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Exploring the landscape of CA-125 testing: A comprehensive analysis of Ministry of Health data

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ABSTRACT

OBJECTIVE: The aim of this study was to investigate the utilization patterns and clinical implications of cancer antigen 125 (CA-125) testing in the diagnosis of ovarian and endometrial cancers using a large-scale dataset obtained from the Ministry of Health.

METHODS: A retrospective analysis was conducted on anonymized data collected between 2017 and 2021, comprising 3.917.240 individuals who underwent CA-125 testing. The data included demographic information, test results, diagnoses, and clinical characteristics. Descriptive statistics and comparative analyses were performed to assess the utilization trends and clinical outcomes associated with CA-125 testing.

RESULTS: Among the study population, CA-125 testing was primarily requested for female individuals, with the highest number of tests performed in the age group of 18–64 years. The overall positive rate for CA-125 was 13.31%, with slightly lower rates observed in females (13.18%) than males (14.07%). The study identified a significant association between elevated CA-125 levels and cancer diagnoses, with 19.88% of positive CA-125 results indicating cancer, whereas 10.51% had no cancer diagnosis. Furthermore, the study revealed a higher likelihood of cancer detection among individuals aged 65 years and above, with a positive rate of 17.79%.

CONCLUSION: Our findings provide valuable insights into the utilization patterns and clinical implications of CA-125 testing in ovarian and endometrial cancer diagnosis. While CA-125 remains a prominent tumor marker, its interpretation should consider age, gender, and clinical context. The study emphasizes the potential benefits of integrating additional markers and imaging modalities to enhance diagnostic accuracy. These findings contribute to optimizing the use of CA-125 testing for early detection and management of gynecological malignancies, thereby improving patient outcomes.

Keywords: Big data; CA-125; clinical laboratory test; national health.

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The cancer antigen 125 (CA-125) is a transmembrane protein produced both from Müllerian (fallopian tube, endometrial, and endocervical) and coelomic (pericardium, pleura, and peritoneum) epithelium. As a tumor marker, it is primarily used in the diagnosis of epithelial ovarian and endometrial cancers [1].

Ovarian cancer is generally asymptomatic before reaching advanced stages, accordingly, approximately 75% of patients with ovarian cancer are diagnosed at an advanced stage (FIGO stages 3 and 4) and have a poor prognosis. Despite surgical and chemotherapy regimens, recurrence occurs within 5 years in 95% of patients. Ovarian cancer is the gynecological malignancy with the highest mortality, and the use of biomarkers for early diagnosis is an unmet medical need [2].

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The dominant tumor marker currently used in the diagnosis of epithelial ovarian carcinoma is CA-125, despite its low sensitivity and specificity. A meta-analysis comprising 77 studies evaluating the diagnostic performance of CA-125 found that a CA-125 level over 35 U/mL had a sensitivity of 78% in detecting adnexal masses [3]. In developed countries, over 90% of ovarian cancers are of epithelial origin, and high serum CA-125 levels are found in 80–90% of patients diagnosed with advanced-stage epithelial ovarian carcinoma. Although CA-125 is a blood test primarily used for the detection of epithelial ovarian cancer and high levels are usually indicative, the presence of cancer, and several other conditions may lead to elevated levels of CA-125, including benign gynecologic conditions, non-gynecological conditions, and non-gynecological cancers, therefore care is required when interpreting the results [4].

The Ministry of Health in Türkiye has gathered a series of data concerning the use of the CA-125 as a tumor marker and has conducted a large-scale analysis using this data. The aim of the study is to further analyze the utility of CA-125 as a marker for ovarian cancer, using the relevant data. The dataset comprises comprehensive information on both patient medical histories and serum levels of the CA-125. The findings of this study could make a significant contribution to the overall body of knowledge on tumor markers and cancer diagnosis strategies. It could also offer practical suggestions and strategies for improving the use and evaluation of tumor markers in health-care delivery.

Highlight key points

- The CA-125 test is more positive among women, a higher rate of positivity in individuals aged 65 and over.
- When CA-125 positivity rates were analyzed by institution type, it was seen that university hospitals had the highest rate, followed by private health institutions and public hospitals.
- When looking at the clinics, the highest rate of positivity was seen in the medical oncology clinic, followed by the emergency medicine clinic, and the gynecologic oncology surgery clinic took the third place.
- Only 19,88% of individuals who test positive for CA-125 have a confirmed cancer diagnosis. These results show that the CA-125 test alone may not be sufficient for cancer diagnosis.

MATERIALS AND METHODS

Data from a 5-year period (2017–2021) were analyzed, including 22.680.568 tests from 3.917.240 individuals. The test counts, test rates per population, and rates of exceeding the reference range were assessed based on gender, age groups, geographic regions, and health-care institution types.

The CA-125 test results were obtained through the immunoassay method and derived from the data transferred to the National Health Database System of the Turkish Ministry of Health. The health-care database service in Türkiye is referred to as e-Pulse. The transmission of health data set packages is facilitated through Extensible Markup Language (XML) web services. This database encompasses the health records of patients who have sought medical services from all public, private, and university health-care institutions in Türkiye, including their demographic characteristics, laboratory data, medication usage, comorbidities, and other health-related records.

Database and e-Pulse

e-Pulse is a platform developed by the Ministry of Health in Türkiye, allowing individuals to store and manage their health information digitally. For this study, patient information and health records were collected from the e-Pulse system. During the data collection process, personal information was protected, and the principle of privacy was fully respected.

SKRS and ICD Codes

Health Coding Reference Server (SKRS) is a data recording and reporting system used by the Ministry of Health in Türkiye. This system aids in the more effective management of health services. In this study, data pulled from the SKRS and International Statistical Classification of Diseases and Related Health Problems (ICD) codes were used to analyze disease diagnoses, treatment plans, and the overall state of health services.

ICD codes are a standard disease and health problem classification system created by the World Health Organization and used worldwide. These codes are an important tool for identifying, monitoring, and treating diseases.

Study Design

This retrospective study utilized data from the Ministry of Health, covering a 5-year period from 2017 to 2021. The data included information on CA-125 tests requested from individuals across different regions and health-care institutions in the country.

Data Collection

The data were collected from medical records and laboratory databases. The information included demographics (gender, age), test requests, test results, cancer diagnoses, and health-care institution types.

Study Population

The study population consisted of individuals who underwent CA-125 testing during the study period. Both men and women were included in the analysis.

Data Analysis

Descriptive statistics were used to analyze the data. The test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates were calculated and compared across different variables, including gender, age groups, geographic regions, and health-care institution types. The study data were transferred to the SPSS Statistics version 26.0 (IBM Corp., Armonk, NY) program, and the analyses were completed.

Ethical Considerations

This study was conducted in accordance with the Helsinki declaration. Ethical guidelines were adhered to in the study. The privacy of the individuals included in the data used in the study was protected. Institutional review board approval was obtained, and all data were anonymized to ensure confidentiality. Relevant approval was obtained from the Turkish Ministry of Health with the waiver of informed consent for retrospective data analysis (95741342-020/27112019).

RESULTS

Between January 1, 2017, and December 31, 2021, a CA-125 test was requested from 3.917.240 individuals, with a total of 22.680.568 tests performed. The average number of tests per person is 5.76, and the number of tests per 100.000 population is 27.445. When comparing the test number ratio between women and men, the ratio was 4.10 in 2017, 4.18 in 2018, 4.14 in 2019, 3.98 in 2020, and 3.90 in 2021. Both for women and men the number of tests, in accordance with the overall population, increased year by year from 2017 to 2019, with a noticeable decline in 2020 and 2021 (Table 1).

Table 1. Total consumption of tumor markers between 2017 and 21

	Number of tests	Number of people	Number of tests per person	Number of tests per 100.000 population
AFP	15.618.083	3.123.258	4.86	18.899
CA-125	22.680.568	3.917.240	5.79	27.445
CA-15.3	21.579.044	2.981.142	7.24	26.112
CA-19.9	25.808.137	4.018.913	6.42	31.230
CA-72.4	911.834	141.974	6.42	1.103
CEA	27.394.778	4.016.178	6.82	33.150
NSE	110.401	24.763	4.46	134
PSA free	12.876.151	3.020.756	4.26	15.581
PSA total	21.547.232	5.812.043	3.71	26.074

AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NSE: Neuron-specific enolase; PSA: Prostate-specific antigen.

It was observed that CA-125 was most frequently requested in the 18–64 age range, followed by >65 range, and least frequently in the 0–17 range. The ratio of test requests between the 18–64 age group and those >65 was 3.06 in 2017, 3.23 in 2018, 3.07 in 2019 and 2020, and 2.84 in 2021. The consumption ratio of tests per 100.000 people between the 18 and 64 age group and those >65 was 1/2.24 in 2017, 1/2.22 in 2018, 1/2.26 in 2019, 1/2.16 in 2020, and 1/2.34 in 2021.

The rate of patients who received a cancer diagnosis at any time after a CA-125 tumor marker test was investigated. The rate of cancer detection increased year by year from 2017 to 2020, with 26% of people diagnosed with cancer in 2017, 36% in 2020, and 32% in 2021. When analyzing the timing of testing and cancer diagnosis was further evaluated, it was observed that the test was most frequently requested before the diagnosis in all years, second-most frequently requested at the same time as the diagnosis, and least frequently requested after the diagnosis. The rate of pre-diagnosis test requests had been increased year by year; the rate was 10.83% in 2017, and this rate has increased to 26.25% by 2021. When comparing test request rates by diagnosis times (before/during/after diagnosis), the rate was 1.01/1.06/1 in 2017, 4.16/1.25/1 in 2018, 6.2/1.35/1 in 2019, 9.37/1.71/1 in 2020, and 14.5/2.4/1 in 2021. Over time, the pre-diagnosis rate had significantly increased (Table 2).

Table 2. Distribution of cancer diagnosis related to CA-125

Year	Diagnosed with cancer-related diseases		Diagnosed with unrelated cancer diseases		The total number of people tested
	n	%	n	%	
2017	23.841	2.30	302.673	29.25	1.034.911
2018	27.072	2.36	357.063	31.10	1.148.277
2019	29.063	2.40	393.215	32.48	1.210.635
2020	25.406	3.04	369.473	44.27	834.591
2021	26.374	2.96	375.979	42.15	891.966

CA-125: Cancer antigen 125.

In 2017, 2.3% of individuals tested for CA-125 received a CA-125-associated cancer diagnosis, whereas 29.25% received a CA-125-unrelated cancer diagnosis. These rates have been increasing up to 2020 when 3.04% of patients received a CA-125-associated cancer diagnosis and 44.27% received a CA-125-unrelated cancer diagnosis. In 2021, these rates are 2.96% and 42.15%, respectively. When comparing the ratio of those diagnosed with CA-125-related cancer to those diagnosed with unrelated cancer, the ratio was 1/12.71 in 2017, 1/13.1 in 2018, 1/13.5 in 2019, 1/14.5 in 2020, and 1/14.23 in 2021.

The clinic from which a CA-125 test was ordered most frequently was obstetrics and gynecology clinic, followed by medical oncology in 2020, and by internal medicine in other years. Family medicine ranked 7th in 2017 and 2018, 5th in 2019, 7th in 2020, and 6th in 2021. The emergency department was 8th in 2017–2020, and 9th in 2021 (Table 3).

The simultaneous ICD codes at the time the CA-125 test ordered were investigated. The most common ICD codes in 2017 and 2018 were "abdominal pain, other and unspecified," "ovarian cysts, other and unspecified" and "essential (primary) hypertension." From 2019 to 2021, the most common ICD codes were "vitamin D deficiency, unspecified," "breast malignant neoplasm, unspecified" (second place in 2020), and "abdominal pain, other and unspecified" (third place in 2020). In 2021, the second-most common ICD code was "abdominal pain, other and unspecified," and the third was "breast malignant neoplasm." Overall, the most common ICD codes were "vitamin D deficiency, unspecified," "abdominal pain, other and unspecified" (in second place), and "ovarian cysts, other and unspecified" (in third place).

Table 3. The rate of the CA-125 test is out of the reference range by clinics

Clinics	Ratio (%)
Gynecology and obstetrics	13.38
Medical oncology	21.91
Internal medicine	9.18
General surgery	9.35
Radiation oncology	8.90
Family medicine	5.02
Gastroenterology	16.72
Gynecological oncology surgery	18.16
Emergency medicine	20.40
Neurology	5.96

CA-125: Cancer antigen 125.

The overall positivity rate of the CA-125 test was 13.31% being highest in 2020 at 15.13%, and lowest in 2018 at 12.73%. Among women, it was 13.18%, and among men, it was 14.07%. Among age groups, the highest rate was 17.79% in >65 group, followed by 12.16% in the 18–64 age group, and 8.63% in the 0–17 age group. When comparing the age groups, the positivity rates were 1.99/1.40/1, respectively. According to the health facility levels, the highest rate was in tertiary care institutions with 14.75%, followed by 11.67% in secondary care institutions, and 6.10% in primary care institutions, and according to the health facility type the highest rate of 17.55% in university hospitals, followed by 15.50% in private health-care institutions, and 11.41% in public hospitals.

The clinic with the highest rate of CA-125 positivity rate was medical oncology with 21.91% followed by emergency medicine with 20.40%, and gynecologic oncology surgery with 18.16%. The clinic with the highest number of test requests was obstetrics and gynecology with a rate of 13.38%, while medical oncology and internal medicine had rates of 21.91% and 9.18%, respectively. The rate in family medicine was 5.02% (Table 3).

Overall, a total of 13.35% of individuals had a positive CA-125 result. Among those who tested positive, 19.88% had a cancer diagnosis, whereas 10.51% did not have a cancer diagnosis.

When the expense of CA-125 testing was investigated, the cost in 2017 was 35.466.680 TL for total costs and 14.474.083 TL for unit costs. In 2021, the total cost was 32.283.656 TL, and the unit cost was 15.905.839 TL.

DISCUSSION

This extensive study encompasses a comprehensive analysis of various parameters related to the CA-125 test. The study examines the distribution of CA-125 test requests, the association of test results with gender, age groups, admission status, and cancer diagnosis. In addition, the study investigates the rates of test requests in different clinics and the costs associated with the test. The findings reveal that the CA-125 test shows a higher rate of positivity among women. Regarding age groups, the study identifies a higher positivity rate among individuals aged 65 and older. However, when examining the association of the test with a cancer diagnosis, it is found that only 19.88% of individuals who tested positive had a confirmed cancer diagnosis. These results indicate that the CA-125 test alone may not be sufficient for cancer diagnosis.

CA-125 is a tumor marker commonly used in the diagnosis of epithelial ovarian and endometrial cancers [5]. In 2020, ovarian cancer accounted for 1.2% of all cancer cases, with 21.750 cases detected. In Turkiye, the incidence of ovarian cancer was 6.4/100.000 in 2016 [6]. According to the Global Cancer Observatory (Globocan) 2018 data, ovarian cancer is the seventh-most common cancer in women in Türkiye, with a rate of 4.1%. It contributes to 5.2% of cancer-related deaths [7].

A meta-analysis conducted by Ferraro et al. [8] reported a specificity of 78% for CA-125 in detecting ovarian cancer. In our study, when analyzing the rates of exceeding the reference range according to cancer diagnosis status, a total of 13,35% of individuals tested positive. Among those who tested positive, 19.88% had a confirmed cancer diagnosis, whereas 10.51% did not have a cancer diagnosis. In 2017, among individuals who underwent the CA-125 test, 2.3% received a cancer diagnosis related to CA-125, whereas 29.25% received a cancer diagnosis unrelated to CA-125. These proportions showed an increase until 2020, with 3.04% of patients receiving a CA-125-related cancer diagnosis and 44.27% receiving a CA-125-unrelated cancer diagnosis. In 2021, these proportions were 2.96% and 42.15%, respectively. When comparing the rates of exceeding the reference range over the years, the highest rate was observed in 2020, at 15.13%, whereas the lowest rate was in 2018, at 12.73%.

The higher positivity rate among women and the prominent use of the test in gynecological clinics suggest its effectiveness in detecting gynecological conditions, particularly ovarian and endometrial cancers. However, it is crucial to acknowledge that a positive CA-125 result does not necessarily indicate the presence of cancer, as evidenced by the low percentage of individuals with a confirmed cancer diagnosis among those who tested positive.

The variations observed in test requests among different age groups and admission statuses raise important considerations. The average age of onset for ovarian cancer is 63, with 70% of patients being diagnosed at stage 3C or higher [5]. In our study, when comparing the number of test requests across different age groups, CA-125 was most frequently requested in the 18–64 age range, followed by the 65 and older age group, and least frequently in the 0–17 age group. The higher positivity rate among individuals aged 65 and older suggests that CA-125 might have greater relevance and diagnostic value in detecting malignancies in older populations. Conversely, the relatively lower positivity rate in the pediatric age group necessitates careful interpretation and cautious utilization of the CA-125 test in this population.

The comparison of test requests among different clinic types also yields valuable insights. The higher rate of test requests in medical oncology clinics highlights the importance of CA-125 in monitoring cancer patients and assessing treatment responses. In addition, the notable rate of test requests in emergency medicine clinics signifies its potential role in evaluating acute conditions and ruling out serious gynecological pathologies in urgent settings. Analyzing the rates of CA-125 positivity by institution type, university hospitals had the highest rate followed by private health-care institutions and public hospitals at 11.41%. Regarding the clinics, the highest positivity rate was observed in the medical oncology clinic, followed by the emergency medicine clinic, and the gynecologic oncology surgery clinic ranked third. It is noteworthy that while CA-125 is primarily believed to assist in diagnosis under ultrasound guidance by specialists in the relevant field, its frequent request from the emergency department raises intriguing questions.

It is worth mentioning that the cost analysis of the CA-125 test indicates a considerable financial burden. Thus, the clinical utility and cost-effectiveness of the test should be carefully evaluated, particularly in resource-limited settings, to ensure its judicious use and allocation of health-care resources.

The present study has several limitations that should be acknowledged. First, the retrospective design of the study introduces inherent limitations, including poten-

tial missing data and bias in data collection. Second, the study's findings are based on a specific group of individuals who underwent CA-125 testing, potentially introducing selection bias. Furthermore, the accuracy and reliability of the recorded data, including test results and diagnoses, may influence the validity of the results. In addition, the study may not account for all potential confounding factors, and the methodology employed in the study, such as reference range selection and laboratory techniques, could have implications for result interpretation and generalizability. Finally, lack of detailed clinical information, limited follow-up periods and human epididymis protein 4 (HE4), and transvaginal ultrasonography (TVUS) findings not being evaluated restrict a comprehensive understanding of the relationship between CA-125 levels and disease outcomes. These limitations should be considered when interpreting the findings and may impact the study's external validity and reliability.

Conclusion

Our study provides valuable insights into the utilization and patterns of CA-125 testing in the diagnosis of ovarian and endometrial cancers. Despite the limitations, CA-125 remains a prominent tumor marker, particularly in the diagnosis of epithelial ovarian carcinoma. The findings highlight the importance of considering age, gender, and clinical context when interpreting CA-125 levels. In addition, the study underscores the need for further research to explore the potential benefits of incorporating additional markers and imaging modalities, such as HE4 and TVUS, to enhance diagnostic accuracy. These findings contribute to the existing knowledge and can inform health-care professionals in optimizing the use of CA-125 testing for the early detection and management of gynecological malignancies.

Ethics Committee Approval: Relevant approval was obtained from the Turkish Ministry of Health with the waiver of informed consent for retrospective data analysis (date: 27.11.2019, number: 95741342-020).

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