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Utilization and Diagnostic Value of CA-15.3 Test in Breast Cancer: Insights from a Longitudinal Study Based on Turkish Ministry of Health Data

CA-15.3 Testinin Meme Kanserinde Kullanımı ve Tanı Değeri: Türkiye Sağlık Bakanlığı Verilerine Dayanan Bir Longitudinal Çalışmadan Elde Edilen Bilgiler

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ÖZ

Amaç: Bu çalışmanın amacı, meme kanseri izleme ve tedavisinde CA-15.3 testinin kullanımını analiz etmek ve farklı popülasyonlar arasındaki örüntülerini değerlendirmektir.

Gereç ve Yöntem: 2017-2021 yılları arasındaki beş yıllık döneme ait veriler toplandı ve bunlar arasında 2.981.142 kişiden alınan 21.579.044 CA-15.3 testi bulunmaktadır. Verilerin analizi için tanımlayıcı istatistikler kullanıldı, bunlar arasında test sayıları, nüfusa göre test oranları, referans aralığının üzerinde olan oranlar ve kanser tanısı oranları bulunmaktadır.

Bulgular: Çalışma, 2017'den 2019'a kadar CA-15.3 testinin istek sayısında artış eğilimi olduğunu ortaya koydu, bunu 2020 ve 2021 yılında önemli bir düşüş izledi. Test daha sık olarak kadınlar için istendi, özellikle 18-64 yaş grubunda. CA-15.3 testine tabi olan bireylerde kanser teşhisi oranı yıllar içinde artan bir eğilim gösterdi. İstanbul, test istek oranının en yüksek olduğu şehir olarak belirlendi, onu Ankara ve İzmir izledi. Üniversite hastaneleri en fazla test talep eden kurumlar oldu, onları devlet hastaneleri, özel hastaneler ve eğitim ve araştırma hastaneleri takip etti.

Sonuç: Bu çalışma, meme kanseri tedavisinde CA-15.3 testinin kullanım örüntülerine değerli bir bakış sunmaktadır. Test, test taleplerinde ve kanser teşhisi oranlarında artan bir eğilim gösterirken, sonuçların yorumlanmasında potansiyel kısıtlamalar nedeniyle dikkatli olunmalıdır. CA-15.3 düzeyleri ile kanser teşhisi arasındaki ilişkinin kesin bir anlayışını sağlamak için daha fazla araştırmaya ihtiyaç vardır. Bulgular, test sonuçlarının kişiselleştirilmiş yorumlanmasının önemini vurgulamakta ve bu bulguların doğrulanması için kapsamlı çalışmalara ihtiyaç olduğunu vurgulamaktadır.

Anahtar kelimeler: CA-15.3, Tümör Belirteci, Meme Kanseri, İzleme, Kullanım Modelleri, Test İstemleri, Kanser Teşhisi

ABSTRACT

Aim: The objective of this study was to analyze the utilization of the CA-15.3 test for breast cancer monitoring and treatment and evaluate its patterns across different populations.

Materials and Method: Data from a five-year period (2017-2021) were collected, including 21.578.044 CA-15.3 tests from 2.981.142 individuals. Descriptive statistics were used to analyze the data, including test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates.

Results: The study revealed an increasing trend in the number of CA-15.3 tests requested from 2017 to 2019, followed by a significant decrease in 2020 and 2021. The test was more frequently requested for women, particularly in the age group of 18-64. The rate of cancer diagnosis in individuals undergoing the CA-15.3 test also showed an upward trend over the years. Istanbul had the highest test request rate, followed by Ankara and Izmir. University hospitals requested the most tests, followed by state hospitals, private hospitals, and training and research hospitals.

Conclusion: The study provides valuable insights into the utilization patterns of the CA-15.3 test in breast cancer management. While the test showed an increasing trend in test requests and cancer diagnosis rates, caution should be exercised in interpreting the results due to potential limitations. Further research is needed to establish a definitive understanding of the relationship between CA-15.3 levels and cancer diagnosis. The findings emphasize the importance of personalized interpretation of test results and the need for comprehensive studies to validate these findings.

Keywords: CA-15.3, Tumor Marker, Breast Cancer, Monitoring, Utilization Patterns, Test Requests, Cancer Diagnosis

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INTRODUCTION

The cancer antigen CA-15.3 is a protein derived from the Mucin-1 (MUC-1) gene. Although it is primarily found in epithelial cells, it has high serum levels in 90% of patients with breast cancer (1).

CA-15.3, also known as Cancer Antigen 15.3, is a tumor marker often utilized in the monitoring and treatment of breast cancer patients. Levels in the blood typically fluctuate in conjunction with disease progression or response to treatment. Elevated CA-15.3 levels are generally observed in patients with advanced breast cancer, although certain other types of cancer or specific diseases and conditions may also elevate this level (2).

However, it is important to underscore that the CA-15.3 level does not always accurately reflect the presence or treatment response of cancer, and hence, should be used in combination with other diagnostic and monitoring tools. Nonetheless, given its widespread use and its potential to provide valuable insights into disease status, the evaluation of CA-15.3 serum levels in breast cancer patients remains a topic of ongoing research and discussion (3).

Breast cancer is the neoplasm with the highest incidence and mortality in women. As a result, several tumor markers (CA-15.3, Carcinoembryonic Antigen (CEA), serum human epidermal growth factor receptor 2 (HER2), tissue polypeptide antigen (TPA), tissue-specific antigen (TPS)) have been studied, among which CA-15.3 is the most valuable (4).

In a retrospective study involving 2.062 untreated primary breast cancer patients, the sensitivity of CEA was 12,7%, and that of cancer antigen 125 (CA-125) was 19,6%. However, when considered together, the rate increased to 28% (5).

Despite this, clinical guidelines do not recommend the use of these tumor markers for breast cancer screening due to their low sensitivity (6). When evaluated in relation to disease spread, they are mentioned as potentially useful for staging; The European Group on Tumor Markers (EGTM) supports the use of both tumor markers for detecting subclinical metastases, prognosis, and staging in patients diagnosed with local breast cancer (7).

The study of serum CA-15.3 levels is crucial as it offers a non-invasive approach to monitoring disease progression and response to treatment. Yet, its efficacy and specificity have been a subject of debate. While some studies suggest a high correlation between CA-15.3 levels and disease status, others show considerable variability. Hence, understanding the role and reliability of CA-15.3 in breast cancer management is essential, which will also be the focus of our study.

MATERIALS AND METHOD

Data from a five-year period (2017-2021) were analyzed, including a total of 21.578.044 tests from 2.981.142 individuals (Table 1). The test counts, test rates per population, and rates of exceeding the reference range were assessed based on gender, age groups, geographic regions, and healthcare institution types.

The CA-15.3 test results were obtained through the immunoassay method and extracted from the data transferred to the National Health Database System of the Turkish Ministry of Health. The healthcare database service in Türkiye is referred to as e-nabiz. 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 healthcare institutions in Türkiye, including their demographic characteristics, laboratory data, medication usage, and comorbidities.

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.

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 healthcare institution types.

Study Population:

The study population consisted of individuals who underwent CA-15.3 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 healthcare institution types.

Ethical Considerations

The study adhered to ethical guidelines and protected the privacy and confidentiality of the individuals included in the data. Institutional review board approval was obtained, and all data were anonymized to ensure privacy. . 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 2017 and 2021, the CA-15.3 test was requested from 2.981.142 people, with a total of 21.579.044 tests conducted. The average number of tests per person is 7,26. while the number of tests per 100.000 population is 26.112 Among all the tumor **markers used in our CA-15.3 study, it ranks 4th in terms of the number of tests per 100.000 population (Table 1).**

Table 1. Total Consumption of Tumor Markers Between 2017-21 and Number of Tests and the Ratio of the Population by Years.

	2017		2018		2019		2020		2021	
	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
CA 15.3	4.158.853	5.146	4.726.395	5.764	5.161.865	6.208	3.646.912	4.362	3.885.019	4.646

Number of Tests	Number of Applications	Number of People	Number of Tests Per Person	Number of Tests Per 100.000 Population
21.579.044	4.077.373	2.981.142	7,24	26.112

Just like in the general population, the number and rate of tests requested for women increased as the years progressed from 2017 to 2019, but there was a significant decrease in 2020 and 2021. In all years, it ranked third among the tumor markers examined in women (Table 2).

Table 2. Number of Test Requests in Women and Men by Years.

	2017		2018		2019		2020		2021	
CA 15.3	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
Women	3.288.303	8.165	3.759.147	9.199	4.125.907	9.958	2.911.983	6.983	3.092.124	7.415
Men	870.55	2.148	967,248	2.351	1.035,951	2.483	734,929	1.753	792,895	1.892

The number of tests requested for men also increased with the progression of the year from 2017 to 2019, just like in the general population, but decreased significantly in 2020 and 2021 (Table2). When the number of tests for women/men is proportioned by year, the ratio is 3,77 in 2017, 3,88 in 2018, 3,98 in 2019, 3,96 in 2020, and 3,89 in 2021.

When the numbers of tests requested by age groups are compared by year, CA-15.3 was requested most often in the 18-64 age range, second most frequently in those over 65, and least frequently in the 0-17 age range. The ratio of the number of tests requested for the 18-64 age group to the over 65s is 3,00 in 2017, 2,97 in 2018, 2,85 in 2019, 2,92 in 2020, and 2,84 in 2021. The test consumption rate per 100.000 individuals between the 18-64 age group and those over 65 is 1/2,46 in 2017, 1/2,43 in 2018, 1/2,44 in 2019, 1/2,27 in 2020, and 1/2,45 in 2021. The number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all age groups, but showed a significant decrease in 2020-2021 (Table 3).

Table 3. Number of Test Requests by Years and Test Consumption Per 100.000 Persons by Years and Age Groups.

CA 15.3	2017			2018			2019			2020			2021		
Number of Test Requests	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	45.941	3.085.073	1.027.839	48.402	3.499.817	1.178.173	49.458	3.786.453	1.325.954	27.751	2.697.698	921.458	26.609	2.816.845	1.041.565
Test Consumption Per 100.000 Persons	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	201	6.045	14.906	211	6.744	16.395	216	7.181	17.561	122	5.099	11.585	117	5.324	13.096

When the rates of receiving a cancer diagnosis at any time in patients for whom the CA-15.3 tumor marker was requested are compared, the cancer detection rate increased as the years progressed from 2017 to 2020, with 32% of individuals diagnosed with cancer in 2017, 43% in 2020, and 38% in 2021 (Table 4).

Table 4. Percentage Distribution of Who Required Tumor Markers were Diagnosed with Cancer at Any Time.

	2017		2018		2019		2020		2021	
CA 15.3	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Diagnosis of Cancer	Diagnosis of Cancer	No Dıagnosıs Of Cancer	Dıagnosıs Of Cancer
	68%	32%	66%	34%	64%	36%	57%	43%	62%	38%

Among the individuals for whom tumor markers were requested, CA-15.3 ranks third in terms of diagnosis percentage in all years.

When the times of test requests of individuals for whom tumor markers were requested are analyzed at the time of diagnosis, it was found that the tests were requested most frequently before the diagnosis in all years, second most frequently at the same time as the diagnosis, and least frequently after the diagnosis. The rate of test requests before the diagnosis increased as the years progressed until 2020, with a rate of 13,88% in 2017, 33,98% in 2020, and 31,41% in 2021. When the test request rates according to diagnosis times are compared with each other (before diagnosis/at the same time as diagnosis/after diagnosis), it was found that there was no significant difference between the years 2017-2021.

When the utilization rates of CA-15.3 by provinces are compared, it was found that it was requested the most in Istanbul in all years, followed by Ankara, and then Izmir. The number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all provinces, but showed a significant decrease in 2020-2021. When the numbers of tests requested by years are compared by provinces, the rate of tests requested in 2017 was 2,47%, while the rate in 2021 was 1,87%. The percentage of the total number of tests requested from 2017 to 2021 was found to be 9,13% in Istanbul, 4,53% in Ankara, and 2,76% in Izmir. These three cities constitute 16,42% of the total requests.

The CA-15.3 test was most frequently requested from university hospitals, followed by state hospitals, private hospitals, and finally training and research hospitals. In all years, the number of tests requested and the test consumption per 100.000 people increased as the years progressed from 2017 to 2019 in all hospitals, but showed a significant decrease in 2020-2021.

When the regions were analyzed based on the number of tests per 100.000 population, the highest demand was in the Eastern Anatolia region in 2017, in the Marmara region in 2018, and in the Central Anatolia region between 2019-2021. The lowest region is the Southeast Anatolia region. In 2021, when the Central Anatolia region, which has the highest test ratio, was compared with the Marmara region in the second rank, the ratio was 1,10, and when compared with the Southeast Anatolia region, which is the lowest, the ratio was 4,31.

When compared based on the number of tests per person, the highest distribution belongs to the Eastern Anatolia region in all years. The second rank belongs to the Central Anatolia region in 2019, and the Aegean region in other years. The region with the lowest distribution is the Southeast Anatolia region. In 2021, when the Eastern Anatolia region, which has the highest distribution, is compared with the Southeast Anatolia region, which has the lowest distribution, the result is 1,16 (Table 6).

Year	Related Cancer Diagnosis		Non-related Cancer Diagnosis		Total Number of People Tested
2017	154.290	19,36%	203.602	25,54%	797.085
2018	175.084	19,49%	246.877	27,49%	898.101
2019	192.828	20,14%	273.485	28,56%	957.420
2020	184.974	27,13%	251.682	36,91%	681.849
2021	190.387	25,63%	252.089	33,93%	742.918

2017		2018		2019		2020		2021	
EASTERN ANATOLIA REGION	6.588	MARMARA REGION	6.927	CENTRAL ANATOLIA REGION	7.550	CENTRAL ANATOLIA REGION	5.467	CENTRAL ANATOLIA REGION	6.089
MARMARA REGION	6.315	CENTRAL ANATOLIA REGION	6.509	MARMARA REGION	7.423	MARMARA REGION	5.230	MARMARA REGION	5.517
AEGEAN REGION	5.746	EASTERN ANATOLIA REGION	6.439	AEGEAN REGION	6.661	AEGEAN REGION	5.016	AEGEAN REGION	5.295
CENTRAL ANATOLIA REGION	5.390	AEGEAN REGION	6.126	EASTERN ANATOLIA REGION	6.381	EASTERN ANATOLIA REGION	3.999	EASTERN ANATOLIA REGION	4.326
BLACK SEA REGION	4.746	BLACK SEA REGION	5.386	BLACK SEA REGION	5.454	BLACK SEA REGION	3.716	BLACK SEA REGION	4.068
MEDITERRANEAN REGION	3.493	MEDITERRANEAN REGION	4.464	MEDITERRANEAN REGION	4.957	MEDITERRANEAN REGION	3.430	MEDITERRANEAN REGION	3.478
SOUTHEAST ANATOLIA REGION	2.053	SOUTHEAST ANATOLIA REGION	2.350	SOUTHEAST ANATOLIA REGION	2.243	SOUTHEAST ANATOLIA REGION	1.426	SOUTHEAST ANATOLIA REGION	1.412

When cities are analyzed based on the number of test requests, Istanbul is the city where the most tests are requested in all years, and the second city is Ankara. Izmir and Bursa are in the third and fourth places. When the number of tests per 100.000 population is examined, Sinop is in 2017, Erzurum in 2018 and 2020, Kırşehir in 2019, and Isparta in 2021. The top 3 cities with the highest test request rate, Istanbul, Ankara, and Izmir, are not among the top 7 cities with the number of tests per 100.000 population.

When clinics are compared based on the number of test requests, the clinic that requests the most tests is the Obstetrics and Gynecology clinic between 2017-2019, and the Medical Oncology clinic in 2020-2021. The second place belongs to the Internal Diseases clinic between 2017-2019, and the Obstetrics and Gynecology clinic in 2020 and 2021. Medical oncology is in the 3rd place between 2017-2019, and it is in the first ranks in 2020-2021. Family medicine is in the 7th place in 2017 and 2018, 6th place in 2019, and 7th place in 2020 and 2021; The Emergency Medicine clinic is in the 8th place between 2017-2020, and it is in the 9th place in 2021 (Table 7).

2017		2018		2019		2020		2021	
GYNECOLOGY AND OBSTETRICS	916.840	GYNECOLOGY AND OBSTETRICS	1.036.325	GYNECOLOGY AND OBSTETRICS	1.093.072	MEDICAL ONCOLOGY	924.438	MEDICAL ONCOLOGY	873.601
INTERNAL MEDICINE	876.543	INTERNAL MEDICINE	946.663	INTERNAL MEDICINE	993.719	GYNECOLOGY AND OBSTETRICS	715.967	GYNECOLOGY AND OBSTETRICS	750.126
MEDICAL ONCOLOGY	633.224	MEDICAL ONCOLOGY	799.195	MEDICAL ONCOLOGY	946.918	INTERNAL MEDICINE	593.676	INTERNAL MEDICINE	721.656
GENERAL SURGERY	543.217	GENERAL SURGERY	585.203	GENERAL SURGERY	576.742	GENERAL SURGERY	375.894	GENERAL SURGERY	394.454
RADIATION ONCOLOGY	169.682	RADIATION ONCOLOGY	196.353	RADIATION ONCOLOGY	200.664	GASTROENTEROLOGY	128.543	GASTROENTEROLOGY	145.908
GASTROENTEROLOGY	144.894	GASTROENTEROLOGY	172.382	FAMILY MEDICINE	187.641	RADIATION ONCOLOGY	120.578	RADIATION ONCOLOGY	116.435
FAMILY MEDICINE	122.378	FAMILY MEDICINE	162.032	GASTROENTEROLOGY	167.706	FAMILY MEDICINE	100.988	FAMILY MEDICINE	111.427
EMERGENCY MEDICINE	76.121	EMERGENCY MEDICINE	83.753	EMERGENCY MEDICINE	113.161	EMERGENCY MEDICINE	82.965	GYNECOLOGICAL ONCOLOGY SURGERY	84.514
NEUROLOGY	57.089	NEUROLOGY	65.882	GYNECOLOGICAL ONCOLOGY SURGERY	86.165	GYNECOLOGICAL ONCOLOGY SURGERY	67.442	EMERGENCY MEDICINE	84.334
CHEST DISEASES	55.133	UROLOGY	58.391	NEUROLOGY	76.157	NEUROLOGY	53.807	NEUROLOGY	64.785

When the diagnoses entered in the application where the CA-15.3 test request was made were examined, the breast malignant neoplasm diagnosis was the most frequently entered diagnosis in 2017-2018 and the second most frequently entered diagnosis in 2019 and 2021. The breast malignant neoplasm, undefined diagnosis is the most entered diagnosis in 2020, the 3rd place in 2017, and the 2nd place in 2018-2021. In 2019 and 2021, the most common diagnosis of vitamin D deficiency, undefined, was entered. In total for five years, the most common diagnosis is vitamin D deficiency, undefined; second frequently is breast malignant neoplasm, undefined; and the third place is breast malignant neoplasm. When the rates of exceeding the reference range of the test are compared by years, the highest rate is in 2021 with a rate of 9,74%, the lowest rate is in 2019 with 7,62%. When the rates of exceeding the reference range of the test are compared by institution levels, the highest rate is 9,92% in third-level institutions, followed by 7,32% in second-level institutions, and 3,73% in first-level institutions.

When the rates of exceeding the reference range by institution types are examined, the total rate is 8,76%, with the highest rate of 11,78% in university hospitals, followed by 10,00% in

private health institutions, and 8,11% in public hospitals.

When the rates of exceeding the reference range by geographical regions are examined, the highest rate is 10,9% in the Aegean region, which has the most frequent test requests in the 3rd region and has the highest number of test requests per 100.000 people in all years except 2018 (it is the Eastern Anatolia region in 2018). The Black Sea region is in the second place with a rate of 9,8%, followed by the Mediterranean region with a rate of 9,5%. The lowest rate belongs to the Southeastern Anatolia region, which has the lowest number of test requests and the lowest number of test requests per 100.000 people, with a rate of 5,0%.

When the rates of exceeding the reference range by gender are examined, the overall positive rate is 8,73%, with 9,67% in men and 8,55% in women.

When the rates of exceeding the reference range by age groups are examined, the highest rate is in those over 65 with 12,95%, followed by the 18-64 age group with a rate of 7,40%, and the 0-17 age group with a rate of 1,22%. When the age groups are ratioed, the positivity rates are 10,6/6,06/1.

When the rates of exceeding the reference range by admission status are examined, it is most frequently requested from outpatient patients with a rate of 12,10%, followed by inpatients with a rate of 11,35%, and outpatients with a rate of 8,22%. When ratioed in order, the ratio is calculated as 1,47/1,38/1. Among the tumor markers examined in the study, all markers exceeded the reference range at a higher rate in inpatients, while CA-15.3 is higher in outpatient patients.

When the rates of exceeding the reference range by cancer diagnosis status are examined, a total of 8,77% of people tested positive, and of those who tested positive, 15,98% have a cancer diagnosis, while 4,17% do not have a cancer diagnosis.

When the rates of tests that exceed the reference range from the clinics requesting the CA-15.3 test are examined; the highest rate is in the Medical Oncology clinic with 19,59%, followed by the Gastroenterology clinic with 9,21%, and the Gynecological Oncology Surgery with 9,20%. In the Obstetrics and Gynecology clinic, which had the highest number of test requests between 2017-2019, the rate is 3,47%, in the Medical Oncology clinic, which had the highest number between 2020-2021, the rate is 19,59 (first place), and in Internal Diseases, which was in the second place between 2017-2019, the rate is 7,14%. The rate in Family Medicine is 4,70%.

When the distribution of test costs by years is examined, the sut cost in 2017 is 33.270.824 TL, the unit cost is 16.392.207 TL, and in 2021 the sut cost is 31.080.152 TL, the unit cost is 15.312.884 TL.

DISCUSSION

This study presents a detailed analysis of the use of the CA-15.3 test between 2017 and 2021. A total of 21.579.044 tests were applied to 2.981.142 individuals, which translates to 26.112 tests per 100.000 individuals. Increasing numbers and rates of tests over the years have shown that this test has risen to 4th place among tumor markers. When viewed by gender, a similar trend has been observed in both women and men: the numbers and rates of tests increased from 2017 to 2019, but a significant decline was seen in 2020 and 2021. In women, the CA-15.3 test has ranked third among all tumor markers examined each year.

When examining the use of the test by age groups, it is found that the CA-15.3 test was most frequently requested from individuals aged 18-64. This age group is followed by individuals over 65 years and leastly by the 0-17 age range. These findings demonstrate the impact of the test on the general population, as well as individuals with specific demographic characteristics.

Breast cancer is the most common and deadly type of cancer among women worldwide and in Türkiye. According to World Health Organization data from 2018, the incidence of breast cancer worldwide in 2018 was 2.000.088. In Türkiye, the incidence is 50/100.000 and the 2018 incidence was 22.500 (8).

In our study, when the rate of receiving a cancer diagnosis at any time was compared in patients for whom the CA-15.3 tumor marker was requested, the cancer detection rate increased as the years progressed from 2017 to 2020. In 2017, 32% of individuals received a cancer diagnosis, 43% in 2020, and 38% in 2021. When the rates of cancer detection were compared in individuals for whom tumor markers were requested, CA-15.3 ranked third in diagnosis percentage every year.

Approximately 1% of breast cancer occurs in men (9). In our study, when the female/male test number ratio was compared over the years, the ratio was 3,77 in 2017, 3,88 in 2018, 3,98 in 2019, 3,96 in 2020, and 3,89 in 2021. In all years, it ranks third among tumor markers tested in women. Additionally, when rates of exceeding the reference range were examined by gender, overall 8,73% were positive, with 9,67% in men and 8,55% in women being positive.

Several studies have shown that high levels of CEA in primary breast cancer lead to a poor prognosis, and similarly, the presence of high CA 15.3 levels at the time of diagnosis is associated with a higher stage of breast cancer, tumor size, lymph node involvement, and lower survival (10,11).

In our study, when the timing of test requests for individuals who had tumor markers requested was analyzed at the time of diagnosis, requests were most frequent prior to diagnosis in all years, second most frequent at the same time as diagnosis, and least frequent after diagnosis. A study conducted by Hou and colleagues showed that it had a sensitivity of 7% in early disease. The same study also evaluated the sensitivity of CA 15.3 in metastatic breast cancer as 82,8% (12).

In our study, in 2017, 19,36% of individuals who had the CA-15.3 test received a diagnosis of a cancer associated with CA-15.3, while 25,54% received a diagnosis of a cancer not associated with CA-15.3. This rate increased until 2020, when 27,13% of patients were diagnosed with a cancer associated with CA-15.3 and 36,91% were diagnosed with a cancer not associated with CA-15.3. In 2021, these rates were 25,63% and 33,93%, respectively.

When the rates of tests exceeding the reference range were examined by the status of receiving a cancer diagnosis, in total 8,77% of tests were positive, with 15,98% of positive tests belonging to individuals with a cancer diagnosis and 4,17% to individuals without a cancer diagnosis.

In a study conducted by Tampellini and colleagues on 526 patients diagnosed with metastatic breast cancer, the time until progression was evaluated in relation to CA-15.3 levels. The time was 15,3 months in patients with normal CA-15.3 levels, 11,7 months in patients whose levels initially rose then fell by 25%, 9,6 months in patients with high levels, and 8,6 months in patients whose levels increased (13).

Breast cancer is more common in the western regions of Türkiye (40-50/100.000) compared to the eastern regions (20/100.000). It is thought that the reasons for this are a higher rate of hormone therapy use, shorter lactation period, dietary habits, and the adoption of a western lifestyle in our western regions (14).

In our study, when regions were analyzed based on the number of tests per 100.000 people, the highest number of requests was in the Eastern Anatolia region in 2017, in the Marmara region in 2018, and in the Central Anatolia region between 2019-2021. The region with the lowest number is Southeastern Anatolia. When compared based on the number of tests per person, the highest distribution in all years belongs to the Eastern Anatolia region.

In the USA, 5,6% of patients diagnosed with invasive breast cancer between 2000-2014 were under the age of 40 (15).

When comparing the rates of cancer diagnosis in patients who had the CA-15.3 tumor marker requested, the cancer detection rate increased from 2017 to 2020. Among individuals who had tumor markers requested, the CA-15.3 ranked third each year in terms of diagnosis percentage.

Considering the CA-15.3 test requests and rates of exceeding the reference range according to years, geography, type of institution, clinic, and patient condition, it is clear that further analysis is required to understand how these factors affect the use and results of the test. In particular, the rates of test results exceeding the reference range have varied significantly. These findings contribute to a broader understanding of how an individual's demographic characteristics and health status can affect test results. In light of these results, it underscores the importance of an individualized approach in interpreting test results.

In our study, when test request numbers were compared by age groups over the years, CA-15.3 was most frequently requested in the 18-64 age range, second most in individuals over 65 years, and least frequently in the 0-17 age range.

When rates of exceeding the reference range were examined based on the admission status, the rates were highest in outpatients, second highest in inpatients, and lowest in walk-in patients.

This study may have several potential limitations. First, the accuracy and consistency in collecting and recording data of patients undergoing CA-15.3 tumor marker tests could directly influence the outcomes, with any errors in data collection and analysis possibly skewing results. Second, the study's retrospective design, which uses existing data, is prone to biases and various errors, which could lead to misrepresented findings. Third, the lack of a control group can make interpreting the results difficult, as control groups provide an objective benchmark for comparison in studies and experiments. Fourth, the study design might overlook the influence of certain confounding factors, such as the patients' genetic history, lifestyle factors, or the presence of other diseases, which could affect the outcomes. Lastly, the study's statistical power, which determines whether the results are statistically significant, can be misleading if it's low. In summary, all these potential limitations need to be carefully considered when interpreting the study's findings.This study may have several potential limitations. First, the accuracy and consistency in collecting and recording data of patients undergoing CA-15.3 tumor marker tests could directly influence the outcomes, with any errors in data collection and analysis possibly skewing results. Second, the study's retrospective design, which uses existing data, is prone to biases and various errors, which could lead to misrepresented findings. Third, the lack of a control group can make interpreting the results difficult, as control groups provide an objective benchmark for comparison in studies and experiments. Fourth, the study design might overlook the influence of certain confounding factors, such as the patients' genetic history, lifestyle factors, or the presence of other diseases, which could affect the outcomes. Lastly, the study's statistical power, which determines whether the results are statistically significant, can be misleading if it's low. In summary, all these potential limitations need to be carefully considered when interpreting the study's findings.

CONCLUSION

In conclusion, our study suggests that the incidence of cancer diagnosis and the levels of CA-15.3 tumor marker are closely related and have shown a general increase over the years. However, these results should be interpreted with caution due to potential limitations in the study design. More comprehensive and robust studies are necessary to establish a definitive understanding of the relationship between CA-15.3 levels and cancer diagnosis and to further validate these findings.

REFERENCES

1. Duffy MJ, Shering S, Sherry F, McDermott E, O'Higgins N. CA 15-3: a prognostic marker in breast cancer. Int J Biol Markers 2000;15(4):330–33.

2. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25(33):5287-312

3. Ebeling FG, Stieber P, Untch M, Nagel D, Konecny GE, Schmitt UM. Serum CEA and CA 15-3 as prognostic fac-

tors in primary breast cancer. Br J Cancer 2002;86(8):1217-22

4. Duffy MJ, McDermott EW, Crown J. Blood-based biomarkers in breast cancer: from proteins to circulating tumor cells to circulating tumor DNA. Tumor Biol 2018;40:101042831877616.

5. Molina R, Auge JM, Farrus B, Zanón G, Pahisa J, Muñoz M, et al. Prospective evaluation of carcinoembryonic antigen (CEA) and carbohydrate antigen 15.3 (CA 15.3) in patients with primary locoregional breast cancer. Clin Chem 2010;56:1148–57.

6. Ayala de la Peña F, Ortiz-Muñoz B, Quintanar-Verdúguez T, Santotoribio JD, de la Cruz S, Trapé-Pujol J, et al. Consensus of the Spanish society of laboratory medicine and the Spanish society of medical oncology on the methodology and criteria for evaluation of circulating tumour markers in breast cancer. Clin Transl Oncol 2021;23:1272–80

7. Molina R, Barak V, van Dalen A, Duffy MJ, Einarsson R, Gion M, et al. Tumor markers in breast cancer. European group on tumor markers recommendations. Tumor Biol 2005;26:281–93.

8. Bray F, Ferlay J, Soerjomataram I, Rebecca I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424

9. Sun HF, Zhao Y, Gao SP, Li LD, Fu WY, Jiang HL, et al. Clinicopathological characteristics and survival outcomes of male breast cancer according to race: A SEER population-based study. Oncotarget 2017;8(41):69680-90.

10. Molina R, Jo J, Filella X, Zanon G, Pahisa J, Muñoz M, et al. c-erbB-2 oncoprotein, CEA, and CA 15.3 in patients with breast cancer: prognostic value. Breast Cancer Res Treat 1998;51:109-19

11. Uehara M, Kinoshita T, Hojo T, Akashi-Tanaka S, Iwamoto E, Fukutomi T. Long-term prognostic study of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in breast cancer. Int J Clin Oncol 2008;13:447-51

12. Hou MF, Chen YL, Tseng TF, Lin CM , Chen MS ,Huang CJ, et al. Evaluation of serum CA27.29, CA15-3 and CEA in patients with breast cancer. Kaohsiung J Med Sci 1999;15:520-28

13. Tampellini M, Berruti A, Gerbino A, Buniva T, Torta M, Gorzegno G, et al. Relationship between CA 15-3 serum levels and disease extent in predicting overall survival of breast cancer patients with newly diagnosed metastatic disease. Br J Cancer 1997;75(5):698-702.

14. Özmen V. Dünya'da ve Türkiye'de Meme Kanseri. 20. Ulusal Kanser Kongresi; 19-23 Nisan 2013; Antalya.

15. Surveillance, Epidemiology, and End Results Program (www.seer.cancer.gov). SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (2000–2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969–2013 Counties. released April 2015, based on the November 2014 submission.