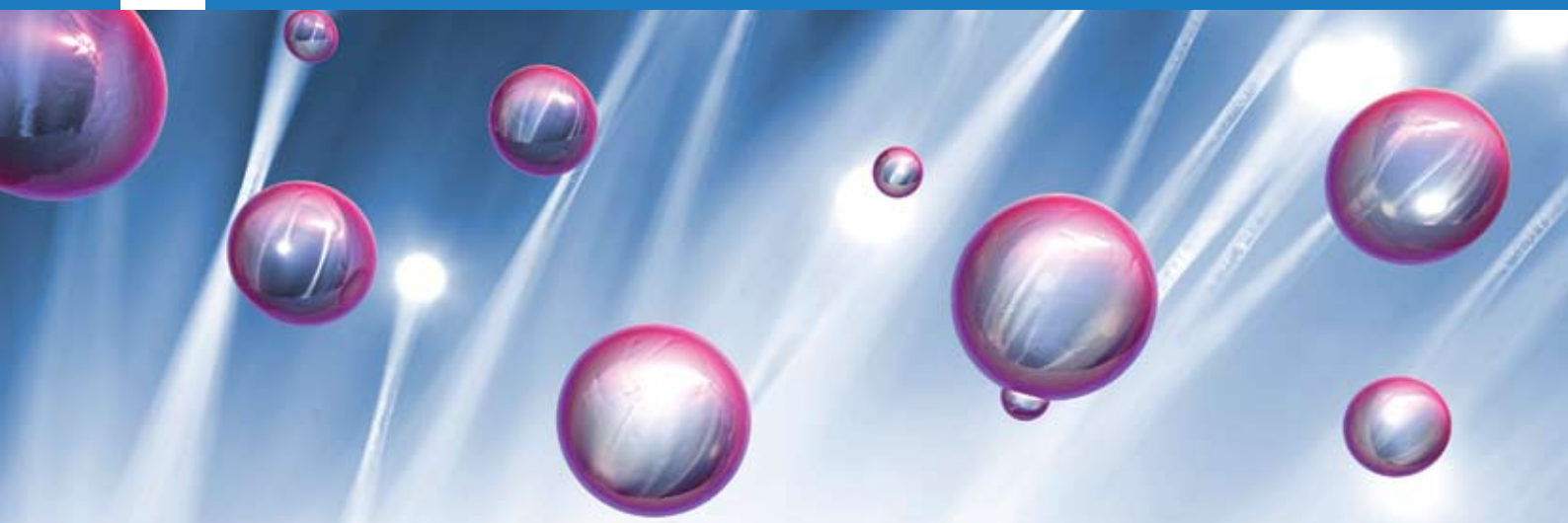


Appropriate use of **tumour markers**

www.bpac.org.nz keyword: tumour-markers

Key messages:

- Tumour markers have a limited role in primary care
- For tumour markers to provide useful information, it is important that they are requested appropriately
- Tumour markers are not indicated as screening tests in primary care
- The key role for individual tumour markers is in the management of patients with established malignancy

The term "tumour marker" embraces a spectrum of molecules with widely divergent characteristics sharing an association with the clinical detection, management, and prognosis of cancer patients.[1]

In most cases, the key role for individual tumour markers is in the management of patients with established malignancy. Nearly all markers show some correlation with the clinical course of disease, with marker elevation in any stage declining to normal after a curative intervention.

The ideal tumour marker would be a "test for cancer" that was easily and reproducibly measured, in which a positive result would occur only in patients with malignancy and quantitative levels would correlate with stage and response to treatment. Unfortunately, no tumour marker currently available meets this ideal.

Table 1 provides an overview of commonly requested tumour markers.

Table 1: Common tumour markers (adapted from[2])

Tumour Marker	Description
Alpha-fetoprotein (AFP)	May be raised in various cancers (liver, germ cell testicular cancers, bowel, stomach, lung, breast, lymphoma) as well as non-cancerous conditions (e.g. chronic hepatitis, cirrhosis)
Beta-human chorionic gonadotropin (ß-HCG)	Is produced during pregnancy but also occurs in cancers originating in the placenta (trophoblastic disease), germ cell tumours of the ovary and in men with germ cell testicular cancer.
Carbohydrate antigen 125 (CA 125)	May be raised in a variety of gynaecological conditions (e.g. menstruation, pregnancy, benign ovarian cysts, endometriosis) as well as ovarian cancer.
Carbohydrate antigen 19-9 (CA 19-9)	May be raised in cancers of the digestive tract (stomach and bowel), and particularly in pancreatic cancer.
Carbohydrate antigen 15-3 (CA 15-3)	May be raised in people with breast cancer but also in non-cancerous condition (e.g. cirrhosis, benign diseases of ovaries and breast)
Carcinoembryonic antigen (CEA)	May be raised with cancer of the colon but also in patients with other cancers (lung, breast, liver, pancreas, thyroid, stomach and ovary) or non-cancerous conditions (e.g. ulcerative colitis, smoking)
Lactate dehydrogenase (LD)	Levels can be raised for a variety of reasons where cellular destruction is present (e.g. lymphoma, pancreatitis, liver and kidney disease)

Tumour markers make poor screening tests

Tumour markers are not recommended for screening asymptomatic patients for malignancy because they generally:

- Lack specificity – many patients may have an elevated result due to benign disease
- Lack sensitivity – many patients with malignancy will have a normal result

An inappropriately ordered test that returns an elevated result, can lead to a cascade of unnecessary investigations, whereas a negative result may give false reassurance.

There is evidence that tumour markers are not always requested appropriately.[3] A 12 month study of tumour marker requesting,[4] found that in the majority of instances, tumour markers were being inappropriately requested as screening or diagnostic tests. In addition, approximately 20% of all requests for CA 125 and CA 15-3 (both usually indicated only in women) were requested in men.

Tumour markers in ovarian cancer

In New Zealand, ovarian cancer is the fourth highest cause of cancer death in women. In 2004, the death rate was 5.4 per 100,000 of the female population. The mortality rate for Māori women was estimated at 8.5 per 100,000.[5]

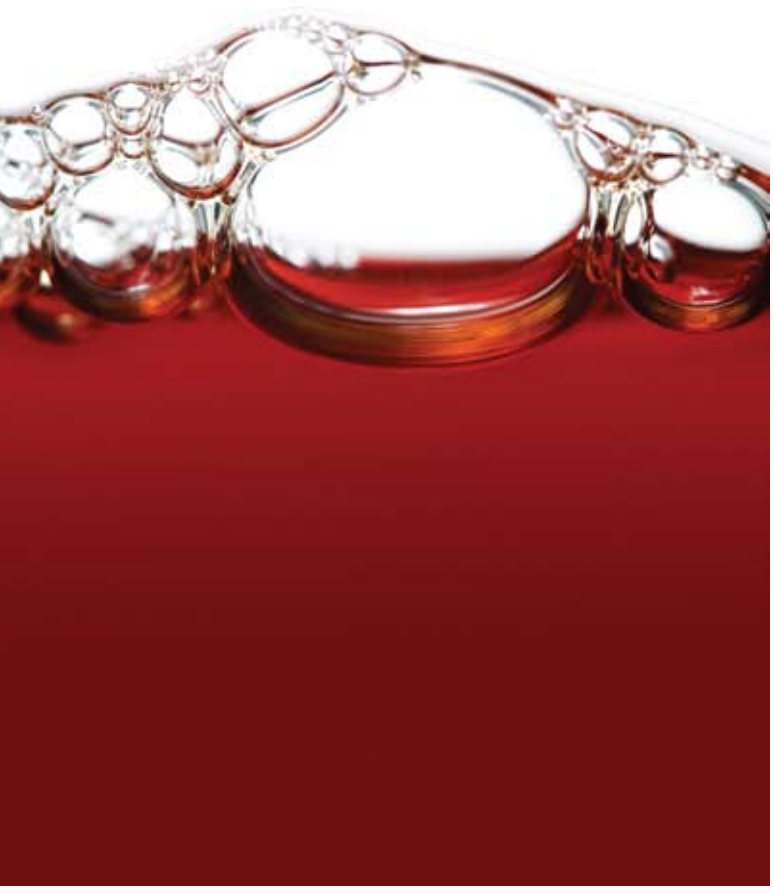
Although CA 125 is frequently requested when investigating suspected ovarian cancer, its main role is for the management of ovarian cancer in secondary care. Because CA 125 is not recommended for screening or diagnosis its role in primary care is limited.

The most common ovarian cancer is serous epithelial cancer but CA 125 is not a useful screening test for this type of cancer because it has poor sensitivity, particularly in early stage disease. Although CA 125 is usually positive

CA 125 may be elevated by a range of other conditions[6]

CA 125 is nonspecific, meaning it may be elevated for a wide range of conditions other than ovarian cancer. Because these conditions occur more frequently than ovarian cancer, a raised CA 125 is more likely to be the result of one of these conditions than ovarian cancer:

- Menstruation
- First-trimester pregnancy
- Benign ovarian cysts
- PID and salpingitis
- Cirrhosis, ascites
- Peritoneal inflammation of any cause
- Pleuritis/pericarditis
- Renal failure
- Endometriosis



at late stages, it will not be elevated in at least 20% of patients with advanced disease.

In addition, most women under 40 years of age with ovarian cancer, have a non-serous type, which does not typically produce CA 125.[6] Therefore a "normal" result can be falsely reassuring.

In rare situations, CA 125 may be used to help distinguish benign from malignant disease, particularly in post-menopausal women, presenting with pelvic masses or in women from families where hereditary ovarian cancer exists. In these situations, it is recommended that CA 125 be performed in conjunction with transvaginal ultrasound.

CA 125 is best used in the monitoring of patients undertaking a course of chemotherapy for epithelial serous ovarian cancer. Serial CA 125 levels have the potential to detect recurrent disease earlier and more cost effectively than radiological procedures. CA 125 levels after chemotherapy are one of the strongest available indicators of disease outcome. Testing frequency will normally be determined by secondary care, with the first sample usually taken within 2 weeks prior to treatment. Patients are frequently monitored every 3–4 months for a number of years.

Tumour markers other than CA 125: New ovarian cancer markers offer promise, however, their contribution to the current standard of care is presently limited and further investigations in large properly designed clinical trials are needed.

Tumour Markers in Colorectal Cancer

In New Zealand, cancer of the colorectum and anus are the most frequently diagnosed cancers, and the third highest cause of cancer death.[5]

Carcinoembryonic antigen (CEA) is the tumour marker most commonly used in management of colorectal cancer. Production of CEA commences during foetal development and it is found in low levels in healthy adults. Colorectal cancer may increase CEA levels, however it is non-specific for this condition and may often be elevated in individuals with gastric, pancreatic, lung, breast and medullar thyroid cancer. In addition it may be elevated in a number of non-cancerous conditions including ulcerative colitis, pancreatitis and cirrhosis, and in people who smoke.

CEA is not recommended as a screening or diagnostic test for colorectal cancer due to its poor sensitivity and specificity, as well as the low prevalence of colorectal cancer in asymptomatic people.[7]

In general, the main application of CEA is for monitoring patients with previously diagnosed colorectal cancer. Testing frequency will normally be determined by secondary care and monitoring may be continued for at least 3 years after diagnosis. CEA may give independent prognostic information that may help with surgical management and provide a baseline level for subsequent determinations.

Tumour markers in testicular cancer

Testicular cancer is one of the more common cancers in young male patients although as a proportion of all cancer types it is relatively uncommon, representing about 1.7% of all cancer registrations. Testicular cancer is two to three times more likely to affect men aged 15–35 years, than it is to affect older men.[5]

Although large numbers of serum markers have been studied, only HCG, alpha fetoprotein (AFP) and lactate dehydrogenase (LD) have been shown to provide independent diagnostic and prognostic value.

About 95% of testicular cancers originate in primordial germ cells and rarely from extra-gonadal sites. Germ cell tumours are classified as seminomas (40%), non-seminoma tumours (40%) and "mixed" germ cell tumours (20%).[8]

Most non-seminomatous tumours have elevated levels of one or more of AFP, HCG and LD, while only hCG and LD are useful markers in seminoma.

Diagnosis of testicular cancer is usually made on clinical signs and symptoms. Investigations include ultrasound and CT scan. Although it is recommended that all patients have AFP, HCG and LD determined prior to the initiation of any therapy.[8]

If AFP or HCG is elevated before therapy, the rate of marker decline reflects the response to therapy. Persistent elevation after chemotherapy indicates residual disease, the need for further therapy and is associated with an adverse prognosis.

CA 19-9 and CA 15-3

CA19-9 is a tumour marker elevated in about 30% of cases of gastric and colon cancer and approximately 80% of cases of pancreatic cancer. It has been proposed as a way to differentiate benign from malignant pancreatic disease, but this capability remains to be established.[9] It has no value for population screening for malignancy and should not be requested for this; the only recognised use is for monitoring known malignancy.

CA 15-3 may be elevated in patients with breast cancer but lacks sensitivity for early disease and has no role in screening or diagnosis. Besides breast cancer, other non-cancerous conditions (e.g. cirrhosis, benign diseases of ovaries and breast) are known to cause elevated levels.[10] CA 15-3 may have a role in monitoring for recurrence or for checking effectiveness of treatment in patients with metastatic disease but there is no high quality evidence of usefulness and it should not be used alone for these purposes.

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Case report

How tumour marker tests can be non-specific

Hypothyroidism mimicking intra-abdominal malignancy[11]

A 74 year old woman was admitted as an emergency with suspected pelvic malignancy.

The presenting features included cachexia, anorexia and ascites. Vital signs were normal. Examination revealed bilateral pleural effusions but no abdominal masses were palpable. Diagnostic and therapeutic paracentesis revealed an exudate (protein 37 g/L) however there were no malignant cells present.

Investigations showed an extremely elevated serum CA 125 level of 1059 U/mL (< 37). CA 19-9, CA 15-3, CEA, and AFP were all normal. At this stage the patient was strongly suspected to have ovarian carcinoma or disseminated peritoneal metastases from an unknown primary tumour.

CT of the abdomen showed extensive ascites but no obvious abdominal or pelvic mass. A diagnostic laparoscopy showed no evidence of intraperitoneal malignancy. Mammography and oral gastroduodenoscopy also gave normal results.

Although the patient was not clinically overtly hypothyroid, thyroid function tests were performed because of hoarse voice and dry skin. These revealed severe primary hypothyroidism with a serum thyroid stimulating hormone level of 73 mU/L (0.2 to 5.7). Over the next 8 weeks, the patient's condition gradually improved with restoration of the euthyroid state.

Discussion

Ascites is a well known but uncommon feature of hypothyroidism and occurs in about 4% of patients. It is thought that the extremely high CA 125 concentrations in myxoedema ascites are due to peritoneal irritation caused by the presence of ascitic fluid. Others have reported that patients with ascites who have benign conditions such as nephrotic syndrome, cirrhosis, tuberculous peritonitis, renal failure, and pancreatitis may sometimes have CA 125 concentrations as high as those seen in ovarian carcinoma. In addition, mildly increased CA 125 concentrations have been reported in women with hypothyroidism.

This case report demonstrates that although a CA 125 test was not an inappropriate test in a 74 year old lady with cachexia and ascites (as this is a high risk group of ovarian cancer) that the focus should not solely be on ovarian cancer as the only possible cause due to the low specificity of the CA 125 test. In this case, the CA 125 was elevated for reasons other than ovarian cancer.

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