

# Tumour Markers

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## What are Tumour Markers?

Tumour markers are substances that can be found in the body when cancer is present. They are usually found in the blood or urine. They can be products of cancer cells or of the body in response to cancer. Most tumour markers are proteins.

For many reasons, tumour marker itself is usually **not** enough to diagnose or rule out cancer. Most tumour markers can also be made by normal cells as well as by cancer cells. Sometimes, non-cancerous conditions can also cause elevation of some tumour markers to be higher than normal. Besides, not every cancer patient may have raised level of a tumour marker. For these reasons, only a **handful** of tumour markers are commonly used by most doctors.

## How Are Tumour Markers Used?

### (I) For Screening and Early Detection of Cancer

Screening refers to looking for cancer in people who have no symptoms of the disease, while early detection is finding cancer at an early stage. Although tumour markers were first developed to test for cancer in people without symptoms, **very few** tumour markers have been found to be helpful in this way because most tumour markers have not been shown to detect cancer much earlier than they would have been found otherwise.

### (II) Diagnosing Cancer

In most cases, cancer can only be diagnosed by a biopsy and tumour markers are usually not used to diagnose cancer. However tumour markers can help determine if a cancer is likely in some patients. It can also help diagnose the origin of the cancer in patients presenting with advanced widespread disease.

### (III) Determining the Prognosis (Outlook) for Certain Cancers

Some newer tumour markers help to assess how aggressive a cancer is likely to be or even how well it might respond to certain drugs.

### (IV) Determining the Effectiveness of Cancer Treatment

One of the most important uses for tumour markers is to monitor patients being treated for cancer. If the initially raised tumour marker level goes down with treatment, it indicates that the treatment is working and is having a beneficial effect. On the other hand, if the marker level goes up, then the treatment is probably not working and change of treatment should be considered.

### (V) Detecting Recurrent Cancer

Markers are also used to detect cancers that recur after initial treatment. Some tumour markers can be useful once treatment has been completed and with no evidence of residual cancer left. These include PSA (for prostate cancer), HCG (for gestational trophoblastic tumours & germ cell tumours of ovaries & testicles), and CA 125 (for epithelial ovarian cancer).

# Tumour Markers In Use:

Tumour Marker	Comments
<b>Alpha-fetoprotein (AFP)</b>	<ul style="list-style-type: none"> <li>• AFP is elevated in hepatocellular carcinoma of liver and is useful to monitor response to treatment.</li> <li>• AFP is also elevated in certain testicular cancers (embryonal cell &amp; endodermal sinus types).</li> </ul>
<b>Beta-2 microglobulin (B2M)</b>	<ul style="list-style-type: none"> <li>• Elevated in multiple myeloma, chronic lymphocytic leukaemia &amp; some lymphomas.</li> <li>• Patients with higher levels of B2M usually have a worse prognosis.</li> <li>• Beta-2 microglobulin is often elevated in chronic renal failure and dialysis patients without cancer.</li> </ul>
<b>Bladder tumour antigen (BTA)</b>	<ul style="list-style-type: none"> <li>• BTA is found in urine of many bladder cancer patients.</li> <li>• Test results are reported as either positive (BTA present) or negative (BTA not present).</li> <li>• It can be used together with NMP22 (see below) to detect recurrent tumour.</li> <li>• This test is not widely used and is still being studied.</li> <li>• It is not certain whether it is as sensitive as cystoscopy for diagnosis &amp; follow-up.</li> </ul>
<b>CA15-3</b>	<ul style="list-style-type: none"> <li>• CA 15-3 can be used to monitor breast cancer patients.</li> <li>• Elevated blood levels are found in &lt;10% of patients with early disease and in about 70% of patients with advanced disease.</li> <li>• CA 15-3 levels usually drop following effective treatment.</li> <li>• But CA 15-3 can also be elevated in other cancers &amp; in some non-cancerous conditions such as benign breast conditions &amp; hepatitis.</li> </ul>
<b>CA27.29</b>	<ul style="list-style-type: none"> <li>• CA 27.29 is another marker to monitor breast cancer patients.</li> <li>• This test measures the same marker as CA 15-3 but in a different way &amp; does not appear to be any better in detecting early or advanced disease.</li> <li>• It can also be raised in other cancers and in some non-cancerous conditions.</li> </ul>
<b>CA125</b>	<ul style="list-style-type: none"> <li>• CA 125 is the standard tumour marker to follow patients with epithelial ovarian cancer during or after treatment.</li> <li>• &gt;90% of patients with advanced ovarian cancer have elevated CA 125.</li> <li>• Because about half of ovarian cancer patients with elevated CA 125 still have tumour confined to the ovary, CA 125 is being studied as screening test for ovarian cancer (See next section for details).</li> <li>• CA 125 can also be raised in patients with endometrial and pancreatic cancer as well as in benign conditions such as endometriosis, pelvic inflammatory disease and benign ovarian cysts.</li> </ul>

### CA72-4

- CA 72-4 is a newer test being studied in ovarian, pancreatic and stomach cancer.
- Studies of this marker are still in progress.

### CA19-9

- CA 19-9 is considered the best tumour marker for following patients with pancreatic cancer.
- A high level in a newly diagnosed patient usually means advanced disease.
- CA 19-9 is not used as a screening test because usually it will not detect early disease.
- CA 19-9 may also be used to monitor colorectal cancer, but because it is less sensitive than CEA test, most would recommend CEA .
- CA 19-9 can also be raised in other cancers such as stomach and bile ducts cancer and in some non-cancerous conditions such as pancreatitis.

### Calcitonin

- Calcitonin is a hormone secreted by parafollicular C cells of thyroid.
- In patients with cancer of parafollicular C cells of thyroid called medullary thyroid carcinoma (MTC), blood levels of calcitonin are raised.
- Calcitonin is one of the rare tumour markers that can be used to detect early cancer: because MTC is often inherited, measurement of blood calcitonin level can be used to detect cancer at its earliest stages in family members at risk.

### Carcinoembryonic antigen (CEA)

- CEA is the preferred tumour marker to monitor patients with colorectal cancer during treatment, but it is not useful as a screening or diagnostic test.
- The higher the CEA level at time of diagnosis, the more likely it is that the disease is advanced.
- CEA can also be raised in cancer of lung, breast, thyroid, pancreas, liver, stomach, ovary and bladder.
- It can also be elevated in non-cancerous diseases and in chronic smokers.

### Chromogranin A (CgA)

- Blood level of CgA is raised in patients with neuroendocrine tumours such as carcinoid tumours, neuroblastoma, small cell lung cancer and some rare cases of prostate cancer that have neuroendocrine features.
- CgA is probably the most sensitive tumour marker for carcinoid tumours: level raised in 1/3 of patients with localized disease and 2/3 with metastatic disease.

### Estrogen / Progesterone receptors

- Breast tumour samples (not blood samples) from patients with breast cancer are tested for these markers.

### HER2 (Human Epidermal Growth Factor receptor, also known as EGFR 2)

- About 25% of patients with breast cancer have tumours that overexpress HER2, which is associated with aggressive disease, poor clinical outcomes and shortened overall survival.
- Samples of tumour tissue (not blood sample) are used to test for HER2 status.

### **Human chorionic gonadotrophin (HCG, also known as beta-HCG)**

- HCG blood levels are elevated in patients with some types of testicular & ovarian cancers (germ cell tumours), gestational trophoblastic disease, (mainly choriocarcinoma), mediastinal germ cell tumour.
- Serum HCG level can be used to help diagnose these tumours, monitor response to treatment and detect recurrence.

### **Immunoglobulins**

- Immunoglobulins are not really tumour markers but antibodies produced by immune system.
- Patients with myeloma or macroglobulinaemia classically have a very high level of one specific (monoclonal) immunoglobulin.

### **Lipid associated sialic acid in (LASA-P)**

- LASA-P has been studied as a marker for ovarian and some other cancers.
- But it is not specific for any particular cancer or even for cancer in general, as it can be raised in some non-cancerous conditions.
- Thus it has been replaced by other more specific tumour markers.

### **Neuron -specific enolase (NSE)**

- NSE, like Chromogranin (CgA), is a marker for neuroendocrine tumours such as small cell lung cancer, neuroblastoma and carcinoid tumours.
- NSE is more useful in follow-up of patients with small cell lung cancer or neuroblastoma, while CgA seems to be a better marker for carcinoid tumours.
- NSE is not used as a screening test.
- Elevated level can also be found in some non-neuroendocrine cancers.

### **NMP22**

- NMP22 is a protein found in nucleus of cells.
- Levels of NMP 22 are often raised in urine of patients with bladder cancer.
- So far, it has not been shown to be sensitive enough for screening purpose.
- It can be used to look for recurrence after treatment, but it is not sure whether NMP 22 monitoring is as accurate as cystoscopy and thus is not widely used.

### **Prostate-specific antigen (PSA)**

- PSA is a tumour marker for prostate cancer.
- It is the only marker used to screen for a common type of cancer: prostate cancer (although some medical groups do not recommend its use).
- For details, please refer to Prostate Cancer Screening Guideline.
- Apart from prostate cancer, PSA level can also be raised in patients with benign prostatic hyperplasia, elderly men and those with larger prostates.

### **Prostatic acid phosphatase (PAP)**

- PAP is another test for prostate cancer which was used before PSA test was developed.
- It is rarely used now because PSA is much more sensitive.

### Prostate cancer antigen 3 gene (PCA 3)

- Prostate Cancer Antigen 3 gene (PCA3) is a new gene-based test carried out on a urine sample.
- PCA3 is highly specific to Prostate cancer and in contrast to PSA, is not increased by conditions such as benign enlargement or inflammation of the prostate.
- PCA3 gene testing holds potential in men with elevated PSA levels but no cancer on initial biopsy.
- PCA3 urine test can provide additional information that help to decide whether a new biopsy is really needed.
- The probability of a positive repeat biopsy increases with rising PCA3 scores. The higher the PCA3 score, the greater was the probability of a positive repeat biopsy.

### Prostate-specific membrane antigen (PSMA)

- PSMA is a substance found in all prostate cells.
- Blood levels increase with age and with prostate cancer.
- PSMA is a very sensitive marker, but so far it has not been proven to be better than PSA.
- Its current use is limited to being part of a nuclear scan to look for spread of prostate cancer in the body.

### S-100

- S-100 is a protein found in most melanoma cells.
- Tissue samples of suspected melanoma are often tested for this marker to aid diagnosis.
- Some studies have shown that blood levels of S-100 are raised in most patients with metastatic melanoma.
- Thus this test is sometimes used to look for spread of melanoma before, during or after treatment.

### TA-90

- TA-90 is a protein found on surface of melanoma cells.
- Like S-100, serum level of TA-90 can be used to look for spread of melanoma.
- Its role in monitoring melanoma is being studied and it is not widely used at present.

### Thyroglobulin

- Thyroglobulin is a protein made by thyroid gland.
- Thyroglobulin levels are raised in many thyroid diseases, including some common forms of thyroid cancer.
- After complete & successful treatment of thyroid cancer, serum thyroglobulin level should fall to undetectable levels. A subsequent rise may suggest that the tumour have recurred.
- In patients with metastatic thyroid cancer, thyroglobulin levels can be used to evaluate the results of treatment over time.

### Tissue polypeptide antigen (TPA)

- TPA is a protein marker that is present in high levels in many rapidly dividing cells (including cancer cells).
- TPA blood test is sometimes used together with other tumour markers to help follow up patients being treated for lung, bladder and many cancers.
- TPA levels are also raised in some non-cancerous conditions.

# Common Cancers and Associated Tumour Markers Used for Early Detection / Follow-up / Screening

Cancer	Comments
<b>Bladder Cancer</b>	<ul style="list-style-type: none"> <li>• At present, no urinary tumour markers are recommended for bladder cancer screening.</li> <li>• Bladder tumour antigen (BTA) &amp; NMP22 can be used along with cystoscopy for diagnosis and follow-up although cystoscopy &amp; urine cytology are still considered the current standard.</li> </ul>
<b>Breast Cancer</b>	<ul style="list-style-type: none"> <li>• At present, no tumour marker has been found to be useful for screening or for diagnosis of early stage breast cancer.</li> <li>• At the time of diagnosis, breast cancer tissue should be tested for estrogen &amp; progesterone receptors, as well as HER2 antigen. These markers provide information on how aggressive the cancer can be &amp; how likely it will respond to certain treatments.</li> <li>• Serum markers such as CA 15-3 &amp; CA 27.29 may be used to measure results of treatment for patients with advanced breast cancer. Blood levels should go down if cancer responds to treatment and rise if disease progresses.</li> <li>• However, most professional groups do not recommend using these markers to follow up women already treated for breast cancer who have no evidence of relapse after treatment, especially for those with early stage breast cancer.</li> </ul>
<b>Colorectal Cancer</b>	<ul style="list-style-type: none"> <li>• At present, neither CEA nor CA 19-9 is useful as a screening test for colorectal cancer.</li> <li>• An elevated CEA level before surgery may indicate worse prognosis. If all the cancer has been removed, CEA should return to normal levels in about 4 to 6 weeks.</li> <li>• After treatment, CEA measurement every 3 to 6 months should be considered to help early diagnosis of recurrence.</li> <li>• CEA is also used to monitor patients being treated for advanced or recurrent disease.</li> <li>• If CEA is not elevated in patients with advanced or recurrent disease, CA 19-9 may be used to follow the disease.</li> </ul>
<b>Gestational Trophoblastic Disease</b>	<ul style="list-style-type: none"> <li>• HCG is elevated in patients with trophoblastic disease and choriocarcinoma.</li> <li>• HCG measurements during treatment are very useful to monitor response to treatment.</li> </ul>
<b>Liver Cancer</b>	<ul style="list-style-type: none"> <li>• Periodic screening by serum AFP measurement and Ultrasound for chronic hepatitis carriers are useful to detect liver cancer at early stage.</li> <li>• AFP can also be used to follow up patients after treatment.</li> </ul>
<b>Lung Cancer</b>	<ul style="list-style-type: none"> <li>• At present, no tumour markers have been proven to be useful as screening tests for lung cancer.</li> <li>• Tumour markers that can be raised in lung cancer include CEA in non-small cell lung cancer and NSE in small cell lung cancer.</li> <li>• Because lung cancer is usually visible on CXR or other imaging studies, tumour markers play a less important role in follow-up.</li> </ul>

## Melanoma Skin Cancer

- At present, no tumour marker is of value in early detection of melanoma.
- Tumour markers TA-90 & S-100 can be used to test tissue samples to help diagnose melanoma.
- Serum level of S-100 is elevated when disease is widespread. Thus it can be used to look for progression of melanoma.
- Blood levels of TA-90 have been used to assess the chance of metastasis of melanoma.

## Multiple Myeloma

- There are no tumour markers commonly used to screen for this disease, although tests for immunoglobulins can be used to aid diagnosis and assess response to treatment.
- Many patients with multiple myeloma have raised blood levels of beta-2-microglobulin, which can provide information on prognosis and response to treatment.

## Ovarian Cancer

- CA125 is very effective to assess response of epithelial ovarian cancer to treatment or to detect recurrence.
- CA125 can be used to screen for ovarian cancer in women with strong family history of ovarian cancers. Such women usually receive regular ultrasounds together with CA 125 measurements.
- At present, most medical groups do not recommend CA 125 for screening in asymptomatic women without family history of ovarian cancer because it is unclear whether it will detect ovarian cancer early enough to increase cure rate. Besides, ovarian cancer is still relatively uncommon and CA 125 level can be raised in other cancers and other benign conditions. Therefore, an elevated CA 125 is more likely to be due to some other cause, although a lot testing might be needed to rule out ovarian cancer.
- Patients with ovarian germ cell tumours often have raised levels of HCG and / or AFP, which are useful in diagnosis and follow-up.

## Pancreatic Cancer

- At present, no tumour markers have been found to be useful in screening for pancreatic cancer.
- CA 19-9 is the most useful tumour marker for pancreatic cancer.
- Most patients with pancreatic cancer have raised level of CA 19-9. The higher the level, the more likely the disease has spread.
- CA 19-9 is also useful in follow-up. Patients whose CA 19-9 levels drop to normal after surgery have a much better prognosis than those whose CA 19-9 levels remain elevated after surgery.
- CA 19-9 can also be used to assess response to treatment for advanced disease.

## Prostate Cancer

- PSA is commonly used to detect prostate cancer at early stage. About 1 out of 3 men with high PSA level has prostate cancer, which means that 2 out of 3 do not. The higher the PSA level, the more likely prostate cancer will be detected if biopsy is done.
- Levels above 4ng/ml suggest cancer whereas levels above 10 ng/ml strongly suggest cancer.
- However prostate cancer can be a slow growing cancer in some elderly men and it is still unclear whether PSA screening actually saves lives.
- Some believe PSA screening may cause more harm than good because it may lead some men to get treated for prostate cancers that would never have caused them problems, and the treatment itself can have significant side effects.
- PSA is very useful in follow-up. After curative surgery, PSA level should be zero or very close to zero. Those treated with radiotherapy should also have a significant drop in PSA after treatment.
- A subsequent rise in PSA after treatment could indicate relapse.
- PSA can also be used to assess response to treatment for advanced disease.
- In rare cases, prostate cancers that do not have raised PSA levels and do not respond well to hormonal therapy may turn out to have neuroendocrine features. Patients with these cancers may have higher levels of Chromogranin A.

## Stomach Cancer

- No specific tumour marker has been developed for stomach cancer.

## Testicular Cancer

- No specific tumour marker has been developed for stomach cancer.
- Tumour markers commonly elevated in patients with testicular cancer are HCG and AFP.
- Seminoma: About 10% of men with seminoma will have raised HCG. None will have elevated AFP.
- Non-seminoma: More than half of men with early stage disease have raised HCG or AFP or both. The markers will be elevated in most men with advanced disease.
- HCG is almost always raised and AFP is never elevated in choriocarcinoma.
- In contrast, AFP but not HCG is raised in yolk sac tumour or endodermal sinus tumour.

## Summary

Tumour markers may be used to help diagnose cancer, predict and monitor response to treatment and determine whether cancer has recurred after treatment. In general, tumour markers alone cannot be used to diagnose cancer, they must be combined with other tests. Studies are being done to determine if tumour markers can be used in early detection and diagnosis of cancer.