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LETTER FROM THE EDITOR

Dear Readers:

This issue of ReFlections contains two articles I hope you will find interesting and informative. In the first article, I review significant facts about melanoma of the skin and its pre-malignant conditions. In addition, I highlight major changes in the staging protocol for skin cancer as discussed in the 7th edition of the Cancer Staging Manual published by the American Joint Committee on Cancer.

The second article, written by Dr. Robert Coates, is a follow-up to an article on prostate cancer that was published in the Winter 2009 issue of ReFlections. In that article, Dr. Coates discussed prostate cancer statistics, risk factors and the histological grading of prostate cancer differentiation. In this article, Dr. Coates discusses the benefits and challenges of the PSA screening test for prostate cancer.

I welcome your feedback on both topics.

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MELANOMA OF THE SKIN AND MAJOR CHANGES IN THE STAGING PROTOCOL

By Dr. J. Carl Holowaty M.D., D.B.I.M.

Melanoma of the Skin and Major Changes in the Staging Protocol

The American Joint Committee on Cancer recently published the 7th edition of its Cancer Staging Manual. The purpose of this article is to review significant facts about melanoma of the skin and its pre-malignant conditions, as well as outline the major changes in the staging protocol between this new edition of the staging manual and its predecessors.

Melanoma is a malignant tumor that originates in melanocytes, the cells of the body that produce the pigment melanin that colors our skin, hair and eyes. Melanoma can occur in the skin as well as the eyes, but for the purpose of brevity only melanoma of the skin will be considered and discussed in this article.

Cancer of the skin is the most common cancer in the United States, and the 6th most common cause of cancer death. Almost 2% of people born today will develop melanoma of the skin at some point during their lifetime. (Source: <http://seer.cancer.gov/statfacts/html/melan.html>).

While melanoma is less common than either basal cell or squamous cell carcinoma of the skin, it is the most serious of these cancers. As of 2006, it is estimated there are approximately 750,000 Americans alive with a history of melanoma. As such, this is a condition that underwriters need to understand thoroughly regarding mortality prognostic factors and risk selection. The National Cancer Institute estimates that in 2009, more than 68,000 men and women will be diagnosed with melanoma, and 8,650 will die from this disease.



Melanoma is relatively rare before the age of 20, but is otherwise distributed fairly evenly though the various age ranges.

Age at diagnosis	Percentage of total
>20	0.9%
20 - 34	7.8%
35 - 44	12.4%
45 - 54	18.9%
55 - 64	19.8%
65-74	17.7%
75 - 84	16.8%
85+	5.7%

Source: <http://seer.cancer.gov/statfacts/html/melan.html>

Melanoma can occur in all races, but much more so in fair-skinned individuals. This is illustrated in the table below, which shows age-adjusted incidence per 100,000.

Race/ Ethnicity	Male	Female
All races	25.0	15.8
White	28.9	18.7
Black	1.1	1.0
Asian/Pacific Islander	1.6	1.3
American Indian/Alaska Native	3.9	2.8
Hispanic	4.6	4.7

Source: <http://seer.cancer.gov/statfacts/html/melan.html>

Survival after diagnosis from this serious condition is very much dependent on the histological stage at diagnosis. Fortunately, with diligent screening and public awareness, the majority of melanomas are being discovered early, before they have had a chance to spread locally or regionally.

Stage	Distribution	5-yr Survival
Localized	84%	98.1%
Regional spread	8%	61.9%
Distant spread	4%	15.3%
Unstaged	4%	75.4%

Source: <http://seer.cancer.gov/statfacts/html/melan.html>

There are four main sub-types of melanoma. Of these sub-types, three have a commonly noted in-situ phase. They are known as Superficial Spreading Melanoma (SSM), Lentigo Maligna (LM) and Acral Lentiginous Melanoma (ALM). A fourth sub-type, known as Nodular Melanoma (NM), is usually only discovered in an invasive form.

The sub-type SSM accounts for 70% of all cases of melanoma and is the leading cause of cancer death in young adults. It usually starts as a flat spot that spreads sideways. LM tends to occur most often on the face in the middle-aged and elderly, and can have an appearance similar to "age-spots". These lesions also tend to be flat and are usually slow-growing, which affords plenty of time for diagnosis and treatment. ALM accounts for only 5% of melanoma cases and develops on the palms, soles, mucous membranes and subungually. Due to the somewhat hidden nature of these lesions, diagnosis and treatment may be delayed. Perhaps the most dangerous of the melanoma sub-types is the NM lesion, which accounts for 15% of all melanoma and is the most aggressive form, tending to grow rapidly in thickness.



There are several uncommon sub-types of melanoma. Amelanotic melanoma usually appears as pink or red nodes rather than the darker colors usually associated with melanoma. Desmoplastic neutrotrophic melanoma (DNM) typically looks either like a non-pigmented scar or cyst.

Melanomagenesis, which is the process of developing a melanoma, is poorly understood. While melanoma often derive from areas of the skin with high concentrations of melanin such as nevi, more than 60% are believed to arise de novo from areas of the skin without prior existing lesions. In spite of the lack of understanding of the precise process of development, many of the risk factors for melanoma are well known.

They include:

- Sun exposure, particularly blistering sunburns in early childhood
- Presence of many moles on the skin
- Fair skin
- Family history of melanoma
- Personal history of melanoma
- A weakened immune system from the use of chemotherapy or from conditions such as AIDS or lymphoma

The most important risk factor for melanoma, both in families with a history of melanoma or in the general population, is the presence of hereditary dysplastic/atypical nevus syndrome. The terms dysplastic and atypical are generally used interchangeably. This condition may also be known as B-K mole syndrome, familial atypical mole melanoma (FAMM) syndrome or nevus syndrome.

The following table illustrates the relative risk of developing a melanoma, depending on the number of both normal and atypical/dysplastic nevi:

Type	Number	Adjusted Relative Risk
Nevi > 2mm and < 5mm	0 – 24 25 – 49 50 – 99 > 100	1.0 1.8 (1.3 – 2.5) 3.0 (2.1 – 4.4) 3.4 (2.0 – 5.7)
Non-dysplastic nevi > 5 mm	0 1 2 – 4 5 – 9 > 10	1.0 0.9 (0.7 – 1.3) 1.3 (1.0 – 1.8) 1.7 (1.0 – 2.7) 2.3 (1.2 – 4.3)
Dysplastic (atypical) nevi	None Indeterminate 1 2 – 4 5 – 9 > 10	1.0 1.0 (0.7 – 1.6) 2.3 (1.4 – 3.6) 7.3 (4.6 – 12.0) 4.9 (2.5 – 9.8) 12.0 (4.4 – 31.0)

Source: American College of Physicians

In families with a history of melanoma, the presence of as few as two atypical or dysplastic nevi is sufficient to categorize the patient with these syndromes. In situations without a family history of melanoma, the precise number of atypical or dysplastic nevi needed to qualify for these syndromes is less well defined. It is interesting to note that these atypical or dysplastic moles may not necessarily change into melanoma, but their presence increases the risk that a person will develop a melanoma. Members of families with dysplastic nevi syndrome have a lifetime melanoma risk that approaches 100%, so it is essential that they be carefully examined on a regular basis for the presence of a melanoma, so that treatment can be performed as early as possible.

There are a number of changes in moles that suggest the presence of either atypia or frank malignancy. These changes are often called the A, B, C, D, E's as summarized below:

- A**symmetry of the mole
- B**order is irregular, scalloped or poorly defined
- C**olor is varied
- D**iameter is > 6 mm
- E**volving in size, shape or color

Other worrisome signs include unexplained itching, scaling or bleeding of the nevi. Definitive diagnosis of this condition is made after reviewing a person's medical history and risk factors, inspection of all unusual nevi, lymph node palpation, and more direct examination including surface microscopy and various types of tissue biopsy. Tissue sampling can be accomplished by incisional, excisional or punch biopsy. Shave biopsy is generally not performed unless there is relatively low suspicion for melanoma. If lymph node involvement is suspected, the node can be removed in toto or a representative sample can be removed with fine needle aspiration (FNA).

Additionally, sentinel lymph node mapping and biopsy (SNLB) preceded by radioactive dye can be performed to maximize the likelihood of detecting spread of the primary lesion. The search for distant metastases can include chest X-rays, computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and bone scans.

The results of these tests, in aggregate, provide post-diagnostic staging, which determines both the treatment and prognosis for this condition as illustrated below:

T classification	% 5– year survival (figures are rounded up)	% 10– year survival (figures are rounded up)
T1a	97	93
T1b	94	87
T2a	91	83
T2b	82	67
T3a	79	66
T3b	68	55
T4a	71	57
T4b	53	39

Source: American Joint Committee on Cancer 2010



In addition to this prognostic data, further refinement is demonstrated in the graph below which shows survival within the T1 stage of melanoma based on varying thickness and mitotic rate:

Thickness (mm)	Mitosis number	% 5-Year Survival (rounded up)	% 10-Year Survival (rounded up)
0.01 – 0.50	< 1.0	99	97
0.01 – 0.50	> 1.0	97	95
0.51 – 1.00	< 1.0	98	93
0.51 – 1.00	> 1.0	94	87

Source: American Joint Committee on Cancer 2010

Additionally, the mitotic rate in stages I and II can be correlated to survival:

Number of Mitoses/mm2	% 5-Year Survival (rounded up)	% 10-Year Survival (rounded up)
0 – 0.99	97	93
1.0 – 1.99	92	84
2.0 – 4.9	87	75
5.0 – 10.99	78	68
11.00 – 19.99	70	58
> 20	59	48

Source: American Joint Committee on Cancer 2010

The following survival graph demonstrates the profound prognostic implications of nodal or metastatic involvement in this condition:

Pathologic Stage	TNM	5-Year Survival %	10-Year Survival %
IIIA	N1a N2a	69 63	63 57
IIIB	N1a N2a N1b N2b	53 50 60 46	38 36 48 39
IIIC	N1b N2b N3	29 24 26	24 15 18
IV	M1a M1b M1c	19 7 10	16 3 6

Source: American College of Physicians

The initial staging system for melanoma was developed in 1983 by the American Joint Committee on Cancer (AJCC). This system divided melanoma into four stages and incorporated tumor thickness and anatomic level of invasion for localized disease. It later recommended using the Breslow depth over the Clark level in cases of discordance. The Breslow depth is measured as the thickness in millimeters, whereas the Clark level considers how far the melanoma has penetrated into the various layers of the skin.

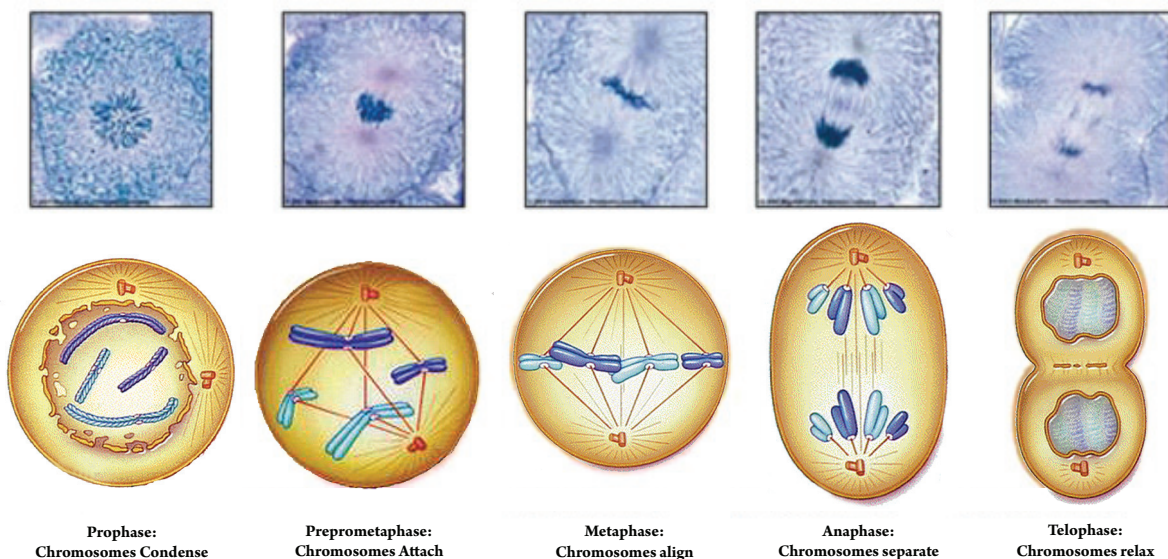
Major revisions in this system in 2002 included the incorporation of histological ulceration and the number, rather than the size, of the lymph nodes involved. It recommended the use of the Clark level only in shallow lesions, since its value in thicker lesions was felt to be minimal. In addition, microscopic lymph node involvement (detected by sentinel lymph node biopsy) was differentiated from macroscopic involvement.

Additional prognostic commentaries, which may be noted on a histological report, include the following terminology:

- Regression
 - This represents evidence the tumor at some point extended deeper into the skin than it did at the time of the biopsy
 - This suggests evidence that the body's immune system is capable of modifying the growth pattern of the melanoma
 - Incomplete spontaneous regression is felt to be common
 - Complete and permanent spontaneous regression is thought to be rare
 - It is suggested that the Breslow depth should be considered to be the maximum depth of noted regression
- “Satellite” lesions
 - These are skin or subcutaneous lesions within 2 cm of the primary lesion and are intralymphatic extensions of the primary lesion
- “In transit” lesions
 - These are locoregional metastases that develop within regional dermal and sub-dermal lymphatics, at least 2 cm beyond the primary lesion, but prior to reaching the regional lymph nodes

New AJCC Staging Guidelines

The latest (7th) edition of the AJCC staging guidelines incorporates most of the same staging information as prior versions, with a few notable exceptions. The first of these changes is that the Clark level has been de-emphasized even further, to the point that it is no longer regularly used.



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The second significant change concerns how the mitotic rate will be described. Whereas in the past, the mitotic rate was expressed as the number of mitoses per high-powered microscopic field (hpf), the 7th edition evaluates the number of mitoses per square millimeter (mm²). Survival statistics have shown that there is a significant correlation between increasing numbers of mitotic figures and declining survival, especially with thin melanomas. In melanomas, the mitotic rate is the second most powerful predictor of survival outcome, after tumor thickness.

Mitotic figures are present during times of cellular reproduction. High levels of mitotic figures suggest accelerated cell reproduction, which can be noted in aggressive tumors. In determining the mitotic count, pathologists identify the area in the tissue sample that has the most mitotic figures. This area is called the “hot spot”. The number of mitoses in this high-powered microscopic field is added to those in the surrounding fields until the total count in 1 mm² is determined. This represents approximately four high-power fields.

The key prognostic considerations for melanoma that are incorporated into the AJCC's staging guidelines are listed below in two large categories:

- Distant disease
 - Number of positive nodes
 - Tumor burden (micro-metastases vs. macro-metastases)
 - Elevated Lactate Dehydrogenase (LDH) in Stage IV disease
 - Age
- Local disease
 - Tumor thickness
 - Ulceration
 - Mitotic rate
 - Regression

These prognostic considerations are incorporated into the TNM classification of melanoma.

TNM Classification	Tumor Depth, Nodes, Metastases	Sub-classification
T classification T1 T2 T3 T4	< 1.0 mm 1.01 – 2.0 mm 2.01 – 4.0 mm > 4.0 mm	(a): Without ulceration and mitosis < 1/mm ² (b): With ulceration or mitoses > 1/mm ²
N classification N1 N2 N3	One lymph node 2 – 3 lymph nodes 4 or more metastatic lymph nodes, or combination of in-transit met(s)/satellite(s) with metastatic lymph nodes	(a): Micrometastasis (b) Macrometastasis
M classification M1a M1b M1c	Distant skin, subcutaneous or lymph mets Lung mets All other visceral mets or distant mets	Normal LDH Normal LDH Normal LDH or Elevated LDH with any M

Complete surgical removal is the primary therapy for localized cutaneous melanoma. The suggested surgical margins are dependent upon the size of the primary lesion. There is no significant survival benefit to using additional therapies, such as adjuvant chemotherapy, non-specific (passive) immunotherapy, radiation therapy, retinoid therapy, vitamin therapy or biologic therapy, for localized lesions.

Adjuvant interferon (IFN) alfa-2b is the only FDA-approved therapy for high-risk melanoma (Stages IIB, IIC and III). Experimental vaccines are showing some early promise for these higher-risk melanomas.

In summary, melanoma is a common condition which, if not detected and treated early, has significant additional mortality. Fortunately, through ongoing public and physician education, there is growing awareness of the risk factors and detection of melanoma. The prognostic factors for this condition are well known as described in the 7th edition of the AJCC Cancer Staging Manual. Hopefully this article has illustrated these risk factors and will be an important guide to risk selection for underwriters. ■

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PROSTATE CANCER AND PSA — PART II

By Dr. Robert Coates M.D., D.B.I.M., FLMI

The earlier an individual is diagnosed with prostate cancer, the greater the likelihood of a cure, which is true for any cancer. In the last issue of ReFlections, I discussed prostate cancer statistics, risk factors and the Gleason method of histological grading of prostate cancer differentiation.

Prostate biopsy is the absolute method to diagnose prostate cancer. In this issue, I will review two commonly used screening tests for prostate cancer, digital rectal exam (DRE) and prostate specific antigen (PSA), which often determine whether a prostate biopsy is needed.

Digital Rectal Exam (DRE)

Approximately 2% to 3% of men over age 50 have an abnormal DRE with induration, nodularity or asymmetry. Smooth, symmetrical enlargement, or benign prostate hyperplasia (BPH), is not included in the abnormal exam category. The findings of an abnormal prostate on examination double the risk of finding a significant prostate cancer, and increase the likelihood that the cancer has spread beyond the prostate capsule. Prostate cancers detected by DRE are more likely to be non-curable, compared to those detected by PSA. DRE misses 23% to 75% of prostate cancers, depending on the source quoted. The DRE is not a very sensitive test to screen for prostate cancer.

Prostate Specific Antigen (PSA)

PSA was discovered in the 1960s by researchers looking for a marker in seminal fluid to assist from a legal perspective in cases of rape. In 1980, a serological test to measure PSA was developed. In 1986, PSA was approved to monitor the progression of prostate cancer and later to detect prostate cancer in symptomatic males. The value and effectiveness of PSA as a general screening test to improve prostate cancer mortality is not resolved. Whether PSA screening causes more harm than good is an area of heated controversy and debate. These topics are beyond the scope of this article. However, it is worthwhile to note that since PSA was first introduced in 1986, today less than 5% of men have metastatic disease at diagnosis and 75% have non-palpable cancer. In 1982, before PSA was used, 33% of men had metastatic disease at diagnosis.

PSA is a single chain glycoprotein with 237 amino acids, four carbohydrate chains and multiple disulfide bonds. The gene encoding PSA is on chromosome 19. PSA is a protease enzyme in the kallikrein family of enzymes and it has chymotrypsin-like properties. PSA is important for normal fertility by helping to maintain the seminal fluid in a liquid state.

PSA is found in very small amounts in urethral glands, endometrium, normal breast tissue, breast milk and salivary glands. PSA, on occasion, also can be found in the serum of some patients with renal or adrenal cancers, and in some women with breast, lung or uterine cancers. However, for underwriting purposes, PSA is considered to be produced exclusively in the prostate gland. The highest concentration of PSA is found in seminal fluid. How PSA enters the bloodstream is unknown.

PSA in the serum is mostly bound to two alpha globulin proteins—alpha-2-macroglobulin or alpha-1-antichymotrypsin. A smaller amount of serum PSA is not bound to proteins and is called “free PSA.” Free PSA is the major form of PSA in the ejaculate. Prostate cancer tends to have a lower percent free PSA than benign prostate disease, BPH. The half-life of PSA is two to three days. So, it takes about two to three weeks for the PSA to become undetectable after a radical prostatectomy, or two to three weeks for PSA to return to normal after surgical manipulation or prostate biopsy.

PSA is increased as prostate volume increases (BPH). PSA can increase with infection (prostatitis), after ejaculation, after surgical manipulation or prostate biopsy, after pelvic trauma, after CPR and with urinary retention, as well as in most cases of prostate cancer. Thus, PSA is an organ-specific test for prostate disease, but it is not specific for a cause of PSA elevation. Prostate volume tends to be higher in black males compared to white and Asian males. PSA is decreased by 5-alpha reductase inhibitors such as finasteride (Proscar) and dutasteride (Avodart). PSA levels decrease by an average of 50% after a six-month course of treatment. However, the range of PSA change can vary widely from an 80% decrease to a 20% increase in PSA level.

The first generation PSA assays have a lower limit PSA detection equal to 0.2 ng/ml. The second generation PSA assays have a lower limit PSA detection equal to 0.1 ng/ml. The third generation PSA assays have a lower limit PSA detection equal to 0.003 ng/ml.

From the data presented, using PSA as a screening tool has resulted in earlier diagnosis of many prostate cancers. However, it is also important to examine some of the problems with utilizing PSA as a screening test for prostate cancer. First, there is no nationally standardized PSA test, so PSA measurement of the same specimen can have varying results from lab to lab. Second, the blood sample used to measure PSA should be centrifuged and frozen within two to three hours for the best reliability of PSA measurement. Third, PSA elevation is specific for prostate disease, but it is not specific for prostate cancer. Fourth, approximately 20% to 30% of prostate cancers can have PSA levels <4.0 ng/ml. So, no PSA level guarantees cancer is not present. PSA in the 4-10 ng/ml range has a sensitivity of 80% and specificity of 60% to 70% for prostate cancer.

Noting the flaws of PSA as a screening test, several methods of improving or refining PSA interpretation have been developed. The first method is using age-specific PSA levels based on the fact that PSA rises with increasing age. Table 1 shows the typical normal age-specific PSA levels. It should be noted once again that black males have higher PSA levels compared to white and Asian males.

Table 1-Age-Specific PSA Levels

Age-Specific Normal Range PSA Levels:	
40-49 years old	0 to 2.5 ng/ml
50-59 years old	0 to 3.5 ng/ml
60-69 years old	0 to 4.5 ng/ml
70-79 years old	0 to 6.5 ng/ml

A second method used to refine a PSA interpretation is called PSA velocity. Normally, for men over 50 years old, PSA levels increase 3% per year, or about 0.04 ng/ml. A PSA increase of 0.75 ng/ml in one year is considered abnormal and increases the likelihood of prostate cancer being present.

A third method used to interpret an abnormal PSA level is the percentage of free PSA. The percentage of free PSA tends to be lower with prostate cancer and higher with BPH. For example, with PSA in the 4-10 ng/ml range, if the percentage of free PSA is less than 10%, there is a 56% probability of prostate cancer compared to an 8% probability if the percentage of free PSA is greater than 25%. The percentage of free PSA is most useful when the PSA is in the 4-10 ng/ml range and more difficult to interpret when the PSA is less than 4 ng/ml.

A fourth refinement method is called PSA density. Prostate volume is estimated by ultrasound. The PSA density equals the PSA/prostate volume in cc or ml. A value greater than 0.15 is considered significant. The prostate density is not used as often as age-specific PSA levels, PSA velocity or percentage of free PSA. Keep in mind that none of the PSA refinements are absolute in diagnosing prostate cancer. They are used to help determine which patients should have a biopsy because of increased risk of having prostate cancer based on PSA and PSA refinements. Prostate biopsy is the absolute method to diagnose prostate cancer.

PSA is an excellent test to monitor patients after treatment of prostate cancer. A return of measurable PSA or a rise in PSA is evidence that prostate cancer is still present. After a radical prostatectomy, PSA should be undetectable within two to three weeks and remain undetectable.

A consensus has not been reached on an acceptable PSA level after radiation treatment. The generally accepted level is 0.2 ng/ml. A PSA nadir may not be reached until two to three years after radiation treatment. Some prostate cancer patients treated with radiation have a blip or slight rise in the PSA level one to two years after treatment and then the PSA level subsequently falls over the next year. This is considered to be a normal possible PSA occurrence after radiation treatment.



In addition to PSA, much research is being done to find markers with better sensitivity or specificity than PSA for prostate cancer. Table 2 has a list of some of the other prostate cancer marker tests being used in research. None of the tests are currently available or widely used clinically, nor clearly superior to PSA. Further studies are underway to confirm the usefulness of these additional markers. For diagnosing and treating prostate cancer, two things are needed: A specific prostate cancer tumor marker and a marker to differentiate the indolent, slow growing prostate cancers from the aggressive, rapidly growing prostate cancers.

Table 2 - Investigational Prostate Cancer Markers and Potential Uses

Chromagranin-A	(CgA)-prognosis
Human glandular kallikrein-2	(hK2)-diagnosis
Urokinase-type plasminogen activator	(u-PA)-diagnosis
Transforming growth factor-beta	(TGF-B)-prognosis
Interleukin	(IL-6)-prognosis
Prostate membrane-specific antigen	(PMSA)-diagnosis
Early prostate cancer antigen 1, 2	(EPCA)-diagnosis
Alpha-methylacyl-CoA racemase	(AMACR) autoantibodies-diagnosis
GSTP1 hypermethylation	diagnosis
Prostate Cancer Gene 3	(PCA3)-diagnosis (used in Europe since 2006)

A key point to remember is PSA is an organ-specific marker for prostate disease, but it is not specific for the cause of the PSA elevation. Age-specific PSA levels, PSA velocity, percentage of free PSA and PSA density are methods to refine the sensitivity and specificity in the evaluation of an elevated PSA; however, none of these refinements are cause-specific either.

Other key points are: PSA and PSA refinements help determine who should receive a prostate biopsy. PSA levels should be undetectable two to three weeks after a radical prostatectomy. PSA levels should fall to 0.2 ng/ml two to three years after radiation treatment for prostate cancer. Detectable PSA levels after prostatectomy indicate prostate cancer persistence or recurrence. A rising PSA, not a single isolated PSA blip after radiation treatment, indicates prostate cancer recurrence.

In summary, it is important to remember PSA and PSA refinements have advantages and disadvantages. The controversy surrounding PSA screening will remain for some time to come until researchers are able to find an alternate tumor marker that will differentiate the aggressiveness of a prostate cancer. For underwriters, PSA screenings can be a valuable tool in assessing morbidity and mortality, but the benefits and challenges of the PSA test must be well understood. ■



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