

**Review Report**
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## Citiscreen Project for Cancer Screening: Colorectal, Prostate, Bladder, Testicular, Thyroid and Skin Cancers

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Evidence demonstrates that annual screening with gFOBT as well as 1-time and every 3 to 5-year flexible sigmoidoscopy or colonoscopy, reduces colorectal cancer deaths [1]. Flexible sigmoidoscopies combined with annual FIT may serve as an alternative to colonoscopy, which is lengthier and more invasive [1].

The American Cancer Society, American College of Radiology, and the US Multi-Society Task Force (including the American Gastroenterological Association, American College of Gastroenterology, and American Society for Gastrointestinal Endoscopy) jointly issued screening recommendations. They include flexible sigmoidoscopy every 5 years, and/or a colonoscopy every 10 years, a double-contrast barium enema every 5 years, and a CT colonography every 5 years as the preferred tests. The American College of Gastroenterology released independent guidelines recommending a colonoscopy every 10 years as a single preferred screening strategy [2-5]. It stated that if a colonoscopy is not available or is unacceptable to a patient, recommended alternative strategies include a flexible sigmoidoscopy every 5 to 10 years or a CT colonoscopy every 5 years (preferred) or an annual FIT, annual Hemocult II SENSA, or FIT-DNA testing every 3 years (acceptable) [6].

### Algorithm for Colorectal Cancer Screening

Low Risk	Age 55	<ul style="list-style-type: none"> <li>• Fecal occult blood test</li> <li>• Fecal immunochemical test</li> <li>• Refer for colonoscopy</li> <li>• Recommend repeating every 3 years</li> </ul>
High Risk <ul style="list-style-type: none"> <li>• Patient tubular adenomas &lt; 1 cm with low-grade dysplasia</li> <li>• Patient adenomas &gt; 1 cm or any adenomas with villous features or high grade dysplasia</li> <li>• Patient with &gt; 10 adenomas on a single examination</li> <li>• Patient with sessile adenomas</li> <li>• Colorectal cancer or adenomas polyps in a first-degree relative before age 60 years or in 2 or more first degree relatives at any age.6</li> <li>• Either colorectal cancer or adenomatous polyps in a first-degree relative 60 years or older or in 2 second-degree relatives with colorectal cancer</li> <li>• Genetic or clinical diagnosis of HNPCC or individuals at increased risk of HNPCC</li> <li>• Inflammatory bowel disease (chronic ulcerative colitis or Crohn's disease)<sup>4</sup></li> </ul>	Age 40	<ul style="list-style-type: none"> <li>• Colonoscopy every 3 years</li> </ul>

<p>HNPCC</p> <ul style="list-style-type: none"> <li>Inflammatory bowel disease (chronic ulcerative colitis or Crohn's disease)<sup>4</sup></li> </ul>	<p>Age 20 to 25 years or 10 years before the youngest case in the immediate family</p> <p>Cancer risk begins to be significant 8 years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis</p>	<ul style="list-style-type: none"> <li>Colonoscopy every 1 to 2 years and counseling to consider genetic testing</li> <li>Colonoscopy with biopsies for dysplasia every 1 to 2 years</li> </ul>
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### Lung Cancer

Lung cancer is the leading cause of cancer deaths worldwide (18.4% of all cancer deaths) and causes more deaths than breast, colorectal, and cervical cancers combined [7]. Only 15% of patients with lung cancer are still alive 5 years after diagnosis, because approximately 70% of patients have advanced disease at the time of diagnosis [8]. Lung cancer and other tobacco related diseases are expected to remain important health problems worldwide for decades [8]. Volume CT screening has led to a substantial shift to lower-stage cancers at the time of diagnosis as well as to more frequent eligibility for curative surgery [9]. In the subsample of women, the effects of screening on lung-cancer mortality were more favorable [7]. Concerns have been raised about the potential for overdiagnosis in lung-cancer screening. Volume CT screening enabled a significant reduction of false positive tests and unnecessary workup procedure without jeopardizing favorable outcomes [7]. In response to criticism on the usefulness of lung cancer screening, the authors of the NELSON (Nederlands-Leuven Longkanker Screenings Onderzoek) trial argued that the, "over detection remains an inevitable but clinically significant harm and had a negative effect on quality of life for some participants. However, the number of persons who will be saved from palliative treatments and who will not have a negative effect on quality of life because of effective screening is approximately 2 to 3 times as high as the number of persons in whom over detection will have a negative effect on quality of life" [10].

### Algorithm for Lung Cancer Screening Risk

<p><b>Low Risk:</b></p> <ul style="list-style-type: none"> <li>Age less than 50 years old and/or</li> <li>Secondhand smoker</li> </ul>	<p>Annual low dose CT Lung Screening (optional)</p>
<p><b>Moderate Risk:</b></p> <ul style="list-style-type: none"> <li>Age greater than or equal to 50 years old and</li> <li>Greater than or equal to 20 pack-year smoking history (including second-hand smoke)</li> </ul>	<p>Annual low dose CT Lung Screening</p>
<p><b>High Risk:</b></p> <ul style="list-style-type: none"> <li>Age 55-80 years old and</li> <li>Greater than or equal to 30 pack-year smoking history and</li> <li>Current or previous smoker</li> <li>Greater than or equal to 20 pack-year smoking history and</li> <li>Additional risk factors (other than second-hand smoke)</li> <li>Family history of lung cancer</li> </ul>	<ul style="list-style-type: none"> <li>Annual low dose CT Lung Screening</li> <li>Cytokeratin fragment 21-1</li> <li>Neuron-specific enolase (NSE)</li> </ul>

### Screening for Prostate Cancer

Prostate cancer is the most common type of cancer that affects men. In the United States, the lifetime risk of prostate cancer is 13%, and the lifetime risk of dying of prostate cancer is 2.5%. The topic

of prostate cancer screening went through major transformation from original excitement over PSA (prostate specific antigen) to a much more cautious approach lately. The major reasons are two-fold: the high false positive rate of PSA screening and indolent nature of prostate cancer. In autopsies of men who died of other causes, more than 20% aged 50 to 59 years and more than 33% aged 70 to 79 years have had a prostate cancer. Many men with prostate cancer never experience symptoms and, without screening, would never know they have the disease. Therefore, current recommendations are stated as follows:

"For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their health care provider.<sup>3</sup> Men will experience potential harms of screening that require additional testing and prostate biopsy; overdiagnosis and treatment complications, such as incontinence and erectile dysfunction.<sup>3</sup>"

African American men have an increased lifetime risk of prostate cancer death compared with those of other races/ethnicities (4.2% for African American men, 2.9% for Hispanic men, 2.3% for white men, and 2.1% for Asian and Pacific Islander men) [11]. PSA-based screening in men aged 55 to 69 years may prevent 1.3 deaths from prostate cancer over 13 years per 1,000 men screened. Screening programs may also prevent approximately 3 cases of metastatic prostate cancer per 1,000 men screened [12,13]. Based on stage tumor and grade, prostate cancer is classified as low, medium, or high risk for clinical progression and death.

Although treatment is thought to be most immediately beneficial for men with high and medium risk prostate cancer, the vast majority of cases of screen-detected cancer are low risk [13]. Evidence in men 70 years and older does not support routine screening [13]. Some older men continue to request screening. Men older than 70 who request screening should be aware of the reduced likelihood of benefit from screening and the increased risk of false-positive test results and complications of treatment [14]. Most researchers recommend screening frequency every 2 to 7 years. Low PSA threshold (< 4.0 ng/mL) for biopsy and more frequent screening intervals offered greater potential reductions in prostate cancer mortality but higher rates of overdiagnosis [15].

### Risk factors

Men with at least 1 first-degree relative with prostate cancer were 30% more likely to be diagnosed than men without a family history. Men with 3 first-degree relatives with prostate cancer or 2 close relatives on the same side of the family with prostate cancer diagnosed before age 55 years may have an inheritable form of prostate cancer [16]. Men who have a first-degree relative with advanced prostate cancer at diagnosis, developed metastatic prostate cancer, or died of prostate cancer are the most likely to benefit from screening. The discussion should include the potential benefits and harms of screening for prostate cancer, so these men have the opportunity to make an informed decision.

### Algorithm for Prostate Cancer Screening

<b>Low Risk</b>	<b>Age 45-75 years</b>	
	PSA less than 1 ng/mL:	Repeat testing at 2-4 year intervals
	PSA 1-4 ng/mL	Repeat testing at 1-2 year intervals
	PSA greater than 4 ng/mL	Refer for diagnostic evaluation
<b>High Risk</b> Race Family or personal history of BRCA1/2 mutations. More than one first degree relative with prostate cancer	<b>Risk and benefit discussion about prostate screening. Baseline PSA at age 40</b>	
	PSA less than 4 ng/mL:	Repeat testing in select patients at 1-year intervals
	Genetic testing:	“My Risk” etc.
	PSA greater than 4 ng/mL:	Refer for prostate biopsy

### Screening for Pancreatic Cancer

Pancreatic carcinoma (PC) is the fourth most common cause of death from cancer in the USA [17]. The International Cancer of the Pancreas Screening Consortium (CAPS) was formed in 2010 [18]. The main tool used by CAPS to quantify PC risk is the number of affected family members [19]. Therefore, gene testing can identify a genetic susceptibility to PC [18]. Individuals with three or more affected blood relatives or with at least one affected first-degree relative should be considered candidates for screening [18].

Current recommendations for screening are primarily based on evidence of increased risk, rather than a proven efficacy [19,20]. This risk has been estimated to be 6.4-fold greater in individuals with two affected relatives (lifetime risk 8-12%) and 32-fold greater in individuals with three or more affected relatives (lifetime risk 40%) [20]. Patients with sporadic pancreatic cancer may have mutations in BRCA2 gene. Incomplete penetrance is relatively common in familial PC susceptibility gene mutation [21]. Germline mutations in the BRCA2, PALB2, p16, STK11, ATM, PRSS1 genes as well as Lynch syndrome, are associated with significantly increased risk of PC.

Patients with Peutz-Jeghers syndrome have a 132-fold increase in PC rate [22,23]. People of Jewish ancestry and a family history of PC should be considered for testing for the BRCA2 gene mutation, which is present in 1% of Ashkenazi Jews [24]. Initial screening tools for PC include endoscopic ultrasonography (EUS), MRI, cholangiopancreatography (MRCP), CT, abdominal ultrasound, and endoscopic retrograde cholangiopancreatography (ERCP) [18]. EUS and MRI are considered the most accurate tools for pancreatic imaging [18]. EUS and MRI are better than CT for the detection of small, predominantly cystic, pancreatic lesions.

MRCP provided the best visualization of cyst communication with the main pancreatic duct [18]. Patients with a non-suspicious cyst should have an imaging test every 6-12 months. Patients with a newly detected indeterminate solid lesions should have follow-up screening in 3 months. If an indeterminate main pancreatic duct stricture is detected, repeat imaging should be performed within 3 months [18]. Long-term survival can be achieved by resecting

small non-metastatic PC, particularly if margins are negative for cancer [25]. Most unscreened patients who undergo a resection of their PC will die from their disease [26]. Survival is expected for patients with T1N0M0 cancers (early stage) [25,26].

Numerous PC genes were also identified as MLL3 and ARID1A [27]. These 4 “mountain” genes are well recognized as contributing to pancreatic carcinogenesis [28]. Existing pancreatic cancer surveillance programs (endoscopic ultrasound, magnetic resonance imaging, and computed tomography scans) have detected a high number of asymptomatic pancreatic lesions (cysts), which represent major precursor lesions to PC (pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms). The majority of lesions detected during surveillance were asymptomatic resectable TNM stage I and II cancers [29]. Similar results were reported in the European study that followed mostly Leiden mutation carriers; 75% of screening detectable PDACs were resectable.

### Pancreatic Cancer Screening

Low Risk	MRI after age 50 (optional)
<b>High Risk</b> <ul style="list-style-type: none"> <li>• Two or more relatives who developed PC</li> <li>• One family member who developed PC before age 50</li> <li>• BRCA2 mutation</li> <li>• ATM mutation</li> <li>• CDKN2A/p16 mutation</li> <li>• STK11 mutation (Peutz Jeghers syndrome)</li> <li>• PRSS1 mutation (Hereditary pancreatitis)</li> <li>• BRCA1 mutation</li> <li>• MMR mutation (Lynch syndrome)</li> <li>• P53 mutation (Li-Fraumeni syndrome)</li> </ul>	MRI early Baseline endoscopic ultrasound

### Skin Cancer Screening

Skin cancer is the most frequent cancer worldwide, and the World Health Organization estimates that there are 200,000 cases of melanoma and 46,000 deaths worldwide annually [30]. In the last 30 years, the incidence of melanoma in the United States and Europe has tripled [30-32]. To reduce skin cancer mortality, a pilot skin cancer screening program, the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) project was conducted in Germany [32]. They reported strong evidence that screening leads to the prevention of a substantial proportion of melanoma deaths [32]. Mortality rates for women were constant at rates of 1.4 per 100,000 from 1990 to 2003 and began to drop during and immediately after the implementation of the statewide screening program. In 2009, mortality rates were almost 50% lower than they were during the 1990 to 2003 period [32].

Mortality rates for men ranged between 1.8 and 2.1 per 100,000 from 1990 to 2006 and also dropped by almost 50% to 1.0 per 100,000 during the most recent period [32]. A favorable prognosis for melanoma relies on a timely diagnosis [30]. Cutaneous melanomas are visible and thus are amenable to early detection. Important strategies aimed at improving early diagnosis of melanoma include physician-based screening and educating patients on melanoma recognition features. Patient involvement in detection is imperative because patients have the most opportunities in examining their own skin, and most melanomas are self-detected [33-37]. The most



common self-reported signs were color and size change of known birthmarks. Most patient-detected melanomas were asymptomatic [33]. Making digital photographs available to the patient helps them identify new and/or changing moles more efficiently [38,39].

**Assessment of risk**

Skin cancer of any type occurs more commonly in men than in women and among persons with a fair complexion, persons who use indoor tanning beds, and persons with a history of sunburns or previous skin cancer. Specific risk factors for melanoma include having a dysplastic nevus (atypical mole), having multiple nevi, and having a family history of melanoma [32,33]. Like most types of cancer, the risk of melanoma increases with age [40,41].

**Skin Cancer Screening Algorithm**

Low Risk	Self-skin assessment annually
<p>High Risk</p> <p>Increased risk:</p> <ul style="list-style-type: none"> <li>Greater than 50 nevi (moles)</li> <li>Tendency to sunburn</li> <li>Red or blonde hair, blue eyes, freckling, albinism</li> <li>History of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)</li> <li>History of actinic keratoses</li> <li>Personal or family history of, or suspicious for germline mutations or polymorphisms related to increased risk of melanoma (including, but not limited to CDKN2a, CDK4, MC1R, BAP)</li> </ul> <p>Environmental exposures:</p> <ul style="list-style-type: none"> <li>Sun/UV exposure: history of multiple sunburns, tanning bed exposure, episodic intense sun exposure</li> </ul>	<ul style="list-style-type: none"> <li>Genetic test for melanoma</li> <li>Yearly skin assessment by healthcare provider</li> </ul>

**Screening for Thyroid Cancer**

The incidence rate of thyroid cancer in the United States was 15.3 cases per 100,000, which represents a significant increase from 1975, when the incidence rate was 4.9 cases per 100,000 [42]. Most cases of thyroid cancer have a good prognosis. The 5-year survival rate of thyroid cancer overall is 98.1% and varies from 99.9% for localized disease to 55.3% for distant disease [43-45].

**Risk factors for thyroid cancer:**

1. A history of radiation exposure to the head and neck as a child.
2. Exposure to radioactive fallout (e.g., Chernobyl nuclear accident).
3. Family history of thyroid cancer in a first-degree relative, and certain genetic conditions, such as familial medullary thyroid cancer or multiple endocrine neoplasia syndrome (type 2A or 2B).

The American Thyroid Association and the American Association of Clinical Endocrinologists, American College of Endocrinology issued guidelines for the diagnosis and management of thyroid nodules in 2016; these guidelines include no recommendation on screening for thyroid cancer

in asymptomatic individuals [46,47]. Screening for thyroid cancer can be performed with ultrasonography. Screening may have the potential for early detection of malignant thyroid nodules that could make treatment more effective. However, screening also may result in overdiagnosis (identification of a thyroid malignancy that likely would not have caused symptoms or death during a patient’s lifetime [48,49]. Ultrasonography of the neck using high-risk sonographic characteristics plus follow-up cytology from fine-needle aspiration can identify thyroid cancers [50].

**Algorithm for Thyroid Cancer Screening**

Low Risk Patients	Neck ultrasound after age 45 (optional)
<p>High Risk Patients</p> <ul style="list-style-type: none"> <li>Family history of thyroid cancer</li> <li>Radiation exposure in childhood</li> <li>Multiple endocrine neoplasia syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Neck ultrasound yearly after age 30. Fine needle biopsy of suspicious nodules.</li> <li>The presence of microcalcification, spiculated margin, marked hypoechogenicity, taller-than wide orientation or irregular shape, solid)</li> <li>Calcitonin level</li> <li>Thyroglobulin level annually</li> </ul>

**Screening for Bladder Cancer**

Bladder cancer is the fourth most commonly diagnosed cancer in men and the ninth most commonly diagnosed cancer in women in the United States. It is the seventh leading cause of cancer-related deaths [51]. The stages of bladder cancer include superficial and muscle-invasive tumors. Many superficial tumors will recur after treatment, with a 10 to 20 percent of the tumor progressing to the invasive stage. One-fourth of all cases of bladder cancer have already metastasized to the lymph nodes at the time of diagnosis. Invasive bladder cancer is associated with a poor prognosis [51]. Screening for bladder cancer include:

1. Microscopic urinalysis for hematuria
2. Urine cytology
3. Urine biomarkers. Screening may yield false-positive results. False-positive results may lead to anxiety, labeling, pain, and additional complications that result from diagnostic cystoscopy and biopsy (e.g., bladder perforation, bleeding, infection, etc) [51].

**Algorithm for High-Risk Bladder Cancer Screening**

Urine dipstick or microscopic urinalysis for hematuria, urine cytology, and tests for urine biomarkers. Chromosome 3,7,17 and gp21.

**Screening for Testicular cancer**

The prevalence of testicular cancer is low [51]. Most testicular cancers are discovered by patients or their partners, either unintentionally or by self-examination, there is little evidence that teaching young men how to examine themselves for testicular cancer would improve health outcomes [51].

Risk factors for testicular cancer:

1. Family history of testicular cancer
2. Undescended testes
3. Testicular atrophy

There is evidence that patients who initially present with symptoms of testicular cancer commonly are diagnosed with epididymitis, testicular trauma, hydrocele, or other benign disorders [51].

### Algorithm for testicular cancer

General population	No screening recommended
High Risk 1. Family history of testicular cancer 2. Undescended testes 3. Testicular atrophy	• Testicular ultrasound every 3 years, starts at age 16

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