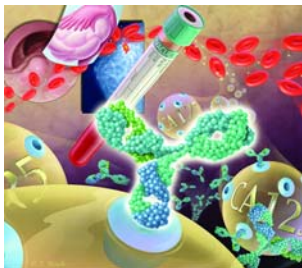


Serum Tumor Markers

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Monoclonal antibodies are used to detect serum antigens associated with specific malignancies. These tumor markers are most useful for monitoring response to therapy and detecting early relapse. With the exception of prostate-specific antigen (PSA), tumor markers do not have sufficient sensitivity or specificity for use in screening. Cancer antigen (CA) 27.29 most frequently is used to follow response to therapy in patients with metastatic breast cancer. Carcinoembryonic antigen is used to detect relapse of colorectal cancer, and CA 19-9 may be helpful in establishing the nature of pancreatic masses. CA 125 is useful for evaluating pelvic masses in postmenopausal women, monitoring response to therapy in women with ovarian cancer, and detecting recurrence of this malignancy. Alpha-fetoprotein (AFP), a marker for hepatocellular carcinoma, sometimes is used to screen highly selected populations and to assess hepatic masses in patients at particular risk for developing hepatic malignancy. Testing for the beta subunit of human chorionic gonadotropin (β -hCG) is an integral part of the diagnosis and management of gestational trophoblastic disease. Combined AFP and β -hCG testing is an essential adjunct in the evaluation and treatment of nonseminomatous germ cell tumors, and in monitoring the response to therapy. AFP and β -hCG also may be useful in evaluating potential origins of poorly differentiated metastatic cancer. PSA is used to screen for prostate cancer, detect recurrence of the malignancy, and evaluate specific syndromes of adenocarcinoma of unknown primary. (*Am Fam Physician* 2003;68:1075-82. Copyright© 2003 American Academy of Family Physicians.)



Because family physicians are assuming a greater role in caring for patients with cancer, an understanding of tumor markers is becoming increasingly important. These soluble molecules in the blood are usually glycoproteins detected by monoclonal antibodies. Each tumor marker has a variable profile of usefulness for screening, determining diagnosis and prognosis, assessing response to therapy, and monitoring for cancer recurrence.

This article describes the use of common tumor markers in primary care practice. Particular emphasis is given to when these tests should be ordered and to common factors that influence the interpretation of tumor marker levels.

Role of Tumor Markers

Screening tests require high sensitivity to detect early-stage disease. These tests also must have sufficient specificity to protect patients with false-positive

results from unwarranted diagnostic evaluations.

To date, no tumor marker has demonstrated a survival benefit in randomized controlled trials of screening in the general population. Nevertheless, tumor markers can play a crucial role in detecting disease and assessing response to therapy in selected groups of patients. In monitoring patients for disease recurrence, tumor marker levels should be determined only when there is a potential for meaningful treatment.

Normalization of tumor marker values may indicate cure despite radiographic evidence of persistent disease. In this circumstance, the residual tumor is frequently nonviable. Conversely, tumor marker levels may rise after effective treatment (possibly related to cell lysis), but the increase may not portend treatment failure. However, a consistent increase in tumor marker levels, coupled with lack of clinical improvement, may indicate treatment failure. Residual elevation after

See page 1039 for definitions of strength-of-evidence levels.

TABLE 1
Conditions Associated with Elevated Tumor Marker Levels

<i>Tumor marker</i>	<i>Normal value</i>	<i>Primary tumor(s)</i>	<i>Additional associated malignancies</i>	<i>Benign conditions</i>
CA 27.29 ^{1,2}	<38 units per mL	Breast cancer	Colon, gastric, hepatic, lung, pancreatic, ovarian, and prostate cancers	Breast, liver, and kidney disorders, ovarian cysts
CEA ^{3,4}	<2.5 ng per mL in nonsmokers <5 ng per mL in smokers	Colorectal cancer	Breast, lung, gastric, pancreatic, bladder, medullary thyroid, head and neck, cervical, and hepatic cancers, lymphoma, melanoma	Cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, cirrhosis, biliary obstruction
CA 19-9 ⁵	<37 units per mL	Pancreatic cancer, biliary tract cancers	Colon, esophageal, and hepatic cancers	Pancreatitis, biliary disease, cirrhosis
AFP ⁶	<5.4 ng per mL	Hepatocellular carcinoma, nonseminomatous germ cell tumors	Gastric, biliary, and pancreatic cancers	Cirrhosis, viral hepatitis, pregnancy
β -hCG ^{7,8}	<5 mIU per mL	Nonseminomatous germ cell tumors, gestational trophoblastic disease	Rarely, gastrointestinal cancers	Hypogonadal states, marijuana use
CA 125 ⁹⁻¹¹	<35 units per mL	Ovarian cancer	Endometrial, fallopian tube, breast, lung, esophageal, gastric, hepatic, and pancreatic cancers	Menstruation, pregnancy, fibroids, ovarian cysts, pelvic inflammation, cirrhosis, ascites, pleural and pericardial effusions, endometriosis
PSA ¹²⁻¹⁴	<4 ng per mL for screening Undetectable level after radical prostatectomy	Prostate cancer	None	Prostatitis, benign prostatic hypertrophy, prostatic trauma, after ejaculation

CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; β -hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen.

*—The greatest possible sensitivity is 95 percent, given that 5% of the population have Lewis-null blood type and are unable to produce the antigen. Information from references 1 through 14.

definitive treatment usually indicates persistent disease. Following tumor marker response is particularly useful when other evidence of disease is not readily accessible.

Cancer Antigen 27.29

Cancer antigen (CA) 27.29 is a monoclonal antibody to a glycoprotein (MUC1) that is present on the apical surface of normal epithelial cells. CA 27.29 is highly associated with breast cancer, although levels are elevated in several other malignancies (Table 1).¹⁻¹⁴ CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts. However, CA 27.29 levels higher than 100 units per mL are rare in benign conditions.¹

Because of superior sensitivity and specificity, CA 27.29 has supplanted CA 15-3 as the preferred tumor marker in breast cancer. The CA 27.29 level is elevated in approximately one third of women with early-stage breast cancer

(stage I or II) and in two thirds of women with late-stage disease (stage III or IV).² CA 27.29 lacks predictive value in the earliest stages of breast cancer and thus has no role in screening for or diagnosing the malignancy.

Disagreement exists about the ability of CA 27.29 to detect asymptomatic recurrence after curative treatment. One trial¹ in patients at high risk for recurrence of breast cancer (stage II or III) found that CA 27.29 was highly specific and sensitive in detecting preclinical metastasis. The average time from initial elevation of CA 27.29 to onset of symptoms was five months. Because CA 27.29 testing may lead to prompt imaging of probable sites of metastasis, it may be possible to decrease morbidity through earlier institution of therapy.

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and overexpressed

Level above which benign disease is unlikely	Sensitivity
> 100 units per mL	Elevated in about 33% of early-stage breast cancers and about 67% of late-stage breast cancers
> 10 ng per mL	Elevated in less than 25% of early-stage colon cancers and 75% of late-stage colon cancers
> 1,000 units per mL	Elevated in 80% to 90% of pancreatic cancers and 60% to 70% of biliary tract cancers*
> 500 ng per mL	Elevated in 80% of hepatocellular carcinomas Nonseminomatous germ cell tumors: see β -hCG below
> 30 mIU per mL ⁷	AFP or β -hCG elevated in 85% of nonseminomatous germ cell tumors; elevated in only 20% of early-stage nonseminomatous germ cell tumors
> 200 units per mL ¹¹	Elevated in about 85% of ovarian cancers; elevated in only 50% of early-stage ovarian cancers
> 10 ng per mL ¹²	Elevated in more than 75 percent of organ-confined prostate cancers ¹⁴

in adenocarcinoma, especially colorectal cancer (Table 1).¹⁻¹⁴ CEA elevations also occur with other malignancies. Non-neoplastic conditions associated with elevated CEA levels include cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and cirrhosis. Levels exceeding 10 ng per mL are rarely due to benign disease.³

Fewer than 25 percent of patients with disease confined to the colon have an elevated CEA level. Sensitivity increases with advancing tumor stage: CEA values are elevated in approximately 50 percent of patients with tumor extension to lymph nodes and 75 percent of patients with distant metastasis.⁴ The highest values (above 100 ng per mL) occur with metastasis,¹⁵ although poorly differentiated tumors are less likely to produce CEA.⁴

CEA is not useful in screening for colorectal cancer or in the diagnostic evaluation of an undefined illness. A CEA level should be ordered only after malignancy has been

confirmed. CEA levels typically return to normal within four to six weeks after successful surgical resection.³

The major role for CEA levels is in following patients for relapse after intended curative treatment of colorectal cancer. When patients with a normal preoperative CEA level have cancer recurrence, CEA elevation is a sign in nearly one half of them.⁴

The American Society of Clinical Oncology recommends monitoring CEA levels every two to three months for at least two years in patients with stage II or III disease who are surgical candidates.¹⁶ [Evidence level C, consensus/expert guidelines] When an abnormal level is found, the test should be repeated; if CEA elevation is confirmed, patients should undergo imaging of potential recurrence sites. Local recurrence or limited metastasis to liver or lung can be resected with curative intent. Clinical trials examined in one meta-analysis¹⁷ demonstrated a 9 percent (absolute value) improvement in survival after five years in patients who underwent CEA monitoring as part of post-treatment management.

Cancer Antigen 19-9

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies (Table 1).¹⁻¹⁴ This tumor marker has a sensitivity and specificity of 80 to 90 percent for pancreatic cancer and a sensitivity of 60 to 70 percent for biliary tract cancer. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations, although values are usually less than 1,000 units per mL.⁵

Patients with Lewis-null blood type do not produce CA 19-9. Thus, about 5 percent of persons are unable to produce this antigen.⁵

Use of CA 19-9 is limited. The antigen has no value in screening because its positive predictive value is less than 1 percent.¹⁸ However, the positive predictive value of levels over 1,000 units per mL is 97 percent when CA 19-9 test-

One trial found that monitoring of cancer antigen 27.29 levels in patients at high risk for recurrence of breast cancer (stage II or III) was associated with identification of relapse an average of five months before onset of symptoms.

Clinical trials have shown that monitoring of carcinoembryonic antigen levels can contribute to improved survival after surgical resection of colorectal cancer.

ing is used in clinical situations that are consistent with pancreatic cancer (e.g., jaundice associated with a pancreatic mass). Furthermore, CA 19-9 levels above 1,000 units per mL predict the presence of metastatic disease.⁵

Alpha-Fetoprotein

Alpha-fetoprotein (AFP) is the major protein of fetal serum but falls to an undetectable level after birth. The primary malignancies associated with AFP elevations are hepatocellular carcinoma and nonseminomatous germ cell tumors. Other gastrointestinal cancers occasionally cause elevations of AFP, but rarely to greater than 1,000 ng per mL.⁶

Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500 ng per mL. Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality.⁶

AFP levels are abnormal in 80 percent of patients with hepatocellular carcinoma and exceed 1,000 ng per mL in 40 percent of patients with this cancer.⁶ Although randomized controlled trials have not shown mortality risk benefit, the use of AFP in hepatocellular carcinoma screening continues to be debated. Retrospective studies^{19,20} in Asia showed improved survival with AFP screening, but the findings of this study have not been duplicated.

Some experts use annual AFP and ultrasound screening in patients with well-compensated nonalcohol-induced cirrhosis.²⁰ In patients with a hepatic mass and risk factors for hepatocellular carcinoma, an AFP level above 500 ng per mL is often used in lieu of biopsy to diagnose hepatocellular carcinoma.⁶

Beta Subunit of Human Chorionic Gonadotropin

The beta subunit of human chorionic gonadotropin (β -hCG) normally is produced by the placenta. Elevated β -hCG levels most commonly are associated with pregnancy, germ cell tumors, and gestational trophoblastic disease. False-positive levels occur in hypogonadal states and with marijuana use.⁷

Both AFP and β -hCG play crucial roles in the management of patients with nonseminomatous germ cell tumors. The AFP or β -hCG level is elevated in 85 percent of patients with these tumors (Table 1),¹⁻¹⁴ but in only 20 percent of patients with stage I disease.⁸ Hence, these markers have no role in screening. Marked elevations of AFP or β -hCG are associated with very few disease states (Table 2).

In patients with extragonadal disease or metastasis at the time of diagnosis, highly elevated AFP or β -hCG values can be used in place of biopsy to establish a diagnosis of nonseminomatous germ cell tumor. AFP values in excess of 10,000 ng per mL or β -hCG levels above 50,000 mIU per mL at initial diagnosis portend a poor prognosis, with a five-year survival rate of 50 percent. Similarly staged patients with lower AFP and β -hCG levels have a cure rate higher than 90 percent.²¹

Following AFP and β -hCG levels is imperative in monitoring response to treatment in patients who have nonseminomatous germ cell tumors. Patients with AFP and β -hCG levels that do not decline as expected after treatment have a significantly worse prognosis, and changes in therapy should be considered.²² Because curative salvage therapy is possible, the tumor markers are followed every one to two months for

TABLE 2
AFP and β -hCG Levels in Germ Cell Tumors and Gestational Trophoblastic Disease

Tumor	AFP elevation	β -hCG elevation
Seminoma and dysgerminoma	Never*	Occasional, minimal
Embryonal cell carcinoma	Yes	Yes
Choriocarcinoma	No	Yes
Yolk sac tumors	Yes	No
Teratoma	No	No
Gestational trophoblastic disease†	No	Yes

AFP = alpha-fetoprotein; β -hCG = beta subunit of human chorionic gonadotropin.

*—Any detectable AFP indicates the presence of a nonseminomatous component; in this situation, the malignancy should be treated as a nonseminomatous germ cell tumor.

†—Gestational trophoblastic disease is not a germ cell tumor; rather, it is a rare gynecologic malignancy related to pregnancy.

one year after treatment, then quarterly for one year, and less frequently thereafter.⁸ AFP or β -hCG elevation is frequently the first evidence of germ cell tumor recurrence; a confirmed elevation should prompt reinstitution of therapy.²³

The β -hCG level is used to diagnose gestational trophoblastic disease, a rare neoplastic complication of pregnancy. The β -hCG value is followed to assess response to treatment and to detect relapse in a manner similar to that for germ cell tumors²⁴ (Table 2).

Cancer Antigen 125

CA 125 is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelopes the ovaries.

Elevated CA 125 values most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies.⁹ CA 125 levels are elevated in about 85 percent of women with ovarian cancer, but in only 50 percent of those with stage I disease. Higher levels are associated with increasing bulk of disease and are highest in tumors with nonmucinous histology.⁹ Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces¹⁰ (Table 1).¹⁻¹⁴

Insensitivity in early-stage disease and low disease prevalence limit the usefulness of CA 125 in ovarian cancer screening. In the largest study to date,²⁵ CA 125 levels were monitored in all patients annually for three years, and elevated values prompted ultrasound examinations. The positive predictive value was 20 percent, translating to five exploratory laparotomies for each ovarian cancer diagnosed. Survival was not improved in the women who were found through CA 125 screening to have ovarian cancer.

Randomized trials are being conducted to assess the role of CA 125 in ovarian cancer screening. Annual ultrasound examination and CA 125 screening have been advocated for women with hereditary ovarian cancer syndromes.²⁶

CA 125 has been used as an adjunct in the diagnosis of pelvic masses. In postmenopausal women with asymptomatic palpable pelvic masses, CA 125 levels higher than 65 units per mL have a positive predictive value of 98 percent for ovarian cancer. Because premenopausal women have more benign causes of elevated CA 125 levels, testing for the marker is less useful in this population.²⁷

Currently, ovarian cancer is treated with maximal surgical reduction, which leaves minimal clinical or radiographic disease.²⁶ Because studies have demonstrated concordance of CA 125 levels with disease activity, oncologists

rely on CA 125 levels to guide therapeutic decisions.²⁸ After definitive treatment of ovarian cancer, CA 125 levels should be obtained every three months for two years, and with decreasing frequency thereafter. Elevated CA 125 levels during follow-up nearly always indicate ovarian cancer recurrence.²⁶

Prostate-Specific Antigen

Prostate-specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. The PSA level can be elevated in prostate cancer, prostatitis, benign prostatic hypertrophy, and prostatic trauma, as well as after ejaculation¹² (Table 1).¹⁻¹⁴

In men with prostatitis, PSA levels return to normal within eight weeks of symptom resolution. Waiting 48 hours after ejaculation to measure the PSA level has been recommended.¹³ Digital rectal examination does not elevate PSA levels above normal values.²⁹ In men who have been taking finasteride (Proscar) for more than six months, reported PSA levels should be doubled to accurately reflect true values, because the drug is an enzyme inhibitor that suppresses normal production of PSA by the prostate gland.³⁰

In prostate cancer, the positive predictive value of PSA levels greater than 4 ng per mL is 20 to 30 percent and rises to 50 percent when PSA levels exceed 10 ng per mL. Nevertheless, 20 to 30 percent of men with prostate cancer have PSA levels within normal ranges.¹²

Modifications to improve the positive predictive value of PSA testing include revised limits of normal based on age, race, velocity, density, and percentage of unbound (free) antigen. To date, these modifications have not resulted in improved outcomes. However, in patients with PSA values between 4 and 10 ng per mL, the PSA velocity and percentage of free PSA have been helpful in making clinical decisions. A velocity of 0.75 ng per mL per year is predictive of cancer.³¹ When less than 10 percent of PSA is unbound, the positive predictive value for prostate cancer is 55 percent, compared with 8 percent when more than 25 percent of PSA is unbound.³²

Prostate cancer screening remains controversial. Surrogate evidence of screening benefits include lower PSA levels³³ and earlier stage of disease at the time of initial diagnosis.³⁴ Limitations of screening include uncertainty about outcome benefit after treatment of localized prostate cancer,³⁵ potential identification of clinically insignificant tumors,³⁶ and attendant morbidity of treatment.³⁵ Experts from the American Urological Association suggest that

Fewer than 2 percent of men with prostate-specific antigen levels below 20 ng per mL have bone metastases from prostate cancer.

patients should be given sufficient information to allow them to make an informed decision about prostate cancer screening using PSA levels (Table 3).³⁷

If PSA testing is undertaken, an age of 40 years has been suggested for initiation of screening in black men and in all men with a family history of prostate cancer.³⁷ In patients without established risk factors and a minimum life expectancy of 10 years, screening could begin at age 50. If elevated PSA values are confirmed, patients should be referred for biopsy.¹² Randomized clinical trials are being conducted to assess the validity of these recommendations.

PSA levels predict the presence of metastatic disease. Patients with newly diagnosed prostate cancer and PSA levels below 20 ng per mL rarely have osseous metastasis and do not need bone scanning, because the incidence of metastatic disease in these men is lower than 2 percent.³⁸ In addition, computed tomographic scanning is unnecessary in men with PSA levels below 25 ng per mL.¹² At our institution, if a prostate nodule is detected, the bone scan is widely positive, and the PSA level exceeds 100 ng per mL, treatment is often instituted without performance of biopsy.

After treatment of prostate cancer, PSA levels should be obtained every six months for five years, and then annually.³⁹ In men who have undergone radical prostatectomy,

TABLE 3

Information for Patients About Prostate Cancer Screening

Prostate cancer is common and potentially lethal; however, more patients die with, rather than from, the disease.

Screening detects more cases of organ-confined disease, but there is no proof that this detection saves lives.

In most instances, prostate cancer is not the cause of an elevated PSA level.

Localized treatment of prostate cancer is effective but is associated with complications that can include impotence and incontinence.

It is likely that prostate cancer screening using the PSA level is beneficial in a subset of men; however, the characteristics of this subset have not been defined.

PSA = prostate-specific antigen.

Information from reference 37.

any detectable PSA is significant.¹² Salvage radiotherapy may be appropriate in these patients if recurrence is limited to the prostate bed as determined by ProstaScint scanning, a nuclear medicine test using a radiolabeled antibody that targets only prostate tissue.

After radiotherapy, a PSA nadir is not reached for one to two years. Three consecutive elevations of the PSA level indicate biochemical relapse in previously irradiated patients.¹² Metastases do not become clinically evident for an average of eight years, and death does not occur for an average of 13 years. Thus, management decisions must include consideration of a patient's age and comorbid conditions.⁴⁰

Cancer of Unknown Primary

Confusion exists about the value of tumor markers in a patient with cancer of unknown primary. Intuitively, a panel of tumor markers should help to establish the origin of the tumor. Unfortunately, most tumor markers are too nonspecific for this purpose. However, with adenocarcinoma in older men, significant PSA elevations have sufficient specificity to make the diagnosis of prostate cancer.

In poorly differentiated tumors, AFP and β -hCG levels should be ordered. Marked elevations of these tumor markers signify the presence of an extragonadal germ cell tumor. In women with peritoneal carcinomatosis or malignant ascites, treatment for ovarian cancer is instituted if the CA 125 level is elevated.⁴¹

Tumor markers in common use are summarized in Table 4.^{1,5,8,12,16,24,26,27,39-41}

The authors indicate that they do not have any conflicts of interests. Sources of funding: none reported.

The authors thank Janet Parker for research assistance in the preparation of the manuscript.

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TABLE 4
Tumor Markers In Common Use

Tumor marker	Primary tumor(s)	Use of tumor marker		Follow-up after primary treatment	Monitoring of treatment response
		Screening	Diagnosis		
CA 27.29 ¹	Breast cancer	No	No	Consider in patients at high risk for recurrence; obtain CA 27.29 level every 4 to 6 months.	Helpful
CEA ¹⁶	Colorectal cancer	No	No	In patients at high risk for recurrence, obtain CEA level every 2 to 3 months for at least 2 years.	Very helpful
CA 19-9 ⁵	Pancreatic cancer, biliary tract cancer	No	Selected pancreatic masses	No	Helpful
AFP ^{8,20,41}	Hepatocellular carcinoma, nonseminomatous germ cell tumor	No*	Poorly differentiated cancer of unknown primary; patients with cirrhosis and a liver mass	In patients treated for nonseminomatous germ cell tumor, obtain AFP and β -hCG levels every 1 to 2 months for 1 year, then quarterly for 1 year, and less frequently thereafter.	Essential in patients treated for nonseminomatous germ cell tumor; very helpful in patients treated for hepatocellular carcinoma
β -hCG ^{8,24,41}	Nonseminomatous germ cell tumor, gestational trophoblastic disease	No	Poorly differentiated cancer of unknown primary; gestational trophoblastic disease	Nonseminomatous germ cell tumor: see AFP above. In patients treated for gestational trophoblastic disease, obtain β -hCG level once a month for 6 to 12 months.	Essential in patients treated for nonseminomatous germ cell tumor or gestational trophoblastic disease
CA 125 ^{26,27,41}	Ovarian cancer	No†	Adjunct for diagnosis of pelvic mass in postmenopausal women; malignant ascites in women with cancer of unknown primary	Obtain CA 125 level every 3 months for 2 years, then less frequently.	Very helpful
PSA ^{12,39-41}	Prostate cancer	Yes	Adenocarcinoma of unknown primary; widely positive bone scan and prostate mass	Obtain PSA level every 6 months for 5 years, then annually. ³⁹ Any detectable PSA after radical prostatectomy indicates recurrence. Three consecutive PSA elevations after radiation therapy indicate recurrence.	Very helpful

CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; β -hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen.

*—Except in highly selected patients with nonalcoholic-induced cirrhosis.

†—Except in heritable ovarian cancer syndromes.

Information from references 1, 5, 8, 12, 16, 24, 26, 27, and 39 through 41.

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