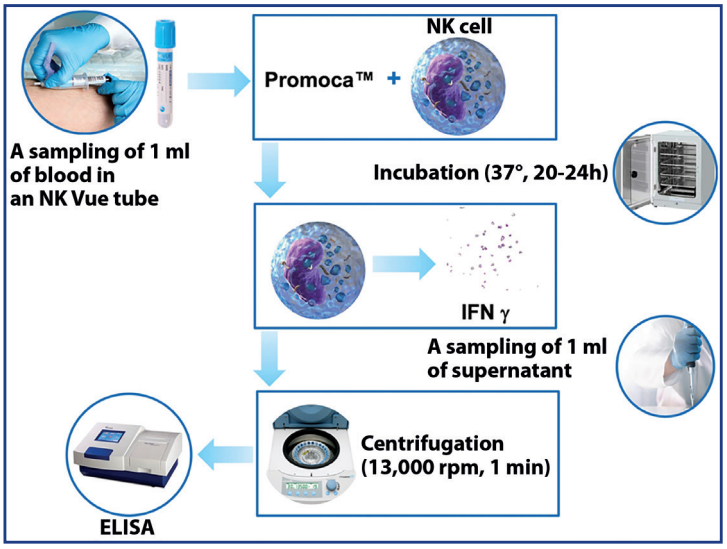

Figure 1 – ELISA stages to determine NK cell activity

All participants underwent CT colonography and were classified into the categories of CT Colonography Interpretation System (C-RADS). [13]. Colonoscopy and histopathological evaluation were performed according to standard methods [14]. According to histopathology results, colonic lesions were classified as carcinoma, serrated or adenomatous polyps. Adenomas greater than 10 mm containing 25% or more villous components and marked dysplasia were classified as AA.

Data analysis

NK cells were counted for the participants with colorectal adenoma and CRC. The informativeness of the NK cell test was assessed using basic statistical measures such as sensitivity, specificity, negative and positive predictive values, likelihood ratio, overall test accuracy, clinical utility index, and others. In addition, a ROC curve was constructed to determine the optimal value of the NK cell cutoff. Pearson correlation analysis was used to determine the relationship between NK cell activity and the sociodemographic and medical characteristics of the participants. The results were statistically significant when the p-value was less than 0.05. All statistical analyses were performed using SPSS software.

Results: A total of 354 asymptomatic individuals at intermediate risk of development who underwent colorectal screening using CT colonography as the primary screening method were included in the present study. The mean age of the subjects was 59 years.

Ten cases of CRC and 32 cases of AA were identified. In addition, 6 cases of acute/subacute colitis were identified. Based on the results of colonoscopy and histological examination, participants were divided into four groups: (1) control, (2) colorectal adenoma, (3) colitis, and (4) CRC.

In qualitative assessment, the median NK cell activity was 549 pg/mL in men and 500 pg/mL in women. Median NK cell activity was higher in nonsmokers (544 pg/mL versus 412 pg/mL) and physically active participants (654 pg/mL versus 413 pg/mL in physically inactive participants). Alcohol abusers had an NC cell activity level of 389 pg/mL, whereas nondrinkers had an activity level of 476 pg/mL.

As shown in Table 1, low levels of NK cells were associated with a 7-times higher CRC frequency ($p<0.001$). This difference was even more significant in women: NK cell presence was associated with a 23-times more likely probability of CRC than in men.

Table 1 – CRC detection frequency depending on NK cell activity

	NK cell activity ≤200 pg/mL			NK cell activity ≥201 pg/mL		
	NN	OR [95% DI]	*p*	NN	OR [95% DI]	*p*
Men	35	3 [0.7-12]	*0.15*	93	0.4 [0.1-1.5]	*0.15*
Women	58	23 [2.8-191]	*0.004*	168	0.04 [0.01-0.4]	*0.21*
Both sexes	93	7 [2-20.3]	*<0.001*	261	0.2 [0.05-0.4]	*0.06*

Median NK cell activity was 140 pg/mL in patients with CRC and 392 pg/mL in patients with advanced colorectal adenomas. In the control group, the NK cell level was higher than in other groups: median – 545 pg/mL, p<0.05 (Figure 2).

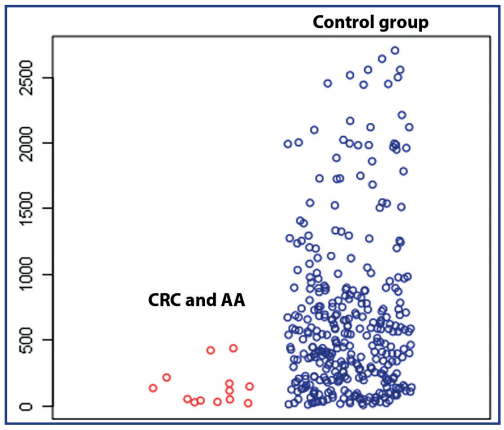

Figure 2 – NK cell activity

The present study achieved the maximum Juden index (0.693) at an NK cell level of 200 pg/mL. The rate of false-negative test results in the diagnosis of CRC at this value was 13%.

The test's sensitivity for CRC detection was significantly higher than that for AA (71% versus 21%). The NK cell test's accuracy for CRC detection was 76%, with a sensitivity of 71% and specificity of 76%. The accuracy of the test in the diagnosis of AA was 72%. The negative predictive value of the test was high for the CRC and AA groups, 99% and 98%, respectively (Table 2).

The NK cell activity test demonstrated good clinical utility for excluding AA and CRC with an unfavorable clinical utility index (CUI-) of 0.7 and 0.6, respectively, whereas the positive CUI was very low, 0.05 [95% CI 0.02-0.1] versus 0.01 [95% CI 0-0.1] for AA and CRC, respectively.

Table 2 - Diagnostic value of the NK cell activity test in the diagnosis of colorectal neoplasia

Indicators	CRC		AA	
	95% CI value		95% CI value	
Sensitivity	71%	[42-91.6]	21%	[8-39.7]
Specificity	76%	[70.7-80]	73%	[68-78]
Positive clinical utility index	2,9	[2.0-4.3]	1.1	[0.4-1.6]
Negative clinical utility index	0,4	[0.2-0.9]	1.1	[0.9-1.3]
Positive predictive value	7,8%	[5.5-11]	1.3%	[0.6-2.7]
Negative predictive value	99%	[98-99.5]	98%	[98-98.5]
Accuracy	76%	[71-79.9]	72%	[67-77]
Prevalence	2.8%		1.7%	

Discussion: This study was the first to evaluate the association of NK cell activity levels with the prevalence of CRC and AA in a population at intermediate risk of cancer. The NK cell test showed good diagnostic accuracy in detecting CRC and AA, but sensitivity and specificity were lower than in previously published studies [7]. Specifically, in a Canadian study involving high-risk individuals with CRC, the NK cell activity test showed a sensitivity of 87% and specificity of 64% in diagnosing CRC.

The test's low sensitivity in detecting AA and the shallow positive CUI values for both CRC and AA limit the clinical utility of this test as a primary screening method for CRC and AA. However, the high negative predictive value of the test for both pathologies suggests its potential ability to rule out disease in persons at intermediate risk of developing CRC.

The present study showed that the likelihood of colorectal cancer is very low in the intermediate-risk population if the NK cell level is above 200 pg/mL. The participants with NK cell activity below 200 pg/mL had a 7-times higher risk of colorectal malignancy. It has been shown that those with low NK cell activity had a 10-fold higher risk of being diagnosed with CRC than those with NK cell activity above 200 pg/mL [7]. However, it should be noted that the participants in the above study had a high risk of developing cancer and differed from those in the present study.

In this study, patients with CRC had reduced NK cell activity. The Tallerico et al. study demonstrated a high resistance of differentiated CRC cells to NK cells [15]. It was also shown that immunohistochemical evaluation of cancerous tissue in CRC showed low density or absence of infiltrated NK cells [16]. However, the authors found an increased density of infiltrated NK cells in colorectal adenoma tissue compared to the surrounding normal mucosa. The results showed that participants with AA had lower median NK cell activity than healthy subjects. Thus, it can be assumed that colorectal adenomas are affected by NK cells because NK cells can still migrate into the adenoma tissue, as shown by the study of Halama et al. [16], but cell function is impaired. However, to date, there are no data to conclude that high serum levels of NK cells or high density of infiltrated NK cells in adenoma tissue can prevent adenoma transformation into cancer or slow down this process. Therefore, studying the effect of NK cells on col-

orectal cancer is essential to find ways to create an oncoprotective environment and develop anti-cancer drugs.

The results of this study confirm that individuals who exercise have higher levels of NK cells than those who are physically inactive. These results are consistent with previously published evidence of increased anti-cancer immunity with regular physical activity [17].

We also found that NK cell activity was higher in non-smokers than in smokers. As for alcohol consumption, the average level of NK cells in this group was lower than in smokers and physically inactive participants. These facts are particularly noteworthy because they suggest that smoking and excessive alcohol consumption may be responsible for decreased immunity and increased cancer risk. Conversely, elevated levels of NK cells may protect against the effects of malignant cells. Recently, Legaz et al. found that the presence of immunoglobulin-like receptors expressed on the surface of NK cells has a protective effect against alcoholic cirrhosis, a significant risk factor for hepatocellular carcinoma [18]. However, these hypotheses require confirmation by further studies.

Conclusion: The presented results show that the NK cell activity test can be used as a potential biomarker to detect individuals at high risk of CRC in a healthy population. High NK cell function, regular exercise, quitting smoking and alcohol abuse habits reduce the likelihood of detecting CRC in a population at intermediate risk for cancer.

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СКРИНИНГ КЕЗІНДЕГІ КОЛОРЕКТАЛДЫ НЕОПЛАЗИЯЛАРДЫҢ ЖИІЛІГІМЕН ТАБИҒИ КИЛЛЕР БЕЛСЕНДІЛІГІНІҢ БАЙЛАНЫСЫ

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ТҰЖЫРЫМ

Өзектілігі: *Табиғи немесе натуралды киллерлер (НК жасушалары) белсенділігінің жоғарылауы колоректалды рак (КРР) қаупін төмендетеді. Бұрын жарияланған зерттеулердің нәтижелері НК жасушаларының қатерлі ракпен байланысын КРР даму қаупі жоғары адамдарда зерттелгенін көрсетеді.*

Зерттеудің мақсаты *– қатерлі рак даму қаупі орташа популяциядағы НК жасушаларының белсенділігі мен үдемелі аденомалар (ҮА) және КРР жиілігі арасындағы байланысты зерттеу болды.*

Әдістері: *НК жасушаларының белсенділігі 25-2500 пг/мл өлшем диапазоны бар орташа қауіп тобына қатысушылардың қанының ферменттік иммундық талдауымен (ИФА) анықталды. НК жасушаларының 200 пг/мл-ден төмен деңгейі патологиялық деп есептелді. НК жасушаларының белсенділігін анықтауға арналған диагностикалық тесттің ақпараттылығы сезімталдық, спецификалық, теріс және оң болжамдық мән, клиникалық пайдалылық индексі сияқты көрсеткіштер арқылы бағаланды. Колоректалды рак дамуының ықтималдық коэффициенті логистикалық регрессия көмегімен есептелді.*

Нәтижелері: *НК жасушаларының белсенділігі орташа қауіп тобындағы 354 адамда бағаланды (орташа жасы 59 жас; олардың 36%-ы ерлер). КРР және ҮА үшін НК жасушаларын анықтауға арналған сынақтың диагностикалық дәлдігі сәйкесінше 76% және 72% құрады, ал теріс болжау мәні 96% болды. НК жасушаларының сынағы КРР және ҮА үшін жақсы теріс клиникалық пайдалылық индексін көрсетті (тиісінше 0,66 және 0,74). НК жасушаларының деңгейі төмен адамдарда КРР диагнозы 7 есе жиі болды (95% СИ 2,3-20,3; p<0,001). НК жасушаларының деңгейі әйелдермен салыстырғанда ерлерде жоғары (549 пг/мл-ге және 500 пг/мл) және жоғарғы деңгей шылым шегетіндерде (412 пг/мл-ге және 544 пг/мл), спортпен айналыспайтын қатысушыларда (413 пг/мл-ге және 654 пг/мл), алкогольді асыра пайдаланатын адамдарда анықталды (476 пг/мл-ге және 389 пг/мл).*

Қорытынды: *Біздің зерттеуіміз көрсеткендей, НК жасушаларының жоғары деңгейі қатерлі ісіктің даму қаупі орташа адамдарда КРР және ҮА жоққа шығаруға мүмкіндік береді.*

Түйінді сөздер: *колоректалды рак, скрининг, аденома, табиғи киллерлер.*

АССОЦИАЦИЯ АКТИВНОСТИ НАТУРАЛЬНЫХ КИЛЛЕРОВ С ЧАСТОТОЙ ВЫЯВЛЕНИЯ КОЛОРЕКТАЛЬНЫХ НЕОПЛАЗИЙ ПРИ СКРИНИНГЕ

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АННОТАЦИЯ

Актуальность: *Повышенная активность естественных или натуральных клеток-киллеров (НК-клеток) связана со снижением риска развития колоректального рака (КРР). В ранее опубликованных результатах исследований изучалась связь НК-клеток и распространенности КРР у лиц с высоким риском развития рака.*

Цель исследования *– изучить взаимосвязь активности НК-клеток с частотой выявления прогрессирующих аденом (ПА) и КРР в популяции со средним риском развития рака.*

Методы: *Активность НК-клеток оценивали методом иммуноферментного анализа (ИФА) крови у участников среднего риска образования КРР. Уровень НК-клеток ниже 200 пг/мл определялся как патологический. Информативность диагностического теста на определение активности НК-клеток оценивалась с помощью таких показателей, как чувствительность, специфичность, отрицательная и положительная прогностическая ценность, индекс клинической полезности. Коэффициент вероятности развития КРР рассчитывали с помощью логистической регрессии.*

Результаты: *Активность НК-клеток оценена у 354 лиц среднего риска (средний возраст – 59 лет; 36% – мужчины). Диагностическая точность теста на определение НК-клеток для КРР и ПА составила 76% и 72%, соответственно, а отрицательное предиктивное значение – 96%. Тест на определение НК-клеток продемонстрировал хороший отрицательный индекс клинической полезности для КРР и ПА (0,66 и 0,74, соответственно). У лиц с низким уровнем НК-клеток вероятность выявления КРР была в 7 раз выше (95%ДИ 2,3-20,3; p<0,001). Уровень НК-клеток был выше у мужчин по сравнению с женщинами (549 пг/мл против 500 пг/мл) и ниже у курильщиков (412 пг/мл против 544 пг/мл), у лиц, не занимающихся спортом (413 пг/мл против 654 пг/мл), у лиц, злоупотребляющих алкоголем (389 пг/мл против 476 пг/мл).*

Заключение: *Исследование показывает, что высокий уровень НК-клеток обладает потенциальной возможностью исключать КРР и ПА у лиц со средним риском развития рака.*

Ключевые слова: *колоректальный рак, скрининг, аденома, натуральные киллеры.*

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