Tumor Markers

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**Tumor Markers** - molecules or genes that are specific for tumors (vs. normal tissues).

N.B. currently used tumor markers have low sensitivities and specificities:

1. are not specific for certain type of cancer
2. may not be elevated in early stages
3. may not be elevated in all cases of certain cancers
4. may be elevated in benign conditions

Use of Tumor Markers

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **marker Type** | **early diagnosis (screening)** | **predicting** **response** to therapy | **monitoring** **response** to therapy | **predicting** **recurrence & survival** | **monitoring** **recurrence (follow-up)** |
| **Serum** Markers | + |  | + |  | + |
| **Tissue** prognostic marker |  |  |  | + |  |
| **Tissue** predictive marker |  | + |  |  |  |
| **Circulating** tumor cells |  |  | + | + |  |

Tissue Markers

**TOP2A FISH pharmDx** - device to test for the TOP2A (topoisomerase 2 alpha) gene in breast cancer patients; for other tests – see p. 2911

Currently high interest exists in defining and clinical use of **profiles** of tissue markers, so called molecular profiling (e.g. *Oncotype DX*, *MammaPrint* in breast cancer).

Circulating tumor cells (CTC)

- cells in blood that possess antigenic or genetic characteristics of specific tumor type.

Detection methods: immunomagnetic beads coated with specific antibodies, RT-PCR.

Most studied for:

1. **Breast cancer**: CellSearch - CTC detection technology approved by FDA for clinical use in breast cancer, but no current guidelines recommend CTC measurement in any clinical setting.
2. **Melanoma**

Serum Markers

**CA** – cancer antigen.

* serum markers (usually glycoproteins) are *detected in serum by monoclonal antibodies*.

Identification of new serum markers

* **high-throughput technologies** (matrix-assisted laser desorption ionization time-of-flight mass spectroscopy, liquid chromatography ion-spray tandem mass spectroscopy) are now being used to compare serum protein profiles of patients with cancer with those of individuals without cancer.
* identification of unique proteins / unique proteomic profiles could dramatically enhance our ability to detect cancers early.

Serum Markers in clinical use

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Marker | Normal value | Benign disease is unlikely | Primary tumor (sensitivity) | Additional associated malignancies | Benign conditions |
| **CA 19-9**  - intracellular adhesion molecule1) | < 37 U/mL | > 1000 | Pancreatic adenocarcinoma (75-90%), biliary cancers (60-70%) | Colon, esophageal, hepatic cancers | Pancreatitis, biliary disease, cirrhosis |
| 1) 5% people (these with Lewis-null blood type) do not produce CA 19-9. | | | | |
| **CA 27.29**  - glycoprotein (MUC1) on apical surface of normal epithelial cells | < 38 U/mL | > 100 | Breast cancer  (33% early-stage cancers, 67% late-stage cancers) | Colon, gastric, hepatic, lung, pancreatic, ovarian, prostate cancers | Breast, liver, kidney disorders, ovarian cysts |
| **CA 15-3** | < 32 U/mL |  | Breast cancer  (less sensitive than CA 27.29) |  |  |
| **CA 125**  - glycoprotein normally expressed in fetal coelomic epithelium (this epithelium lines body cavities and envelopes ovaries) | < 35 U/mL | > 200 | Epithelial ovarian cancer (85%; but only 50% early-stage cancers) | Endometrial, fallopian tube, breast, lung, esophageal, gastric, hepatic, pancreatic cancers | *Stimulation of serosal surfaces* - menstruation, pregnancy, fibroids, ovarian cysts, pelvic inflammation, endometriosis, cirrhosis, ascites, pleural / pericardial effusions |
| **CEA** (carcinoembryonic antigen)  - glycoprotein expressed on normal embryonic endodermal epithelium | < 2.5 μg/L (nonsmoker)  < 5 μg/L (smoker) | > 10 | Colorectal cancer  (< 25% early-stage cancers, 75% M1 cancers) | Breast, lung, gastric, pancreatic, bladder, medullary thyroid, head and neck, cervical, ovarian (mucinous epithelial), hepatic cancers, lymphoma, melanoma | Cigarette smoking, peptic ulcer, inflammatory bowel disease, pancreatitis, hypothyroidism, cirrhosis, biliary obstruction |
| **AFP** (α-fetoprotein) - major protein of fetal serum | < 5.4 μg/L | > 500 | Hepatocellular carcinoma (60-80%), nonseminomatous germ cell tumors (85%)2) | Gastric, biliary, pancreatic cancers | Cirrhosis, viral hepatitis, pregnancy (esp. open neural tube defects) |
| 2) endodermal sinus (yolk sac) tumors (!!!), embryonal cell carcinomas, immature teratomas (mature teratomas do not secrete AFP). | | | | |
| **β-hCG** (β subunit of human chorionic gonadotropin)  - normally produced by placenta | < 5 mIU/mL | > 30 | Gestational trophoblastic disease,nonseminomatous germ cell tumors (85%)3) | GI cancers (rarely) | Pregnancy (!!!), hypogonadal states, marijuana use |
| 3) choriocarcinomas (!!!), embryonal cell carcinomas, mixed germinomas with syncytiotrophoblastic giant cells (pure germinomas are nonsecretory). | | | | |
| **PSA** (prostate-specific antigen)  - glycoprotein (androgen-regulated serine protease) produced by prostatic epithelium | ≤ 4 μg/L 6)  (undetectable after radical prostatectomy) | > 10 | Prostate adenocarcinoma  (25-92% depending on tumor volume;  > 75% of organ-confined cancers) | None | Prostatitis4), benign prostatic hypertrophy, prostatic trauma5), ejaculation before < 48 hrs |
| 4) up to 8 weeks of prostatitis symptom resolution.  5) digital rectal examination does not elevate PSA levels above normal.  6) finasteride suppresses normal PSA production of prostate - for men who have been taking finasteride for > 6 months, reported PSA levels should be doubled to accurately reflect true values. | | | | |
| **Thyroglobulin** |  |  | Differentiated thyroid carcinoma |  |  |
| **Calcitonin** |  |  | Medullary thyroid carcinoma (RET proto-oncogene) |  |  |
| **Tyrosinase mRNA** |  |  | Circulating melanoma cells |  |  |
| **Prostatic acid phosphatase** |  |  | Prostate carcinoma |  |  |
| **S-100** |  |  | Melanoma, astrocytomas |  |  |
| **Alkaline phosphatase** |  |  | Bone metastases, Paget’s disease of bone |  | obstructive biliary disease |
| **Bombesin** |  |  | Neuroblastoma, lung and gastric cancer |  |  |
| **TRAP** (tartrate-resistant acid phosphatase. |  |  | Hairy cell leukemia |  |  |

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|  | **Use of tumor marker** | | | |
| *Screening* | *Diagnosis in certain clinical situations* | *Monitoring for recurrence (follow-up) after treatment* | *Monitoring of treatment response* |
| **CA 27.29** | No | No | No / Patients at high risk for recurrence: q 4-6 mo. | No / Helpful |
| **CA 15-3** | No | No | No | No |
| **CEA** | No | No | Patients at high risk for recurrence: q 2-3 mo for at least 2 years. | Very helpful\*\* |
| **CA 19-9** | No | Selected pancreatic masses | No | Helpful |
| **CA 125** | *In heritable ovarian cancer syndromes* | A) pelvic mass in postmenopausal women;  B) malignant ascites in women with cancer of unknown primary | Every 3 mo for 2 years → less frequently. | Very helpful |
| **AFP** | *In nonalcoholic cirrhosis* | A) poorly differentiated cancer of unknown primary;  B) cirrhosis and liver mass | Nonseminomatous germ cell tumor: q 1-2 mo for 1 year → q 3 mo for 1 year → less frequently. | Essential for nonseminomatous germ cell tumor.  Very helpful for hepatocellular carcinoma |
| **β-hCG** | No | A) poorly differentiated cancer of unknown primary;  B) gestational trophoblastic disease | Nonseminomatous germ cell tumor - see AFP.  Gestational trophoblastic disease: q 1 mo for 6-12 mo. | Essential for both -nonseminomatous germ cell tumor and gestational trophoblastic disease |
| **PSA** | General Population\* | A) adenocarcinoma of unknown primary;  B) widely positive bone scan and prostate mass | q 6 months for 5 years → annually. | Very helpful |

\**see “4800. Screening Tests.doc”*

\*\**CEA is the most cost-effective approach for detecting recurrences/metastases*

*Panaudota literatūra*:

“Sabiston Textbook of Surgery”, 15th ed., 1997

“The Merck Manual”, 17th ed., 1999

F. Brunicardi “**Schwartz's** Principles of Surgery”, 9th ed. (2009); Publisher: McGraw-Hill Professional; ISBN-10: 007154769X; ISBN-13: 978-0071547697 (ch. 10) [>>](http://www.amazon.com/gp/product/007154769X)