REVIEW

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Inappropriate Use of Tumor Markers in Asymptomatic Patients: A Systematic Review and Proposed Follow-Up Algorithm

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Abstract

Background: Serum tumor markers such as CA 125, CA 19-9, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and CA 15-3 are widely available, inexpensive, and easily measured, which has led to their inappropriate use for cancer screening in asymptomatic individuals. Despite guideline recommendations against this practice, these tests remain common, contributing to false positives, unnecessary anxiety, and avoidable invasive procedures. **Methods:** We conducted a systematic review of PubMed, Cochrane Library, and LILACS from inception to May 10, 2025, identifying studies evaluating the use of the aforementioned tumor markers in asymptomatic populations. Eligible studies reported diagnostic accuracy or clinical outcomes. Two reviewers independently screened, extracted data, and assessed risk of bias using study design–specific tools (ROBINS-I, Newcastle–Ottawa, QUADAS-2, RoB-2). The GRADE assessment was used for certainty of evidence. **Results:** Of 1,179 records, 38 studies were included (10 retrospective, 18 prospective, 3 cross-sectional, 3 RCTs, others). CA 125 was the most frequently assessed marker, followed by CA 19-9, CEA, CA 15-3, and AFP. Across studies, sensitivity and specificity varied, but positive predictive value (PPV) was consistently low in general asymptomatic populations. False-positive results frequently led to imaging, invasive procedures, and surgery, with complication rates up to 15%. No mortality benefit was demonstrated in large RCTs. Certain subgroups (e.g., new-onset diabetes with elevated CA 19-9) showed improved PPVs, but evidence was insufficient to support population screening. **Conclusion:** Routine use of serum tumor markers for cancer screening in asymptomatic individuals is unsupported by evidence and may cause harm. We propose a structured follow-up framework to guide the evaluation of incidentally elevated tumor markers, aiming to reduce unnecessary interventions and optimize resource use.

Keywords: Cancer screening- Overtesting- Screening harms- Serologic biomarkers

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Introduction

Serum tumoral markers are molecules that are released into the bloodstream in large quantities when a malignancy is present. Common examples include Carcinoembryogenic antigen (CEA), CA-125, CA19-9 and Alpha fetoprotein (AFP). Their ease of measurement, wide availability and low cost make these substances attractive to monitor cancer in a non-invasive way. In cancer screening, the ideal tumoral marker must be produced in an organ-specific manner, allow for an early and accurate diagnosis, avoid unnecessary distress to patients and limit overtreatment [1, 2]. Unfortunately, the most common tumoral markers in practice do not fulfill these criteria for several reasons. These markers are also produced by normal cells in response to benign conditions, lacking specificity. In addition, most tumoral markers lack sensitivity for early disease detection, thus not being ideal for cancer screening. Moreover, the majority of tumoral markers are only present in about 70-80% of the patients with a particular type of cancer even in the setting of advanced disease [1, 3, 4]. These factors highlight the disadvantages associated with the use of commonly used tumor markers in cancer screening.

In fact, a number of studies have demonstrated a lack of clinical benefit associated with the use of tumoral markers for screening average-risk, asymptomatic populations [5, 6]. Therefore, major clinical guidelines recommend against the use of serum biomarkers for cancer screening, citing lack of mortality improvement, absence

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of cost-benefit associations and the possibility of harmful consequences following false-positive results [7–9]. Nevertheless, tumoral markers continue to be ordered for asymptomatic patients in routine health checkups over the world.

In spite of clear recommendations to avoid this practice, it is frequent for oncologists and internists to see asymptomatic patients with inappropriately ordered elevated serum tumor markers. Unfortunately, there is a lack of evidence on how to conduct a cost-effective work up once such a patient seeks medical care. Therefore, to date, there is no guideline-directed recommendations to orientate physicians in this clinical situation.

In this context, we aim to assess the literature regarding the broader and inappropriate use of tumor markers as screening tools in asymptomatic patients through a systematic review. We will focus on the diagnostic performance of these markers–particularly their sensitivity, specificity and positive predictive value- as well as the clinical implications of their use, including unnecessary follow-up procedures and potential harms. Following this, we present a clinical algorithm for the work up and follow-up of asymptomatic patients with elevated tumoral marker levels in the least invasive and cost-effective manner.

Materials and Methods

A search for eligible articles published up to May 10 2025 was carried out in three databases: PubMed, Cochrane library and LILACS. The employed search strategy is as follows: ("CEA" OR "carcinoembryogenic" OR "AFP" OR "alpha fetoprotein" OR "alpha-fetoprotein" OR "CA 15-3" OR "CA 19-9" OR "CA 125" OR "CA-125") AND ("asymptomatic" OR "healthy" OR "no symptoms") AND ("cancer" OR "carcinoma" OR "tumor" OR "malignancy") AND ("screen" OR "screening" OR "early screening" OR "early detection"). The search in each database was imported into Rayyan software [10], where a deduplication was done. After this process, two independent blinded investigators screened for eligible articles. Any discrepancies were resolved by a third investigator.

PICO strategy

The adopted PICO strategy had the following components: I) Population: asymptomatic population; II) Intervention/exposure: screening for cancer with tumor biomarkers; III) Not applicable for some studies, but when applicable: no screening with tumor biomarkers; IV) Outcomes: diagnostic performance and clinical outcomes.

Selection criteria

The inclusion criteria are as follows: I) studies involving asymptomatic individuals with no underlying medical conditions screened for cancer with one or more of the commonly used tumor biomarkers (without an indication for screening): CEA, AFP, CA 15-3, CA 125, CA 19-9; II) studies assessing the diagnostic accuracy of those biomarkers; III) publications with original patient data; IV) studies from any country written in English language.

Exclusion criteria are as follows

I) studies with biomarker measurement in patients with cancer diagnosis or underlying health conditions associated with higher risk for cancer

II) studies without original patient data

III) case reports, reviews, non-human studies or review articles

Data extraction

Two independent reviewers extracted information on the following variables: last name of the first author, country, year of publication, years of enrollment, years of implementation, follow-up duration, population, assessed biomarker(s), endpoints, sensitivity, specificity, PPV, key findings. The collected information was entered into Microsoft Excel (2019), with any discrepancies resolved by a third independent reviewer.

Risk of bias assessment

The risk of bias was assessed with the use of tools which varied according to each study's design. The ROBINS-1 tool was used for observational studies; the Newcastle-Ottawa scale was used for case-control studies; the QUADAS-2 tool was used for cross-sectional studies and RoB-2 tool was used for RCTs and their secondary analyses [11–13]. Two independent investigators assigned an evaluation according to the tool in question. If any discrepancies were present, a third investigator resolved the conflict.

Certainty of Evidence (GRADE) Assessment

The Certainty of Evidence for each was assessed by two investigators. Discrepancies were resolved by a third investigator

Results

Study selection

The search in the three databases yielded a total of 1179 articles. After the deduplication process, 22 articles were eliminated and the remaining 1157 articles were screened based on titles and abstracts. This process resulted in the selection of 35 articles for inclusion. Three additional articles were not present in the generated list and were deemed to be eligible. Therefore, the total number of included studies was 38 [5, 6, 14–49]. The selection process is depicted in Figure 1.

Study characteristics, diagnostic performance and clinical outcomes

The included studies were published between 1990 and 2024, spanning a variety of World's regions. Most of the studies are observational in nature, with 10 retrospective [14, 15, 20, 22, 32, 35, 37, 40, 41, 49] and 18 prospective articles [16, 17, 19, 21, 23–25, 30, 33, 34, 36, 38, 39, 42, 44, 45, 47, 48]. Moreover, three of the included studies are cross-sectional analyses [18, 29, 43], three are randomized controlled trials (RCT) [5, 6, 26], two are secondary analyses of RCT [27, 28], one is a single-arm screening

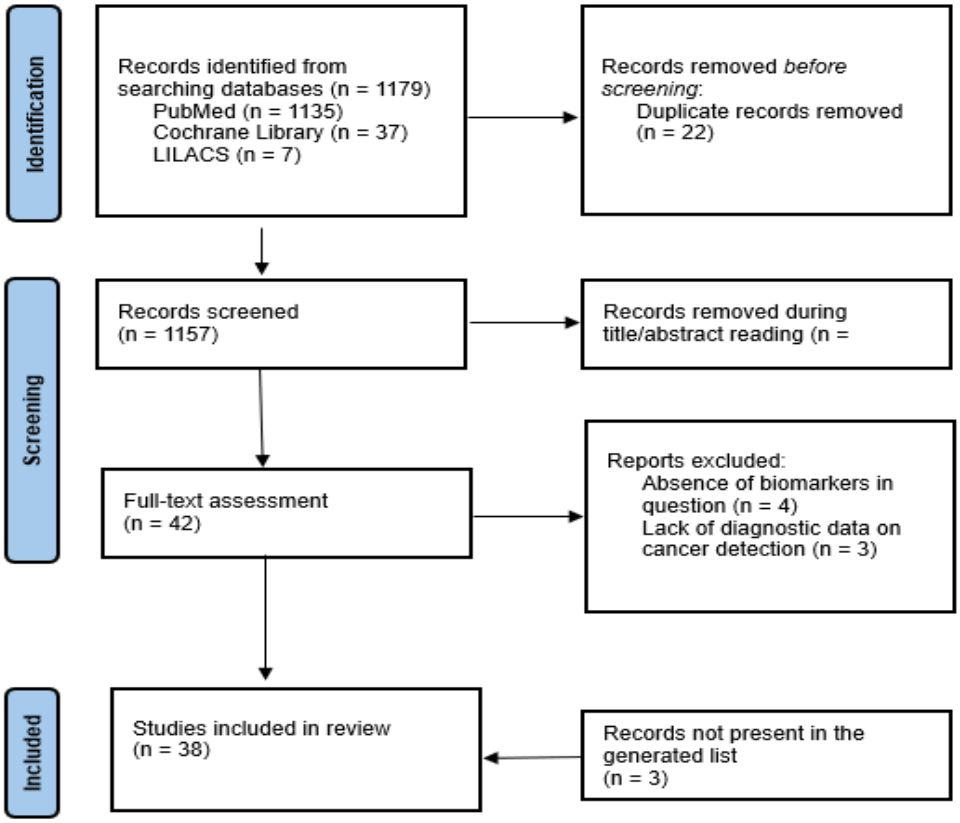

Figure 1. PRISMA Flow Chart Depicting the Selection Process

trial [31]. The most commonly investigated biomarker was CA 125 [5, 6, 14–17, 21–23, 25–28, 30–33, 35, 36, 39, 42–46, 48, 49]. Other biomarkers included CA 19-9 [14, 15, 18–20, 24, 29, 34, 36–38, 41, 47, 49], CEA [24, 29, 36, 49], CA 15-3 [14, 36, 49] and AFP [14, 49]. Some studies utilized a multiplex of four or more biomarkers [14, 36, 49].

Across malignancies and populations, specificity was often moderate-to-high, yet positive predictive values (PPVs) remained consistently low, rarely exceeding 20% in average-risk groups [16–18, 22, 24, 27, 28, 32, 34, 35, 38–41, 49]. Mortality benefit was not demonstrated in the large randomized trials, despite intensive monitoring and multimodal strategies [5, 6, 26]. In many studies, elevated tumor markers were more often associated with benign conditions or biological variability than with malignancy [15, 38, 41, 48]. Some settings yielded comparatively higher PPVs- for example, targeted screening in postmenopausal women with combined biomarker and abnormal ultrasound morphology [5, 21, 26, 35, 44] - but remained unsatisfactory. In fact, among the RCTs, none reported statistically significant differences in cancer detection rates between the arm that included CA 125 measurement and the arm that did not.

High false-positive rates were a consistent finding, leading to additional imaging, invasive procedures, and surgery [5, 6, 16, 20, 26, 28, 35, 38, 44, 49]. In the PLCO trial, almost one-third of false positives underwent surgery, with complication rates reaching 15% [5]. Benign causes for elevated results included ovarian teratomas and hypothyroidism (CA 19-9) [18], in addition to endometriosis and fibroids (CA 125) [15]. In some studies, combining multiple biomarkers improved sensitivity but substantially increased false-positive rates, limiting clinical utility [43, 49].

A minority of studies suggested possible benefit from targeted use of tumor markers in specific subgroups, including high-risk cohorts such as women with BRCA mutations [46], individuals with new-onset diabetes undergoing CA 19-9 based pancreatic cancer screening [20, 37] particularly when hyperbilirubinemia was also present and patients monitored longitudinally using algorithms such as ROCA or personalized thresholds [31], which slightly improved early-stage detection and positive predictive value compared to single-cutoff approaches. While encouraging, these scenarios often lacked mortality endpoints and some were not confirmed in diverse settings.

Note on studies' naming

A study group from China screened asymptomatic populations with tumor markers, publishing two papers, one focused in the detection of benign gynecological condition, while the the other focused in diagnosis of malignancies. These were named Tsao (I) et al. [15] and Tsao (II) et al. [14] respectively. Four study groups from South Korea explored the role of CA 19-9 in asymptomatic individuals, therefore we named these studies Kim (I) et al. [18], Kim (II) et al. [29], Kim (III) et al. [38] and Kim (IV) et al. [41]. Two study groups from China investigated tumor markers as screening tools, with one focusing on CA 19-9 and the other focusing on multiple biomarkers. We named these studies Yang (I) et al. [19] and Yang

Table 1. ROBINS-1 Tool for Risk of Bias Assessment in Observational Studies

Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall
Tsao (II) et al.[24]	Serious	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious
Tsao (I) et al.[35]	Serious	Moderate	Low	Low	Moderate	Low	Serious	Serious
Crump et al. [44]	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Jacobs et al.[45]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Kim (I) et al.[46]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Yang (I) et al.[47]	Serious	Low	Low	Low	Moderate	Moderate	Low	Moderate
Choe (I) et al.[48]	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Adonakis et al.[49]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Sjovall et al.[14]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sekiguchi et al.[16]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Cane et al.[17]	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Wang et al.[43]	Serious	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Urban et al.[22]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Han et al.[23]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Lim et al.[25]	Moderate	Moderate	Low	Serious	Low	Moderate	Moderate	Serious
Menon (I) et al.[26]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Tong et al.[27]	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
Woodward et al.[28]	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
Woolas et al.[29]	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
Choe (II) et al.[30]	Moderate	Low	Low	Low	Low	Low	Low	Low
Kim (III) et al.[31]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Zurawaski et al.[32]	Low	Low	Low	Low	Low	Low	Low	Low
Kim (IV) et al.[34]	Serious	Moderate	Low	Low	Moderate	Low	Low	Serious
Karlan et al.[38]	Serious	Moderate	Low	Low	Serious	Moderate	Moderate	Serious
Lowe et al.[39]	Moderate	Low	Moderate	Low	Serious	Low	Moderate	Serious
Meeuwissen et al.[40]	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious
Vuento et al.[42]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

(II) et al. [43]. One study group from South Korea conducted an investigation regarding the use of CA 19-9 in asymptomatic patients with new-onset diabetes. They published two studies based on this investigation, one evaluating the pancreatic cancer detection rate within the first two years and the other evaluating the same rate over an extended period of time. We named these studies Choe (I) et al. [20] and Choe (II) et al. [37] respectively. One study group from the United Kingdom carried out two investigations of ovarian cancer screening using CA 125 in different periods of time. We named these studies Menon (I) et al. [33] and Menon (II) et al. [6]. Full details on the included studies are shown in Supplementary Table 1.

Risk of bias assessment

Risk of bias was assessed with a variety of tools, according to each study's design. The ROBINS-1 tool was employed to prospective or retrospective observational studies, scrutinizing the following domains: confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes and selection of reported results. The results are displayed in Table 1. The Newcastle-Ottawa scale was adopted for bias assessment in case-control studies, assessing three domains: selection, comparability and exposure. Studies scoring 7 points or more were considered as having a low risk of bias. The results are displayed in Table 2. The QUADAS-2 tool was used for analyses of bias and applicability in cross-sectional studies, examining the following domains: patient selection, index test, reference standard, flow and timing. The results are shown in Table 3. The RoB 2 tool was adopted for RCTs and their secondary analyses, assessing five domains: randomization, deviations

Table 2. Newcastle-Ottawa Scale for Risk of Bias Assessment in Case-Control Studies

Study	Selection	Comparability	Exposure	Score	Risk of bias
Jeyarajah et al. [15]	4	2	3	9	Low risk
Lee et al. [33]	4	2	3	9	Low risk
Thomas et al.[36]	4	2	2	8	Low risk
Fahrmann et al. [41]	4	2	2	8	Low risk

Table 3. QUADAS-2 Tool for Risk of Bias and Applicability Assessments in Cross-Sectional Studies

Study	Domains	Risk of bias	Concerns regarding applicability	Overall risk of bias	Overall concerns regarding applicability
Kim (II) et al. [21]	Patient selection	High	High	High	High
	Index test	High	High		
	Reference standard	Low	Low		
	Flow and timing	Low	Low		
Yang (II) et al. [37]	Patient selection	High	High	High	High
	Index test	High	High		
	Reference standard	Unclear	Low		
	Flow and timing	Low	Low		

Table 4. RoB-2 Tool for Risk of Bias in RCTs and Their Secondary Analyses

Study	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported result	Overall risk
Buys et al. [5]	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Kobayashi et al. [18]	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
Terada et al. [19]	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
Partridge et al. [20]	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
Menon (II) et al. [6]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

from intended interventions, missing outcome data, measurement of outcome and selection of reported results. Overall, risk of bias was frequently moderate to serious, particularly among observational screening cohorts. The most common sources of bias were confounding and participant selection, all of which are especially relevant in screening research. RCTs generally showed lower risk of bias but consistently failed to demonstrate mortality benefit, reinforcing the limited clinical utility of tumor markers for screening in asymptomatic individuals. The results of individual risk of bias assessment can be appreciated in Table 4.

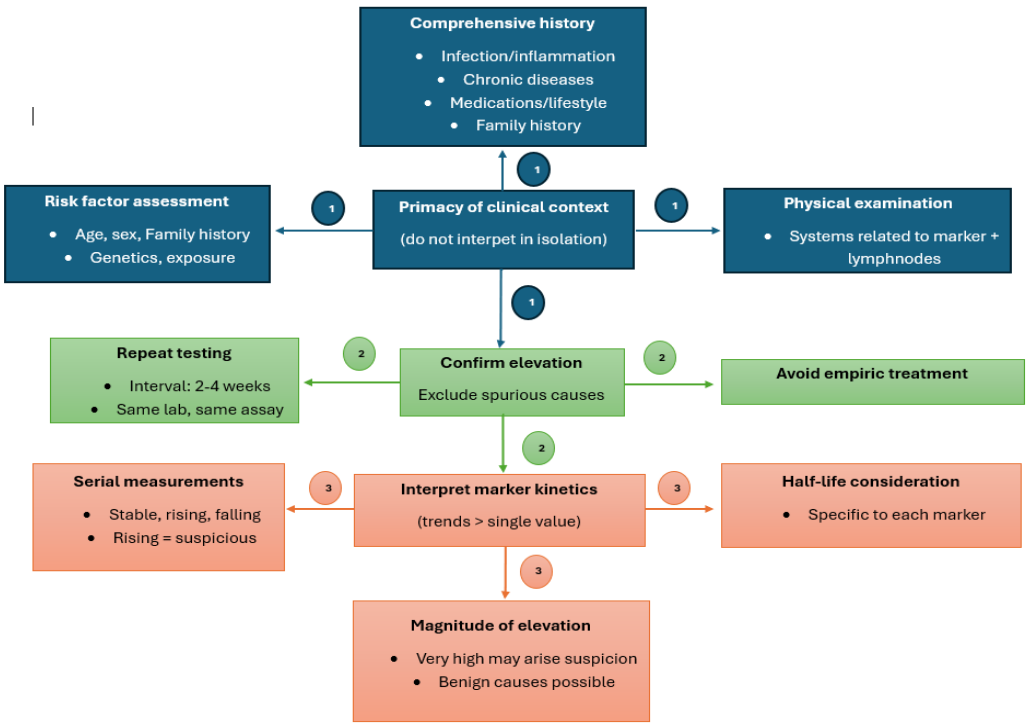

Figure 2. General Initial Approach to Asymptomatic Patient with Elevated Tumor Marker

Table 5. Suggested Frameworks for Biomarkers

Marker	Associations	Context/Use	Half-life	Initial Steps	Proceed When	Considerations for this article	Follow-up
CEA	CRC, lung, breast, gastric, pancreatic, HCC, other GI cancers; non-malignant causes include smoking, IBD, pancreatitis, cirrhosis, COPD, diverticulitis, pneumonia, peritonitis, peptic ulcer, renal failure, hypothyroidism [56]	Regardless of presentation; CRC screening, surveillance post-treatment, prognosis, recurrence detection	~3–5 days (57)	Repeat in 2-4 weeks if elevated; assess symptoms, history (smoking, inflammation), imaging if persistent elevation	If CEA >10 ng/mL or persistent elevation after workup	Strength: strong link with CRC prognosis; Limitation: low sensitivity for early disease, many benign causes	3–6 monthly in first 3 years after treatment, then 6 monthly to 5 years
CA 125	Ovary (serous epithelial), endometrium, peritoneum, pancreas, breast, GI, lymphoma; benign causes include endometriosis, fibroids, menstruation, pregnancy, PID, ascites, pleural effusion, hepatitis, peritonitis, diverticulitis [1]	Not for early detection in asymptomatic; useful in post-treatment surveillance, high-risk screening (BRCA), evaluation of pelvic masses	~5-10 days (58)	Repeat/confirm after resolution of benign causes; ultrasound ± MRI; CA 125 trend	If >35 U/mL persistent; rapid rise; rising trend	2008 USPSTF: no mortality benefit in asymptomatic; false positives common	Every 3 months in high-risk or post-treatment; intervals may vary
CA 19-9	PDAC, cholangiocarcinoma, gastric, CRC, ovarian, other GI; non-malignant causes: pancreatitis, cholestasis, cirrhosis, hepatitis, cholangitis, diabetes, inflammatory diseases, cystic fibrosis [59]	Poor screening performance; used in symptomatic patients and monitoring in known disease	~0.5–1 day (60)	Repeat after resolving benign causes; imaging (US, CT, MRI); consider ERCP if biliary obstruction	If >37 U/mL persistent; rising trend	Limitation: false positives in benign cholestasis; not expressed in Lewis-negative individuals	Every 1–3 months in active disease
AFP	HCC, germ cell tumors (non-seminomatous), gastric, pancreatic, lung; benign causes: hepatitis, cirrhosis, pregnancy [55]	Linked with liver mass in high-risk patients; used for HCC surveillance in chronic HBV, HCV, cirrhosis; diagnosis/monitoring in germ cell tumors	~4-5 days (55)	Repeat if >20 ng/mL; imaging (US, CT, MRI)	If >200 ng/mL in high-risk patient → HCC can be likely without biopsy	Strength: inexpensive, widely available; Limitation: low sensitivity for early HCC	Every 6 months in high-risk; more frequent in active disease

Certainty of Evidence (GRADE)

Using the GRADE approach, the overall certainty of evidence across evaluated outcomes was rated as low. Although some studies employed randomized designs, confidence in the estimates was downgraded due to serious methodological limitations, including high or unclear risk of bias. Additional downgrading resulted from substantial clinical and methodological heterogeneity across studies, with variability in populations, comparators, outcome measures, and timing of assessments. Indirectness and imprecision further reduced certainty, particularly due to heterogeneous study populations. Consequently, confidence in the magnitude and direction of the observed effects remains limited, and further well-designed, adequately powered randomized studies are required to strengthen the evidence base.

Initial Approach to the Asymptomatic Patient with Elevated Tumor Markers

Primacy of Clinical Context

An incidentally discovered elevated tumor marker should never be interpreted in isolation; clinical context is paramount. The initial evaluation must integrate the laboratory finding with a thorough patient assessment:

Comprehensive History

This includes detailed questioning about potential non-malignant causes for the elevation, such as current or recent infections or inflammatory conditions, known chronic diseases (especially liver, kidney, pancreatic, or thyroid disease; endometriosis in women; BPH in men), current medications (including over-the-counter drugs and supplements), and lifestyle factors like smoking history and alcohol use [50]. A careful review for subtle symptoms that the patient may have overlooked or deemed unimportant is necessary. A detailed family history of cancer is also critical for risk stratification.

Physical Examination

A thorough physical examination should be performed, focusing on systems potentially related to the specific marker elevated or common malignancies. This may include abdominal palpation (masses, hepatosplenomegaly), pelvic examination (adnexal masses), breast examination, lymph node assessment, and examination for signs of liver disease or other relevant conditions.

Risk Factor Assessment

Evaluate the individual's overall risk profile for relevant cancers based on factors such as age, sex, family history, genetic predisposition, smoking status, occupational or environmental exposures, and relevant medical history.

Confirming the Elevation

Given the possibility of laboratory error, transient physiological fluctuations, or resolving benign conditions causing a temporary rise, confirming the persistence of the elevation is a crucial first step before embarking on an extensive workup. This acts as an essential filter against unnecessary investigations prompted by potentially spurious results.

Repeat Testing

It is strongly recommended to repeat the tumor marker test after an appropriate interval. The timing depends on the marker's estimated biological half-life and clinical judgment, but intervals of 2-4 weeks or longer are often reasonable [51].

Consistency

Whenever possible, the repeat test should be performed at the same laboratory using the same assay method to ensure results are comparable and minimize inter-laboratory variability.

Avoid Empiric Treatment

Based solely on an elevated marker in an asymptomatic individual, empiric treatments are discouraged, as they lack evidence and can delay appropriate evaluation.

Interpreting Marker Kinetics

The behavior of the marker level over time often provides more valuable information than a single isolated value. This emphasis on kinetics shifts the assessment from a static snapshot to a dynamic process, potentially better reflecting the underlying biology – distinguishing a stable benign condition from a resolving issue or a progressive malignancy.

Serial Measurements

Establishing a trend through serial measurements (e.g., stable, rising, or falling) is key. A consistently rising level, particularly a rapid rise, is generally more concerning for malignancy than a stable or declining level. This requires patience and a planned follow-up strategy rather than immediate, potentially invasive, action based on a single result.

Magnitude of Elevation

While not definitive, the degree of elevation can sometimes inform risk assessment. Very high levels may increase the index of suspicion for malignancy. However, it is critical to remember that markedly elevated levels can also occur in benign conditions (e.g., extremely high CA 19-9 in benign cholestasis or Mirizzi syndrome) [52]. Some guidelines incorporate specific high thresholds into risk stratification tools (e.g., the Risk of Malignancy Index for CA-125) or suggest increased suspicion above certain levels if benign causes are excluded [53].

Half-Life Consideration

Knowledge of the marker's biological half-life (e.g., AFP: 5–7 days) is useful when interpreting changes over time, especially after a potential intervention or removal of a benign stimulus [54]. Levels should decline predictably if the source is removed or treated effectively.

The heterogeneity of tumor markers, their varying associations with different malignancies and benign conditions, and their distinct biological characteristics necessitate tailored workup strategies. A single algorithm

cannot apply to all incidental elevations. The following sections outline suggested approaches for common incidentally elevated markers, based on available evidence and guideline principles. These are intended as frameworks, always requiring adaptation to the individual patient context and emphasizing shared decision-making (Table 5). A general initial approach algorithm can be seen in Figure 2.

Discussion

The concept of utilizing blood-borne tumor biomarkers for cancer screening is underpinned by the potential to identify malignancies at an early stage, ideally preceding radiologic detection. This proposition is both clinically and scientifically appealing, as it suggests the possibility of intervening when disease burden is minimal and prognosis is most favorable. However, biological realities have consistently tempered these expectations.

Mathematical modeling studies have demonstrated that, for widely used biomarkers such as cancer antigen 125 (CA-125), the minimal detectable tumor volumes often exceed those present in early-stage disease, particularly when background secretion from normal tissues and the limited access of tumor-derived biomarkers to the circulation are considered [60]. More recent investigations, incorporating biomarker kinetics and tumor growth dynamics in animal models, corroborate these findings [61]. These models indicate that only highly aggressive tumors, characterized by substantial biomarker shedding, are likely to be detectable well before clinical imaging becomes positive, whereas indolent or small-volume malignancies the ideal targets of screening may remain below the threshold of biomarker detectability for prolonged periods [60, 61].

Despite these well-characterized limitations, tumor markers continue to be ordered extensively and frequently inappropriately in asymptomatic populations [62–65]. A 2020 study conducted in Brazil revealed that inappropriate use of tumor markers ranged from 82.4 to 100% across most medical fields, with medical oncology representing the sole field with relatively low inappropriate usage. This widespread ordering may be explained by the accessibility, noninvasive nature, and perceived simplicity of these tests. Nevertheless, availability should not be conflated with clinical utility. Leading professional organizations, including the ASCO and the USPSTF, recommend against the use of tumor markers for screening asymptomatic individuals, citing a lack of evidence for mortality reduction, low specificity, and the potential harms of false-positive results leading to unnecessary diagnostic procedures and interventions [7, 8].

The findings of the present systematic review are consistent with these recommendations. Across malignancies, the majority of included studies demonstrated limited sensitivity and predictive value for serum tumor markers when used in asymptomatic populations. Large randomized trials, such as PLCO and UKCTOCS, failed to show a reduction in ovarian cancer-specific mortality despite intensive CA-125 monitoring and structured follow-up algorithms [5, 6]. Positive predictive values (PPVs) in these settings remained unacceptably low [17]. Even in higher-risk cohorts, such as carriers of BRCA mutations or those with a strong family history of cancer, tumor markers demonstrated only marginal utility [16, 25, 44, 46]. Moreover, positive results were frequently attributable to benign conditions or interindividual biological variability [27, 35], often triggering unnecessary surgical interventions [5, 46], associated complications, patient anxiety, and increased healthcare utilization.

When evaluated individually, each biomarker demonstrated consistent performance limitations in the asymptomatic setting. CA-125, while a cornerstone in ovarian cancer follow-up, lacks sufficient sensitivity and specificity for use as a primary screening tool [6, 31]. CA 19-9 exhibited similarly poor PPV in general population screening [18], with elevated values more often linked to benign hepatobiliary or gastrointestinal conditions than to malignancy [19, 24, 41]. Although some evidence supports its use in selected high-risk groups—such as individuals with new-onset diabetes and concomitant hyperbilirubinemia [20, 37]—its performance remains suboptimal for widespread application. Carcinoembryonic antigen (CEA), traditionally associated with colorectal cancer, demonstrated low sensitivity and PPV in large-scale screenings [24, 42, 49], often resulting in costly and low-yield investigations, such as unnecessary colonoscopies and advanced imaging [32,40]. Alpha-fetoprotein (AFP) and cancer antigen 15-3 [CA 15-3] were similarly inadequate for population-wide screening [14, 36], with roles confined to specific high-risk surveillance protocols or post-treatment monitoring.

Our Certainty of Evidence assessment (GRADE) was classified as low due to a number of factors, including the heterogenous populations and study designs. Despite this, our findings are in accordance with the current understanding of avoiding measurement of tumoral markers for asymptomatic populations as screening tools.

This study doesn't come without limitations. One of the limitations is the inclusion of studies with heterogeneous designs. Another limitation is the limited number of studies investigating specific malignancies such as CRC and breast cancer. Moreover, a very limited number of studies examined AFP and CA 15-3, two of the biomarkers we intended to assess. More studies should be conducted in the future to validate our findings. In addition, our approach considerations should be validated by future studies before a large scale implementation.

In conclusion this review highlights the limited evidence supporting the use of serum tumor markers for cancer screening in asymptomatic individuals and proposes a practical framework to guide their evaluation. Adoption of structured, evidence-based approaches may reduce unnecessary investigations, improve diagnostic accuracy, and optimize patient care.

Author Contribution Statement

Conceptualization: Silvio Matsas; Methodology: Silvio Matsas; Investigation: Silvio Matsas, Allan Roberto Bueso Pineda; Sakditad Saowapa; Andrea Ortiz

Maldonado; Carolina Molina Llata; Data curation: : Silvio Matsas; Investigation: Silvio Matsas, Allan Roberto Bueso Pineda; Sakditad Saowapa; Andrea Ortiz Maldonado; Carolina Molina Llata; Writing - original draft: : Silvio Matsas; Investigation: Silvio Matsas, Allan Roberto Bueso Pineda; Sakditad Saowapa; Andrea Ortiz Maldonado; Carolina Molina Llata; Writing – review and editing: J Drew Payne; Dolores Buscemi; Asif Farooq; Kishore Karri; Auro del Giglio; Auro Del Giglio6; Validation: Auro del Giglio; Visualization: Silvio Matsas; Supervision: Auro del Giglio; Resources: Auro del Giglio.

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Approval

This study was conducted using previously published and publicly available data. Therefore it didn't require approval from any bodies.

Availability of Data

The data collected for this study was obtained from publically available articles.

Registration dataset

This study was not registered in any registration dataset.

Conflicts of interest

All authors declare no conflicts of interest.

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