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The Clinical Use of Tumor Markers in Select Cancers: Are You Confident Enough to Discuss Them With Your Patients?

Deanna Sanchez Yamamoto, RN, MS, CS, ANP, AOCNP, Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP, Karen Roesser, RN, MS, CNS, AOCN®, and Albert Lin, MD, PhD

Purpose/Objectives: To review the clinical use of tumor markers in select cancers and highlight future directions in tumor marker development.

Data Sources: Guidelines from national and international societies, scientific literature, and Internet resources.

Data Synthesis: Tumor markers are important tools in the management of cancer. Sequencing of the human genome has led to new tumor marker development in the fields of proteomics and DNA microarray technologies.

Conclusions: Tumor marker technology is expanding rapidly; almost a dozen tumor markers currently are being used in the oncology arena, with many more in development. The use of tumor markers can be controversial, particularly because guidelines have not been established for all of the markers.

Implications for Nursing: Oncology nurses need to be well versed in the use of tumor markers to educate and counsel patients with cancer.

When patients are presented with a tumor marker laboratory value, they often ask about its meaning. Oncology nurses should be prepared to describe the significance of various tumor markers and help patients to understand the debate surrounding their use in making clinical decisions. Leading medical societies have formed committees to review the scientific literature and publish guidelines on the use of tumor markers. However, this process is slow, often spanning years, and in the interim, assays of reputed tumor markers may become available before sufficient evidence supports their use in clinical practice. The recommendations from published guidelines on the appropriate use of tumor markers may differ among medical societies and may add to the confusion (Sturgeon, 2002).

As a result, oncology nurses must be aware of these inconsistencies, understand how and when individual tumor markers are used, and stay informed about new tumor markers. Patients can become aware of tumor markers from the Internet, lay literature, and support groups; therefore, oncology nurses should be as knowledgeable about tumor markers

Key Points . . .

- Tumor markers are used to screen and diagnose cancer, monitor treatment, and help determine recurrence.
- Elevations in tumor markers can be caused by benign conditions other than the presence of cancer.
- The role of tumor markers will continue to grow as new targeted drug therapies are used to treat patients with cancer.

Goal for CE Enrollees:

To enhance the nurse's knowledge regarding the use of clinical tumor marker data with patients with cancer.

Objectives for CE Enrollees:

1. Discuss the importance of tumor marker use and their indications in specific diseases.
2. List examples of factors that may affect the reliability of tumor marker values.
3. Examine the differences in application of tumor marker information depending on the disease.

Deanna Sanchez Yamamoto, RN, MS, CS, ANP, AOCNP, is a rheumatology/oncology nurse practitioner at Santa Clara Valley Medical Center in San Jose, CA; Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP, is a nurse practitioner in the Hematology/Oncology Department at Camino Medical Group in Sunnyvale, CA; Karen Roesser, RN, MS, CNS, AOCN®, is an oncology clinical nurse specialist at CJW Medical Center in Richmond, VA; and Albert Lin, MD, PhD, is a medical oncologist at Santa Clara Valley Medical Center. *(Submitted May 2004. Accepted for publication November 29, 2004.)* *(Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society.)*

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as they are about chemotherapy. Then, they can confidently answer the patient's question, "What does my tumor marker number mean?"

Tumor Markers

Henry Bence-Jones, MD, discovered the first tumor marker in 1864. He found that acidification of boiled urine produced a heavy precipitate, identified as a monoclonal light chain in immunoglobulin, in patients with multiple myeloma. The Bence-Jones protein tumor marker still is used in clinical practice (Schrohl et al., 2003; Sell, 1990). Since 1864, new tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and oncogenes, were discovered. The rapid increase in the number of new tumor markers since the 1980s has outpaced all prior discoveries (Fischbach, 2000; Schrohl et al.; Sell) (see Figure 1).

"Tumor marker" is a broad term used to describe a tool that allows practitioners to analyze clinical aspects of a cancer (Schrohl et al., 2003). More specifically, a tumor marker is a molecule, process (e.g., apoptosis, angiogenesis, proliferation), or substance that can be altered by cancer and measured quantitatively or qualitatively by biochemical or immunochemical means in the tissues or body fluids of some individuals with cancer (Fischbach, 2000; Harish, 2000; Schrohl et al.). Consequently, tumor markers are a myriad of substances and may consist of proteins, DNA, genetic markers (abnormal chromosomes or oncogenes), oncogene receptors, hormones, hormone receptors, oncofetal antigens, enzymes, or substances produced by tumor cells or in response to tumor growth (e.g., cell-reactive protein, circulating immune complexes, prostate-specific antigens [PSAs]) (Fischbach; Harish).

Tumor markers are biologic or biochemical substances or processes and not solely serum-derived markers (Pamies, 1996; U.S. National Library of Medicine, 2004). Given the entirety of tumor markers, limiting a review to only serum markers would not be justifiable. Therefore, several authors have suggested that tumor markers can be described best by function and categorized into their diagnostic, prognostic, predictive, staging, and monitoring clinical uses (Nordenson, 1999; Schrohl et al., 2003; Sturgeon, 2002). Diagnostic tumor markers, which include screening markers, aid in identifying cancer in an individual, whereas prognostic tumor markers estimate the risk of death or cancer recurrence following surgical removal of cancer without adjuvant therapy. Predictive tumor markers forecast how patients will respond to a given therapy, and monitoring markers help to detect the recurrence or remission of cancer after treatment has been completed (Mincey, Palmieri, & Perez, 2002; Schrohl et al.). Thus, the uses of tumor markers are multifaceted, with the newest application in targeting cytotoxic agents.

1800s	Bence-Jones protein
1940s	Acid phosphatase
1960s–1980s	Alpha-fetoprotein, carcinoembryonic antigen, monoclonal antibodies, cancer antigen 125, prostate-specific antigen, carbohydrate antigens, oncogenes, tumor-suppressor genes
1990s–2000+	Proteomics, mass spectrometry, microarray technologies

Figure 1. Timeline of Tumor Marker Discovery

Clinical Applications of Tumor Markers in Select Cancers

Germ Cell Tumors

The most established tumor markers for the management of testicular (nonseminomatous) and other germ cell tumors are AFP, beta-human chorionic gonadotropin (B-hCG), and lactate dehydrogenase (LDH). Most published guidelines generally agree that these markers are essential for the appropriate treatment and care of patients diagnosed with these tumor types (Sturgeon, 2002).

AFP and B-hCG are oncofetoproteins (Ebb, Green, Shamberger, & Tarbell, 2001). Normally, the placenta produces B-hCG, and levels rise during pregnancy, with germ cell tumors, and in patients with gestational trophoblastic disease (Perkins, Slater, Sanders, & Prichard, 2003). In men and nonpregnant women, the B-hCG level should be less than 2.5 IU/L and less than 5.0 IU/L, respectively; however, certain noncancerous conditions (e.g., hypogonadism) and marijuana use may cause elevations of B-hCG (Perkins et al.) (see Table 1).

AFP is a normal fetal serum protein made by the liver, yolk sac, and gastrointestinal tract and is an important part of fetal plasma; after birth, the protein clears quickly from the circulation (Ebb et al., 2001). Normal levels of AFP in nonpregnant women should be less than 15 ng/ml, and 96% of nonpregant women have levels less than 6 ng/ml (Doherty, Bower, & Christmas, 1997; Lamerz et al., 1999). Serum AFP levels higher than 400 mcg/l are associated with a neoplasm or other pathology. Although very specific to germ cell tumors, AFP also is elevated in some hepatocellular cancers and can be used as a tumor marker (Ebb et al.).

Measurement of AFP or B-hCG in nonseminomatous germ cell tumors is fundamental to the treatment of patients, allowing clinicians to help diagnose disease, monitor patients for response to treatment, and determine prognosis. Approximately 85% of patients with germ cell tumors have elevation of either marker on diagnosis (Perkins et al., 2003). Preoperative measurement of tumor markers is important in helping to make an original diagnosis. The markers generally are remeasured three to four weeks after orchiectomy (Sonpavde & Einhorn, 1999). Measuring the markers in extragonadal tumors can be extremely helpful as well because the tumors do not originate in the testes and can carry a poorer prognosis.

When monitoring patients for response to treatment, levels that do not decline as expected help to identify patients who will not do well with standard therapy and have a poorer prognosis (Perkins et al., 2003). Tumor markers must be measured prior to each chemotherapy cycle to help to determine the response to therapy; a 90% decline in tumor markers is expected every 21 days (Bringhurst & Amato, 1997). If tumor markers do not decline as anticipated, clinicians may use marker results to determine appropriate subsequent therapy and identify disease recurrence early after the original therapy (Perkins et al.) (see Figure 2).

Lamerz et al. (1999) made recommendations for the use of tumor markers in germ cell tumors. Although they endorsed the use of AFP and B-hCG in this population of patients, they also described placental alkaline phosphatase (PLAP) and LDH as helpful. Elevations of serum PLAP are present in as many as 80% of patients with metastatic germ cell tumors;

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Table 1. Tumor Markers

Marker	Uses	Elevations From Noncancerous Conditions	Normal Values
Germ cell tumors			
• AFP	Diagnosis, prognosis, monitoring	Viral hepatitis, biliary cirrhosis, partial hepatectomy, ataxic telangiectasia, pregnancy	Nonpregnant individuals < 15 ng/ml
• B-hCG	Diagnosis, prognosis, monitoring	Pregnancy, marijuana smoking, testicular failure, hypogonadism	< 2.5 IU/L in men and < 5.0 IU/L in nonpregnant women
• LDH	Diagnosis, staging, prognosis, monitoring	Skeletal muscle disease, myocardial infarction, pernicious anemia, leukemia, thalassemia, pulmonary embolism	100–210 U/L
• PLAP	Diagnosis	Cigarette smoking	< 500 mU/L in nonsmokers
Prostate cancer			
• PSA	Screening, monitoring	Benign prostatic hypertrophy, prostatitis	0–4 ng/ml
• Percent-free PSA	Diagnosis, staging	Benign prostatic hypertrophy	The greater the value, the less likely a cancer; no established criterion
Bladder cancer			
• NMP22	Monitoring	Recent invasive genitourinary procedure, urinary tract infection, renal or bladder stones, chemotherapy	< 10 U/L
• BTA	Monitoring	Recent genitourinary trauma (cystoscopy), renal or bladder stones, urinary tract infection	Normally not detected
Lung cancer			
• NSE	Diagnosis, monitoring	–	< 13 ng/ml
• CEA	Monitoring, prognosis	See colorectal cancer.	–
• CYFRA 21.1	Diagnosis, prognosis, monitoring	Chronic hepatitis, pancreatitis, chronic airway obstruction	No international reference standard
• CA 125	Diagnosis, prognosis	–	No international reference standard
Colorectal cancer			
• CEA	Monitoring	Cigarette smoking, peptic ulcer, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, cirrhosis, COPD, pulmonary infections, chronic renal failure	< 3 ng/ml in nonsmokers and < 5 ng/ml in smokers
Pancreatic cancer			
• CA 19.9	Diagnosis, monitoring	Pancreatitis, cirrhosis, acute cholecystitis, extra hepatic cholestasis	< 70 U/ml
Breast cancer			
• ER/PR	Determine endocrine therapy.	–	Positive (favorable)
• HER2/neu	Determine anthracycline trastuzumab therapy.	–	IHC 1+ negative and IHC 2+ → FISH
• CA 15.3, CA 27.29	Monitoring	Chronic hepatitis, liver cirrhosis, tuberculosis, sarcoidosis, systemic lupus erythematosus	< 31 U/ml
Ovarian cancer			
• CA 125	Monitoring	Peritonitis, endometriosis, nonmalignant ascites, menstruation, pregnancy	0–35 U/ml

AFP—alpha-fetoprotein; B-hCG—beta-human chorionic gonadotropin; BTA—bladder tumor antigen; CA—cancer antigen; CEA—carcinoembryonic antigen; COPD—chronic obstructive pulmonary disease; ER—estrogen receptor; FISH—fluorescence in situ hybridization; IHC—immunohistochemistry; LDH—lactate dehydrogenase; NMP22—nuclear matrix protein 22; NSE—neuron-specific enolase; PLAP—placental alkaline phosphatase; PR—progesterone receptor; PSA—prostate-specific antigen

Note. From "Tumor Marker Tests" (www.vh.org/adult/patient/cancercenter/tumormarker/index.html), by Virtual Hospital, 2005. Copyright 2005 by Virtual Hospital and the University of Iowa. Adapted with permission.

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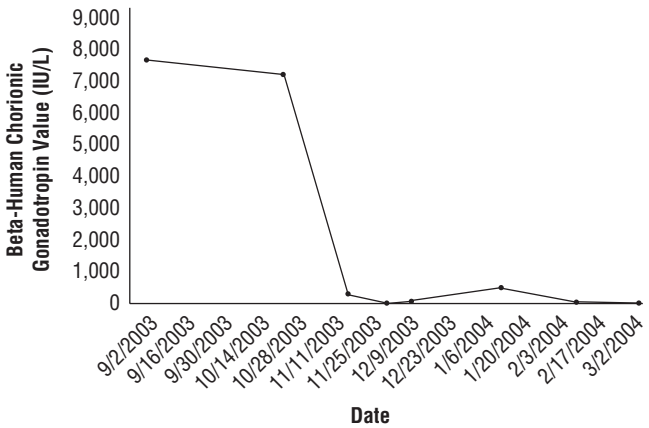

Case Study

In July 2003, a 35-year-old male was diagnosed with germ cell nonseminomatous cancer of the testes and started on vinblastine, etoposide, and cisplatin (VIP) chemotherapy. After four cycles of VIP, his markers had normalized; however, on December 23, 2003, his beta-human chorionic gonadotropin value was elevated. Because a nonmalignancy may have caused the elevation, the marker was measured again on January 6, 2004, and again revealed an increase from 107–360 UI/L. A computed tomography scan was ordered and showed residual disease. The patient's chemotherapy regimen subsequently was changed to bleomycin, etoposide, and cisplatin.

Figure 2. The Use of Beta-Human Chorionic Gonadotropin Values to Monitor Testicular Cancer

however, the use of PLAP is not indicated for patients who smoke because their levels will be increased (Lamerz et al.). LDH is elevated in testicular germ cell tumors but also is high in a number of other conditions, including skeletal muscle disease, myocardial infarction, pernicious anemia, leukemia, thalassemia, and pulmonary embolism. In addition, total LDH activity refers to five different LDH isoenzymes, of which LDH isoenzyme 1 is considered by some clinicians to be the most significant marker in testicular germ cell tumors (von Eyben, Liu, Amato, & Fritsche, 2000). Despite their sensitivity in monitoring, prognosis, and determination of recurrence, tumor markers are not recommended when screening for germ cell tumors.

Prostate Cancer

Although tumor markers do not play a role in screening for testicular and other germ cell tumors, they can be useful when screening for prostate cancer, which is the most common male cancer and the second most-common cause of all cancer deaths in men (Vashi & Oesterling, 1997). PSA, which is used when screening for prostate cancer, is a glycoprotein found in the ductal epithelial cells of the prostate gland and is present in low concentrations in healthy men (range = 0–4 ng/ml); however, levels increase with age (Merck & Co., Inc., 2004). The advantage to using PSA as opposed to the older screening tumor marker, prostatic acid phosphatase, is that a digital rectal examination should not elevate PSA levels above normal values and the PSA is more sensitive (Perkins et al., 2003). However, PSA levels can be elevated in men with nonmalignant conditions such as benign prostatic hypertrophy or prostatitis (Sturgeon, 2002).

Because PSA is produced only in the prostate, the test is very specific and may be the most specific tumor marker test currently available. The sensitivity of the PSA test is reported to be 67.5%–80% (Goolsby, 2001). Approximately 20% of patients with prostate cancer have a PSA value of less than 4 ng/ml, but 75% of men with prostate cancer have an abnormal PSA test (Goolsby). Once individuals are diagnosed with prostate cancer, measurement of PSA levels is useful in determining the success of treatment and can help to detect disease recurrence.

The use of PSA as a screening tool has not been adopted universally by all medical organizations (Canto & Slawin, 2002; Frankel, Smith, Donovan, & Neal, 2003). The American College of Physicians, American College of Preventive Medicine, and U.S. Preventive Services Task Force do not recommend routine screening with PSA. The American Urological Association and American Cancer Society recommend offering annual PSA testing along with digital rectal examination starting at age 50 for all males and at age 45 for African Americans with a significant family history of prostate cancer (American Cancer Society, 2005a; American College of Preventive Medicine, 2001).

Using PSA to monitor the progression of prostate cancer can be controversial because some patients present with biochemical evidence of recurrence without developing metastatic disease (Coldman, Phillips, & Pickles, 2003). In addition, PSA may be unreliable, particularly in patients with poorly differentiated tumors and in patients with early-stage prostate cancer treated with external beam radiation or ultrasound-guided prostate brachytherapy. The latter of the two groups may experience a benign rise of their PSA, a "PSA bounce," that can be misinterpreted as treatment failure (Balmer & Greco, 2004; Sturgeon, 2002).

The U.S. Food and Drug Administration approved the use of percent-free PSA for early detection of prostate cancer (Canto & Slawin, 2002). Percent-free PSA is the portion of the total prostate antigen not bound to protein and, as such, can distinguish prostate cancer from other benign conditions that can cause mild elevations in standard PSA in high-risk patients (Vashi & Oesterling, 1997). The use of percent-free PSA can increase the specificity of serum PSA measurement and reduce unwarranted biopsies in men with a mildly elevated PSA. The prescribed method of interpreting percent-free PSA and PSA has not been been derived; therefore, this practice has not achieved universal acceptance (Vashi & Oesterling).

Bladder Cancer

The use of tumor markers in detecting bladder cancer is not well established and still is under study. Urinary tumor markers are more prominent, with several currently approved by the U.S. Food and Drug Administration and commercially available. The bladder tumor antigen is a qualitative test that identifies a human complement factor H-related protein that is secreted by several human bladder cell lines (Glas et al., 2003). Nuclear matrix protein 22 (NMP22) is a protein that is associated with the nuclear mitotic apparatus and is released during apoptosis (Glas et al.). In healthy individuals, very small amounts of NMP22 should be present in the urine.

False positives can occur with the bladder tumor antigen and NMP22 testing in individuals who recently have undergone an invasive procedure or infection of the genitourinary tract. With the use of NMP22, false positives also may occur in patients who have a benign genitourinary disease or renal

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or bladder stones (Glas et al., 2003). One study examined the use of NMP22 compared to urinary cytology and office cystoscopy as a screening test for bladder cancer (Zippe, Pandrangi, & Agarwal, 1999). The researchers found that the negative predictive value of the test was 100%, meaning that essentially all 18 cancers were detected in a group of 330 screened patients; in addition, no bladder tumors went undetected (Zippe et al.). However, specificity was low (i.e., a high false-positive rate) in the study; further study of both urinary and serum tumor markers as well as identification of epidermal growth factor receptor (EGFR) expression in cells for bladder cancer is ongoing (Gazzaniga et al., 2001). Bladder tumor fibronectin, another urinary tumor marker, also is under study (Mutlu, Turkeri, & Emerk, 2003; Sanchez-Carbayo, Urrutia, Gonzalez de Buitrago, & Navajo, 2000). Additional interest has been generated in the study of telomerase, which is produced by most neoplastic cells but rarely by healthy cells. Telomerase expression may prove to be beneficial in the identification of initial and recurrent bladder cancer (Melissourgos et al., 2003).

Colorectal Cancer

Eighty percent of patients diagnosed with colorectal cancer in the United States will have curative surgery; unfortunately, 40% of those patients will develop incurable recurrence of the disease (Meyerhardt & Mayer, 2003). Therefore, tumor markers have become an integral element of surveillance programs after primary resection to herald the earliest possible recurrence in asymptomatic patients with potentially curable disease (Meyerhardt & Mayer). CEA, an oncofetal protein, is overexpressed in adenocarcinomas, especially colorectal cancer, and is the most established marker for the disease (Fletcher, 1986; Perkins et al., 2003).

The value of CEA testing in patients with a history of colorectal cancer has been studied comprehensively and is based on clinical studies. Meyerhardt amd Mayer (2003) reported that the sensitivity of CEA ranges from 58%–89%, with a specificity of 75%–98%. CEA sensitivity increases with tumor progression and elevates to 50% when the tumor extends to the lymph nodes and 75% with distant metastasis. A CEA level of more than 100 ng/ml generally indicates metastasis (Perkins et al., 2003). After surgical resection, CEA should return to normal within four to six weeks (Perkins et al.).

The specific value of CEA testing remains controversial. Although the lead time from the elevation of CEA to clinical evidence of cancer recurrence is 1.5–6 months, long-term survival after subsequent surgery may not improve (Meyerhardt & Mayer, 2003). However, the 2000 American Society of Clinical Oncology guidelines recommended CEA testing in stage II or III disease every two to three months for two years or more after diagnosis and, if elevated, confirmation by retesting. If elevation of CEA is confirmed, further investigation for metastatic disease is warranted; the guidelines do not advocate initiating therapy solely based on rising CEA (Bast et al., 2001). The European Society for Medical Oncology did not make a specific recommendation regarding postoperative surveillance with serial CEA testing and neither has the Canadian Society of Surgical Oncology or the Canadian Society of Colon and Rectal Surgeons (Meyerhardt & Mayer).

Using CEA to detect colorectal cancer recurrence has several limitations. Approximately 30% of all colorectal cancer recurrences do not produce CEA, and poorly differentiated tumors may have reduced expression of CEA (Canil & Tannock, 2002; Perkins et al., 2003). A preoperative elevation of CEA is predictive of a greater likelihood of cancer recurrence, but a normal CEA level should not preclude continued testing postoperatively because CEA could rise if a patient has metastatic disease (Meyerhardt & Mayer, 2003).

Initially, researchers hoped that CEA would have a role in screening for colorectal cancer; however, the screening tool was proven to be ineffective because of its low sensitivity and specificity (Fletcher, 1986; Perkins et al., 2003). Testing for CEA can be problematic because it is not specific to colorectal cancer and can be elevated when other neoplasms and benign conditions such as peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and cirrhosis are present (Fletcher; Perkins et al.). Even cigarette smoking can elevate CEA falsely, and although levels greater than 10 ng/ml seldom are caused by benign conditions, on occasion, such levels have been observed in the absence of clinical disease. As a result, repeat testing is recommended to confirm an increase in CEA level (Bast et al., 2001; Meyerhardt & Mayer, 2003; Perkins et al.).

In the American Society of Clinical Oncology's 2000 clinical practice guidelines, tumor markers were reviewed for their clinical utility in colorectal cancer; the markers included lipid-associated sialic acid, cancer antigen (CA) 19.9, DNA flow cytometrically derived ploidy, p53, and the *ras* oncogene, but ultimately only CEA was recommended as having shown efficacy in the management of colorectal cancer (Bast et al., 2001). More recently, EGFR has generated a great deal of interest because targeted therapy has been approved for the treatment of colorectal cancer. An estimated 65%–70% of human colon cancers express EGFR, which correlates with more aggressive disease and a poorer prognosis (O'Dwyer & Benson, 2002; Ritter & Arteaga, 2003). The future role of EGFR testing in colorectal cancer has yet to be determined and currently is being evaluated in other cancers (e.g., pancreatic cancer) (Ritter & Arteaga).

Pancreatic Cancer

An estimated 32,180 new cases of pancreatic cancer will be diagnosed in 2005, and the disease continues to be the fourth most-common cause of cancer-related death (American Cancer Society, 2005b). Early symptoms of pancreatic cancer often are nonspecific and vague, thereby delaying diagnosis and increasing the probability of patients presenting with advanced disease. The serum tumor marker CA 19-9 is considered the best tumor marker for pancreatic cancer because of its high sensitivity and specificity (Kim et al., 2004). Although CA 19-9 is detectable in liver, stomach, and colon cancers, it also can be elevated in other nongastrointestinal cancers such as a lung neoplasm (Minghini, Weireter, & Perry, 1998; Perkins et al., 2003). Furthermore, benign conditions can cause elevations in CA 19-9 (e.g., cirrhosis, cholestasis, cholangitis, pancreatitis) (Minghini et al.; Perkins et al.).

CA 19-9 has a reported sensitivity of 70%–90% and specificity of 90% in pancreatic cancer, making it an invaluable tumor marker for the disease (Kim et al., 2004; Perkins et al., 2003). The CA 19-9 level is directly related to tumor burden and the degree of tumor expression; thus, small tumors are not reflected by rising CA 19-9 (Barkin & Goldstein, 2000). The positive predictive value of CA 19-9 is only 0.9% for detecting

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pancreatic cancer in asymptomatic individuals, rendering it ineffective as a screening tool (Barkin & Goldstein; Kim et al.; Perkins et al.). The value of CA 19-9 in the management of pancreatic cancer is in identifying patients with malignancies and unresectable tumors. The positive predictive value is 100% for a malignancy when the CA 19-9 level is 120 U/ml or more; levels greater than 1,000 U/ml indicate advanced pancreatic cancer with low resectability (Barkin & Goldstein). Likewise, a decrease in the CA 19-9 level postoperatively after resection followed by subsequent secondary elevation confirms metastases of a local recurrence (Safi, Schlosser, Falkenreck, & Beger, 1996).

Presently, investigators are determining EGFR's role in pancreatic cancer development. An elevated receptor level has been detected in 90% of human pancreatic cancers. Both K-*ras* and p53 mutations are being investigated actively as diagnostic tools in pancreatic cancer, but their ultimate value has yet to be defined (Xiong & Abbruzzese, 2002).

Breast Cancer

In 2005, in the United States alone, an estimated 211,240 new cases of invasive breast cancer and 58,490 new cases of in situ breast cancer will be diagnosed. More than 40,000 deaths are predicted to occur because of breast cancer, with a five-year survival rate of 98% for localized disease, 80% for regional disease, and 26% for distant metastases. Breast cancer continues to be the second most-common cause of cancer death for women, and the survival rate after diagnosis of the disease continues to decline beyond five years. The five-year survival rate for all stages of breast cancer is 88% and 77% at 10 years (American Cancer Society, 2005b).

Many types of tumor markers are used in breast cancer (e.g., *BRCA1, BRCA2,* p53, Ki-67, BAX, EGFR, pS2, DNA flow cytometry), but addressing each individually is beyond the scope of this article. Instead, this section will focus on the breast cancer tumor markers used most frequently in clinical practice and thus is limited to estrogen receptor (ER) and progesterone receptor (PR) status, HER2/neu, MUC1, CA 15.3, CA 27.29, and CEA. Hormone-responsive breast cancers are determined by the presence of positive ER and PR status. ER status is a prognostic and predictive tumor marker (Yamauchi, Stearns, & Hayes, 2001). Researchers have agreed that ER and PR status should be determined for all primary breast cancers to evaluate patients' candidacy for endocrine therapy and therapy for recurrent or metastatic disease (Bast et al., 2001; Sturgeon, 2002). Approximately 30%–40% of hormone receptor-positive metastases from primary breast cancers do not respond to hormone therapy. Subsequent retesting of ER and PR status may be done in such cases because ER and PR can convert to negative status resulting in poor response to hormone therapy (Kuukasjarvi, Kononen, Helin, Holli, & Isola, 1996; Swain et al., 2004).

HER2/neu, a proto-oncogene, usually is present in two copies in all somatic cells, as well as most breast cancer cells (Thor, 2001). The number of HER2/neu gene copies increases with amplification and protein overexpression in 20%–40% of breast cancers (Thor; Yamauchi et al., 2001). Generally, HER2/neu is used as a predictive tumor marker in breast cancer to help to determine patients' candidacy for treatment with anthracyclines and trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, CA) (Sturgeon, 2002; Thor). The 2000 American Society of Clinical Oncology guidelines support testing for HER2/neu in identifying patients who would benefit from trastuzumab for metastatic, refractory breast cancer (Bast et al., 2001). Commonly in clinical practice, HER2/neu is used to identify patients who may benefit from anthracycline agents, but the use of HER2/neu testing in this manner was not supported by the 2000 National Institutes of Health consensus meeting (Munster & Norton, 2001; Ross & Gray, 2003). The lack of support was the result of several studies conducted by the Cancer and Leukemia Group B protocol 8541 and the National Surgical Adjuvant Breast and Bowel Project that suggested a benefit of treating HER2/neu-positive patients with anthracyclines, but the results did not reach statistical significance (Munster & Norton). Nevertheless, the suggestion of a clinical benefit of treating HER2/neu-positive patients with anthracyclines was the impetus for changing clinical practice (Thor).

The MUC1 serum tumor markers CA 15.3 and CA 27.29 typically are used to detect breast cancer, but only metastatic disease (Sturgeon, 2002). CA 15.3 was one of the first useful tumor markers to correlate with therapeutic response (Cheung, Graves, & Robertson, 2000; Duffy, 1999). CA 15.3 is a mucin and a product of the MUC1 gene, which is a breast cancer-associated antigen (Duffy). MUC1 typically is found in milk-fat globules, but in cancerous conditions, MUC1 mucin is released into the circulation, where it can be measured by immunoassays. The neoplasms will cause deviations in the MUC1 gene, leading to aberrant and upregulated expression, signaling the development of monoclonal antibodies. The altered antibodies then can be identified by the immunoassays for CA 15.3 and CA 27.29 (Cheung et al.).

In breast cancer, CA 15.3 is the most widely used tumor marker and considered the gold standard for the development of newer breast cancer tumor markers (Cheung et al., 2000). CA 15.3 is elevated in approximately 54%–80% of patients with metastatic breast cancer. An elevated CA 15.3 value is not seen exclusively in breast cancer and may be associated with benign conditions such as chronic hepatitis, liver cirrhosis, tuberculosis, sarcoidosis, and systemic lupus erythematosus. Other malignant conditions associated with an elevated CA 15.3 level include lung, ovarian, endometrial, gastrointestinal, and bladder carcinomas (Cheung et al.; Duffy, 1999). The use of CA 27.29 is gaining popularity. Like CA 15.3, CA 27.29 is used to detect metastatic disease; however, the superiority of CA 27.29 to CA 15.3 has yet to be determined (Duffy).

The timing of MUC1 antibody tumor marker testing is crucial because starting a new therapy can influence a patient's results. The phenomenon of a transient tumor marker elevation or "spike" and return to or below baseline can occur in approximately 30% of patients who show a response to therapy. The spike can appear within 30 days after starting a new therapy and last as long as 90 days. To determine a true progression of disease, tumor markers should be retested two to three months after a patient starts treatment or after one and two months of therapy (Cheung et al., 2000).

To improve sensitivity and specificity in the clinical arena, as well as therapeutic response for metastatic disease, an MUC1 tumor marker may be combined with CEA (Cheung et al., 2000). The combination has been shown to be more efficacious than using any single tumor marker because of the heterogeneous nature of breast cancer (Cheung et al.). However, not all investigators agree that tumor markers should be combined to monitor breast cancer. The Standards, Options,

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and Recommendations project guidelines recommended that CEA only be used if CA 15.3 was not elevated at presentation (Sturgeon, 2002).

None of the tumor markers is recommended for breast cancer screening, diagnosis, or staging because of their limited sensitivity for detecting early disease (Bast et al., 2001; Sturgeon, 2002). Currently, among patients with breast cancer post-treatment, the clinical benefit of detecting an elevated tumor marker, which can be elevated five to nine months before clinical diagnosis, is debatable without effective salvage therapy. Earlier detection of recurrence will only herald the event without resulting in a significant clinical outcome for patients (Duffy, 1999; Emens & Davidson, 2003). Nevertheless, American Society of Clinical Oncology guidelines have supported the use of tumor markers to help in identifying breast cancer treatment failure where disease is not measurable (Bast et al.).

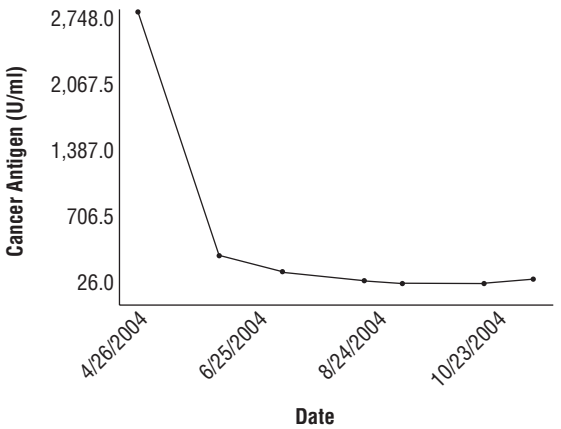
Ovarian Cancer

Ovarian cancer is the leading cause of death for all female cancers of the reproductive system and is estimated as the fourth most-common cause of mortality for women in 2005 (American Cancer Society, 2005b). Seventy-five percent of patients with ovarian cancer present with advanced disease (i.e., stage III and IV), and despite aggressive therapy, 60%–85% experience a recurrence. The amount of residual disease present after initial debulking surgery is directly related to survival rates; the five-year survival rates for stage III and IV are 20%–50% and 5%–20%, respectively (Vaidya & Curtin, 2003).

The serum tumor marker CA 125, a large glycoprotein, is the best and most widely researched marker for ovarian cancer (Guppy & Rustin, 2002; Sturgeon, 2002; Vaidya & Curtin, 2003). CA 125 is present throughout the reproductive system and is found in healthy ovarian tissue and on the epithelium of the endometrium, the endocervix, and fallopian tubes, as well as the mesothelial cells of the pleura, peritoneum, and pericardium (Guppy & Rustin; Vaidya & Curtin). CA 125 can be elevated in more than 90% of women with advanced ovarian cancer and in 40% of patients with any primary cancer with extensive intra-abdominal disease (Guppy & Rustin). The increase can be directly related to tissue destruction, inflammation, and vascular invasion (Guppy & Rustin). Because CA 125 is associated with inflammatory cells, the antigen often can be elevated in peritonitis, endometriosis, and nonmalignant ascites, as well as other benign conditions, including menstruation and pregnancy (Guppy & Rustin; Vaidya & Curtin).

Surgery and chemotherapy remain the treatments of choice for epithelial ovarian cancer, and disease monitoring is needed to determine a patient's response to chemotherapy treatment. Using traditional diagnostic imaging is difficult because microscopic disease is undetectable. CA 125 is a valid and effective tool for monitoring treatment response and has become a cornerstone in the management of ovarian cancer (Guppy & Rustin, 2002) (see Figure 3). As much as 80% concordance exists with the CA 125 level and clinical course of patients undergoing treatment for ovarian cancer (Vaidya & Curtin, 2003).

In approximately 70% of patients, rising CA 125 may be the first indication of relapse (Guppy & Rustin, 2002; Vaidya & Curtin, 2003). CA 125 elevation can occur in an asymptomatic patient one to six months before becoming clinically



Case Study
In April 2004, a 49-year-old female was diagnosed with primary peritoneal papillary serous carcinoma and underwent surgical resection to remove a 10 x 16 cm mass in her pelvis. She was started on carboplatin and paclitaxel every three weeks for a total of six cycles. The serial cancer antigen 125 shows a decline after optimal debulking surgery and then returns to a normal range after the fourth cycle of chemotherapy, indicating a good response to therapy.

Figure 3. The Use of Cancer Antigen 125 Values to Monitor Ovarian Cancer

evident (Guppy & Rustin; Vaidya & Curtin). A serial decrease in CA 125 levels has been associated with response to treatment (Guppy & Rustin). Disease progression can be defined as a doubling from nadir or a doubling from a persistently high level despite chemotherapy (Guppy & Rustin; Vaidya & Curtin). In a study of 225 patients, a doubling of CA 125 above the upper normal limits after initial chemotherapy had a sensitivity of 86% and a specificity of 91% for disease progression (Vaidya & Curtin). The Standards, Options, and Recommendations project guidelines have suggested remeasuring the CA 125 level after two to three weeks if it was previously normal to confirm the increase and calculate doubling (Sturgeon, 2002). A 25% or greater rise in CA 125 in three serial samples is almost 100% specific for disease progression, after which additional evaluation is needed and a computed tomography scan should be performed (Guppy & Rustin; Sturgeon).

Timing the measurement of CA 125 is critical because the antigen can be elevated after surgery or paracentesis (Guppy & Rustin, 2002). The half-life of CA 125 is approximately six days, with an expected decline for three to six weeks (Guppy & Rustin). Currently, no evidence supports early intervention solely based on rising CA 125 because the level will not improve the survival of relapsed patients (Guppy & Rustin; Sturgeon, 2002). Although a normal CA 125 level can be reassuring, it cannot exclude the presence of a tumor (Guppy & Rustin; Vaidya & Curtin, 2003).

CA 125 does not have a role in ovarian cancer screening or diagnosis because of its low sensitivity and specificity (Sturgeon, 2002). The prognostic value of CA 125 following surgery and during chemotherapy has been established in various trials but currently has not been adopted as part of the tumor-node-metastasis staging system (Sturgeon). Other tumor markers have been investigated for use in ovarian cancer, but none has achieved practical clinical application. Many

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of the promising tumor markers have demonstrated potential, but only in small studies, and active investigation is being conducted on BCL-2, BAX, p53, Ki67, lysophosphatidic acid, macrophage colony-stimulator factor, OVX-1, and EGFR (Alper et al., 2001; Camilleri-Broet et al., 2004; Hensley, Castiel, & Robson, 2001).

Lung Cancer

The use of tumor markers in lung cancer is not yet well defined in clinical practice and may be seen most frequently in trial settings. Lung cancer still is diagnosed in advanced stages in 50%–70% of patients, and the disease accounts for approximately 29% of all cancer mortalities in the United States (American Cancer Society, 2005b; Kulpa, Wojcik, Reinfuss, & Kolodziejski, 2002; Ma et al., 2003). Tumor marker use for diagnosis, follow-up, and treatment for lung cancer in general is intriguing; however, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are two distinctly different disease entities.

NSCLC includes three types of lung cancer: adenocarcinoma, squamous cell carcinoma, and large cell cancer (Satoh et al., 2002). SCLC is an aggressive form of the disease with a poor survival rate (Ma et al., 2003). Researchers have identified serum neuron-specific enolase as a tumor marker in SCLC, although elevated levels of the marker have been found in some patients with NSCLC (Ferrigno, Buccheri, & Giordano, 2003; Satoh et al.). In fact, one study reported that neuron-specific enolase was a predictor of survival among patients with NSCLC after the sample population (N = 448) had significantly shorter survival times when the value was elevated along with CEA (Ferrigno et al.). Increased CEA levels have been established as a marker of the presence of distant metastases (Kulpa et al., 2002); however, serum CEA levels are not very sensitive for the initial diagnosis of lung cancer, which affects its value in the clinical arena (Seidler, Conrad, Katipamula, & Mahmood, 2003). CYFRA 21.1 (serum-soluble fragments of cytokeratin 19) and CA 125 have been found to be elevated in patients with NSCLC and may function as independent prognostic factors of significance (Lamerz et al., 1999). Additionally, HER2/neu, EGFR, and cyclooxygenase-2 are being studied for use in NSCLC. NSCLC tumors expressing HER2/neu and EGFR had a poor prognosis, but adjuvant treatment with HER2/neu antagonists may be another option for patients (Brattstrom et al., 2004).

Patients with lung cancer have a poor prognosis in general, and the use of tumor markers for these patients is controversial. Because the tumor markers in lung cancer are not very specific, their use in screening is not helpful.

Future Development of Tumor Markers

In recent years, remarkable progress in molecular biology and biotechnology has enabled further delineation of fundamental tumor processes, leading to new tumor marker discoveries. The discoveries have resulted from the sequencing of the human genome and have led to the development of new disciplines in scientific research in tumor marker development such as proteomics and DNA microarray technologies.

Proteomics technology is a rapidly growing field that allows simultaneous analysis of multiple protein patterns in blood or tissue and the promise of discovery for new diagnostic and prognostic markers for a multitude of cancers (Petricoin & Liotta, 2002; Touchette, 2003). OvaCheck™, a proteomic test developed by Correlogic Systems, Inc., of Bethesda, MD, for ovarian cancer screening, currently is awaiting approval from the U.S. Food and Drug Administration (Correlogic Systems, Inc., 2005; Pollack, 2004). Investigators were able to identify a proteomics pattern, a distribution of key proteins or peptides, that distinguished women with ovarian cancer from those without it. The sensitivity and specificity of OvaCheck were reported as 100% and 95%, respectively, with a positive predictive value of 94% (Petricoin et al., 2002). Although OvaCheck has been generating great public interest, it also has been met with controversy concerning its validity (Pollack). Since the mid-1990s, approximately 10 proteomic-based tests have received approval from the U.S. Food and Drug Administration, including NMP22 for bladder cancer screening (Pollack).

Traditional methods in molecular biology generally focus on a single gene in a single experiment, which results in limited information. DNA microarray has the potential to study the entire genome, allowing investigators to monitor interactions among thousands of genes simultaneously (Shi, 2002). The application of DNA microarray in the oncology arena has improved prognostic accuracy and prediction of therapeutic outcomes, resulted in a better understanding of the mechanisms of drug resistance, and perhaps identified new therapeutic targets. For example, using complementary DNA microarray analysis, scientists were able to discover two distinct types of diffuse large B-cell lymphomas and determine prognosis by gene-expression profiling (Alizadeh et al., 2000).

Microarray technology has emerged as a powerful tool to study genomics, but it is not without challenges and concerns, particularly variability issues among testing instruments and methods. Although many challenges remain regarding the use of array-based technology in routine clinical practice, the technology, along with the aid of bioinformatics, holds great promise in breakthrough biomarkers for clinical utility (Mohr, Leikauf, Keith, & Rihn, 2002).

Nursing Implications

Oncology nurses need to be familiar with tumor markers to educate patients about their purpose and explain how therapies are chosen based on their results. Patients may become anxious about their tumor marker results, especially if the results do not change the treatment plan; therefore, alleviating fears should be a primary concern. According to Guppy and Rustin (2002), patients can experience "CA 125 psychosis," resulting from the extreme distress from routine CA 125 monitoring. A similar term, "PSAdynia," was coined for patients in emotional or physical distress caused by fear of elevated PSA (Canil & Tannock, 2002). To ease distress, oncology nurses should be able to interpret tumor marker results using the most current knowledge available while recognizing that tumor marker values and their significance constantly are changing with technology. Should a tumor marker indicate a new cancer or cancer recurrence, oncology nurses must be prepared to offer support, consultation, and referral services. Although the focus of this article was to describe the most commonly used tumor markers, oncology nurses must continue to seek information about many other

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tumor markers not presented here, such as β²-microglobulin, calcitonin, CA 50, thyroglobulin, TA-90, S-100, and interleukin-2.

Conclusion

The diagnosis of cancer continues to be essentially based on a comprehensive patient history, physical examination, and appropriate diagnostic studies. Ideally, tumor markers should be highly sensitive and specific for detecting cancer, but, in reality, markers may be elevated for a number of benign conditions (Perkins et al., 2003; Seleznick, 1992). Cell lysis resulting from effective therapy is one of several theories proposed as the cause of a benign increase of a tumor marker value (Perkins et al.). Although several medical societies have defined how to confirm a rising tumor marker from disease, the issue of when to retreat a patient with an elevated marker is not standard and remains controversial. As such, tumor markers should be used only when a significant therapy is available to improve a patient's outcome or quality of life or lower the cost of care (Perkins et al.; Schrohl et al., 2003).

With the explosion of new technologies, tumor markers' utility in cancer management will continue to grow. As new targeted drug therapies are applied to clinical practice, the use of tumor markers to determine predictive outcomes has become a reality. HER2/neu testing has become routine before treatment with trastuzumab, and with the release of cetuximab (Erbitux™, Bristol-Myers Squibb, Princeton, NJ), EGFR testing is likely to become a new standard of practice because it is required prior to initiation of therapy with the drug.

The molecular diagnostic industry has been projected to grow approximately 25% every year (Ross & Gray, 2003). The industry already accounts for more than $3 billion annually and is expected to revolutionize drug discovery and customize targeted therapeutics into clinical practice through the early 2010s (Ross & Gray). In fact, the Division of Clinical Laboratory Devices, a branch of the U.S. Food and Drug Administration, annually reviews 10–20 tumor marker applications (Gutman, 2002). Healthcare providers are practicing in an exciting era, with the possibility of truly individualized medical care and better outcomes for patients with cancer on the horizon.

Author Contact: Deanna Sanchez Yamamoto, RN, MS, CS, ANP, AOCNP, can be reached at deanna.yamamoto@hhs.co.santa-clara.ca.us, with copy to editor at rose_mary@earthlink.net.

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