

## Principles of Cancer Screening

Petrikovsky BM\*

Department of Gynecology, Professor and Former Chair of Obstetrics and Gynecology, Nassau University Medical Center, NY, USA

**\*Corresponding author:**

Boris M Petrikovsky,  
Department of Gynecology,  
Professor and Former Chair of Obstetrics and Gynecology,  
Nassau University Medical Center, NY, USA,  
Email: bpetriko@gmail.com

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In 1968, Wilson and Jungner (WJ) put together the following criteria of screening approved by the World Health Organization (WHO) [1].

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Recently, the WHO officers have updated the WJ criteria taking into account recent developments in genetic and genomic medicine, among many other factors.

Synthesis of emerging screening criteria proposed over the past 40 years

1. The screening program should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening program effectiveness.
5. The program should integrate education, testing, clinical services and program management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The program should ensure informed choice, confidentiality and respect for autonomy.
8. The program should promote equity and access to screening for the entire target population.
9. Program evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

The perfect example of successful screening is cervical cancer (CC), a "fairytale" of gynecological oncology.

- The HPV virus is a known cause of cervical dysplasia and cancer. CC, therefore, is a sexually transmitted disease.
- CC has known precursors – various degrees of cervical dysplasia.

- PAP smear and HPV testing are noninvasive and reliable screening tests.
- CC precursors are amenable to detection via cytology, colposcopy, and tissue biopsy. Treatment of precursors largely eliminate the risk of CC.
- Finally, a vaccine was developed (Gardasil) and was successfully used.

#### CitiScreen Steps of Cancer Screening:

- Screening for risk factors (healthy individuals at risk), e.g., BRCA gene for breast cancer.
- Screening for cancer precursors, e.g., cervical dysplasia for cervical cancer, complex endometrial hyperplasia for endometrial cancer.
- Screening for early stage cancers, e.g., tumor markers like CA125 for ovarian cancer.

CitiScreen is designed to utilize the latest achievements in cancer prevention research and follow the general recommendations of the ACS. However, most public policies are based on principles of cost-effectiveness, sometimes at the expense of allowing some cancers to appear and spread. CitiScreen provides potential patients with updated information and allows them to make their choices of screening procedures, which may not be covered by their insurance policies.

### 1. Scientific Basis for Cancer Screening

A 2003 review published by Nature addressed the scientific base for early cancer screening [3]. The reviewers used accepted categories of evidence and consensus [4].

#### Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform consensus.

**Category 2A:** The recommendation is based on lower-level evidence and there is uniform consensus.

**Category 2B:** The recommendation is based on lower-level evidence and there is nonuniform consensus (but no major **disagreement**).

**Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

For the overall population, shifting all cases to early detection would have a significant impact on mortality. Tests that can detect precursor lesions or in situ disease hold the possibility of eliminating the invasive disease. An example of this being done successfully is that of cervical cancer [3]. Research into cancer screening and prevention can be divided into five steps [5].

**Step 1:** Step one studies that evaluated the expression of genes or proteins. New proteomics technologies will allow discovery to be performed directly in fluids (serum or urine), which will greatly

facilitate the process of early-detection biomarker research. The study, which combined algorithms with computational optimization and peaks from protein mass spectra that provided discrimination between ovarian cancer cases and healthy controls, is an example of step one research [6].

**Step 2:** The goals of step two studies are to develop clinical assays that are reproducible within and between laboratories.

**Step 3:** Retrospective, longitudinal studies.

Step 1 and 2 studies focus on discriminating between established cases and healthy controls [3]. Step 3 studies focus on biomarker measurements before diagnosis. Step 3 studies provide information on how marker levels change over time in disease cases and in healthy individuals.

**Step 4:** Prospective screening studies. Step 3 studies can determine how long before clinical diagnosis a marker might be able to detect disease. Prospective studies are necessary to determine whether the marker is able to detect the disease while it is still localized.

**Step 5:** Cancer control studies.

Steps 1-4 focus on developing tests that are feasible for widespread use and evaluating their diagnostic performance. Even if a test performs well, this does not necessarily imply that the test will reduce the cancer mortality [3].

**Step 6:** Step 5 studies include randomized, controlled cancer screening trials, case-control studies, computer modelling, and population studies. The goal of evaluation is to document or refute efficacy.

Because of the difficulties in assessing early-detection interventions, the standard of evidence for efficacy of a screening test is the randomized controlled trial (RCT). Only in the context of a randomized trial can the mortality reduction due to screening be directly estimated [3, 6].

Other than RCT, research methods also offer important information. Non-randomized approaches (epidemiological case-control studies) have been adapted for assessing the efficacy of cancer screening tests [7, 8]. Both case-control and population studies allow for the evaluation of screening tests [9]. Case-control studies compare the screening results of 'cases' (individuals who died from the disease) with 'controls' (individuals from the same population who did not die from the disease) [3, 8].

### 2. Summary of CitiScreen Project\*

The American Cancer Society (ACS) publishes guidelines for early cancer screening based on age, gender, family history, among other factors [9]. Cancer screening is a complex process, which includes physical diagnosis, family history, genetic and genomic assessments, tumor markers, and imaging techniques, among others. In most health systems, including in the United States, cancer

screening is performed by healthcare providers of various specialties: general and internal medicine practitioners, gynecologists, family physicians, and others. Although cancer screening is a part of the residency and fellowship training for many specialties, it is not their primary goal. Most of these health care providers spend the majority of their time treating hypertension, flu, diarrhea, etc. On the other hand, specialists in oncology, whose primary goal is the treatment of cancer, are usually occupied with treating patients with already established diagnoses of various malignancies. The screening and early detection of the majority of tumors is important because the success of therapy and survival is better in early stages of cancer. The goal of this manuscript is to present an algorithm for cancer screening that combines imaging, genetic, tumor markers, and other technologies.

The goal of cancer screening is to detect cancer or its precursor lesions at an early stage when treatment is most effective, preferably prior to the onset of symptoms. Cancer mortality has decreased by 25% from 1990 to 2015 for the United States with greater declines in the mortality for colorectal cancer (47% among men and 44% among women) and breast cancer.<sup>1</sup> This may be attributed to the introduction of screening programs for colorectal and breast cancers.<sup>1</sup> The most successful cancer screening programs are concentrated on the detection of the precursor lesions (e.g., cervical intraepithelial neoplasia (CIN) in cervical cancer screening and colonic polyps in colorectal cancer screening programs [10, 11].

### 3. Screening Patterns of Individual Cancers

**3.1. Breast Cancer:** Risk-prediction models have been created to identify individuals who are at higher risk for breast cancer, (i.e., family history, personal history) as well as hormonal exposure (i.e., age of menarche) and genetic markers (i.e., single nucleotide polymorphisms) in an effort to improve risk-stratification [12]. The input of genetics and genomics became important after the identification of the germline p53 mutation: the ability to identify individuals with a germline mutation improves risk-stratification and helps identify those who will benefit from frequent screening and possibly preventive procedures [13]. Women at high risk of breast cancer (carrier of a BRCA1 or BRCA2 mutation) should undergo extensive screening and may also consider prophylactic mastectomy to reduce their risk.

**3.2. Ovarian Cancer:** It is the most lethal of all cancers of the female reproductive system. Recent evidence suggests that high-grade serous ovarian cancer arises from malignant cells in the fimbriated end of the fallopian tube [14]. Much of this lethality is due to the difficulty in diagnosis because of vague symptoms (abdominal fullness and bloating, low abdominal dull pain, and fatigue). This often leads to a delayed detection, with 60% of cases diagnosed at either stage III or IV. The median age for a patient at the time of ovarian cancer diagnosis is 63. For low-risk women,

the strategies for ovarian cancer screening have included transvaginal (TV) ultrasonography and Doppler studies. Serum biomarkers (CA-125 and others) have also been used to screen for ovarian cancer. Other serum biomarkers such as human epididymis protein (HE4) and human chorionic gonadotropin (HCG) have been tested in combination with CA-125 to improve the screening program's performance. Currently, the most promising approach for ovarian cancer screening is a strategy combining serum CA-125, with or without other biomarkers, and TV ultrasound.

**3.3. Lung Cancer:** Lung cancer escapes early detection in women because most gynecologists, as primary care providers for women, have no training and/or experience in detection of lung cancer. Lung cancer is the most common cancer affecting both men and women, accounting for an estimate 228,150 new cases in 2019 [17]. Lung cancer is the leading cause of death from cancer in men and women, accounting for an estimated 142,670 deaths in 2019, which is approximately 25% of all cancer deaths in the United States [18]. Trends in lung cancer incidence and mortality vary by gender. For men, mortality rates have declined by 45% since 1990. For women, mortality rates have declined by only 19% since 2002. The recent data indicates that 79% of lung cancers are diagnosed as distant disease, for which a 5-year survival is very poor (30% for regional disease, and 5% for distant disease) [17]. ACS recommends annual screening for lung cancer with low-dose CT (LDCT) in the high-risk group (past and/or current history of active or passive smoking). The National Comprehensive Cancer Network (NCCN) recommends annual lung cancer screening for adults who do not have additional risk factors. The NCCN does not specify a specific age for ending screenings, stating that they should be continued until individuals are no longer candidates for definitive treatments [9]. The NCCN recommends that adults who have additional risk factors for lung cancer, such as a personal history of other cancers or lung disease (chronic obstructive pulmonary disease and diffuse pulmonary fibrosis), a family history of lung cancer, radon exposure, or occupational exposure to carcinogens that elevate their 5-year risk above 1.3%, should begin screening at age 50. The Lung Screening Trial Research Team (LSTRT) reported a reduced lung cancer mortality after the initiation of low dose CT screening [19]. Molecular markers in blood, sputum, and bronchial brushings have been studied but are currently unsuitable for clinical applications [20]. Advances in multidetector Computed Tomography (CT) have made high-resolution volumetric imaging possible in a single breath hold at acceptable levels of radiation exposure [21]. Several observational studies have shown that low-dose helical CT of the lung detects early-stage cancers more effectively than chest radiography [20]. Scanners that are currently used are technologically more advanced than those that were used in the past. This difference may mean that screening with today's scanners will result in a further reduction in the rate of death from

lung cancer.

**3.4 Colorectal Cancer (CRC) Screening:** In 2019, the ACS estimated that 145,600 new cases of CRC will be diagnosed in men and women, and 51,020 men and women will die from this disease [9]. CRC mortality has been declining for the past 2 decades among adults aged 50 years and older, which is largely attributable to the increase in screening and early detection. Among individuals aged  $\geq 50$  years, CRC incidence declined by 32% between 2000 and 2013 [22, 23]. The ACS recommends that: 1) average-risk adults with a life expectancy of greater than 10 years continue CRC screening until the age of 75; and 2) clinicians individualize CRC screening decisions for individuals aged 76 through 85 years, based on patient preferences, life expectancy, health status, and prior screening history. The options for CRC screening are: fecal immunochemical test (FIT) annually, high-sensitivity guaiac-based fecal occult blood test (gFOBT) annually, multitarget stool DNA test every 3 years, colonoscopy every 5 years, or flexible sigmoidoscopy every 5 years [24]. The ACS updated its guidelines for CRC screening in 2018. The ACS recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening with either a high-sensitivity, stool-based test or a structural (visual) examination. As part of the screening process, all positive results from non-colonoscopy screening tests should be followed with colonoscopy.

**3.5. Recommendations for High-Risk Adults:** The ACS recommends more intensive surveillance for individuals at higher risk for CRC [25-27]. Those at higher risk for CRC include individuals with: 1) a history of adenomatous polyps [28]; 2) a history of resection of CRC; 3) a family history of either CRC or advanced adenomas diagnosed in a first-degree relative [29]; 4) the presence of hereditary syndromes (e.g., Lynch syndrome or familial adenomatous polyposis); 5) a history of inflammatory bowel disease; 6) a history of abdominal or pelvic radiation [30]; and 7) patients with cystic fibrosis [31]. Adenomatous polyposis account for 2% of all colon cancers. We incorporated a myriad genetic program into CitiScreen, including COLARIS, which detects mutations in the APC and MYH genes. [They gauge] adenomatous polyposis related colon cancer syndromes, including familial adenomatous polyposis (FAP), attenuated FAP (AFAP) and MYH-associated polyposis (MAP). COLARIS uses blood or oral rinse sample to detect APC or MYH mutation.

**3.6. Benefits of COLARIS AP Testing:** The result of the COLARIS AP test enable patients to develop an individualized medical management plan to:

- Personalize patient care to individuals with APC or MYH gene mutation(s);
- Improve outcomes through early diagnosis of cancer;
- Counsel patients on the underlying cause of the cancer or

adenomas;

- Avoid unnecessary interventions involving family members who do not test positive for the mutation(s);
- Differentiate between AFAP, MAP, and Lynch syndrome.

**3.7. Endometrial Cancer (EC):** EC is the most common type of gynecologic cancer in the United States. In 2007, 61,380 new cases of EC were diagnosed, and 10,920 deaths occurred [32]. In 2008, the American College of Obstetricians and Gynecologists (ACOG) put together a special committee to develop recommendations on the role of transvaginal sonography to evaluate the endometrium in postmenopausal women [33]. An endometrial thickness of 4mm or less has a greater than 99% negative predictive value for EC [33]. In women of reproductive age, in the absence of ovulation, the endometrium is exposed to continuous estrogen, which can lead to endometrial hyperplasia (EH) [34]. If identified in a timely fashion, EH can be treated. Complex EH can progress to EC in up to one-fourth of women [35, 36]. Complex EH with atypia can lead to EC in up to one-half of women [37]. The leading risk factors for EH and EC include age, nulliparity, diabetes, and obesity [38, 39]. Among women found to have endometrial polyps, the prevalence of premalignant or malignant polyps was 5.42% in postmenopausal women compared with 1.7% in reproductive-aged women. The prevalence of endometrial neoplasia within polyps in women with symptomatic bleeding was 4.15% compared with 2.16% for those without bleeding. Among symptomatic postmenopausal women with endometrial polyps, 4.47% had malignant polyps in comparison to 1.51% of asymptomatic postmenopausal women [40, 41]. In these cases, an office hysteroscopy can be utilized for EC screening [41]. In 2000, we presented our preliminary results using menstrual blood content to screen for endometrial cancer in menstruating younger women [42]. We concluded that menstrual smears do have diagnostic potential for EC screening in a high-risk population. Although endometrial histology remains the gold standard, cytology may also be helpful for screening purposes [43]. The sensitivity of the endometrial cytology for detecting hyperplasia/carcinoma was 57% and the specificity was 98%. Although the accuracy of our approach has yet to be established, it may be similar to the guaiac method for colorectal screening [44].

#### 4. CitiScreen Tumor Markers (TM) Program

The topic of TM in cancer screening is confusing and controversial. It is known that the presence of a number of malignancies is associated with the appearance of TM in body fluids (blood, urine, saliva, etc.). The main problem with TM is that they have low specificity and may be abnormal in numerous conditions unrelated to cancer. Many of the TM appear late in the course of the disease and are used to monitor progress in treatment. CitiScreen incorporates TM into the screening protocols according to the recommendations of the National Cancer Institute (NCI).

Several of the TM applicable for cancer detection in women with ovarian cysts/tumors are reflected in table 1.

Cancer antigen (ovarian cancer)
Carcinoembryonic antigen
Inhibit (granulosa cell tumor)
Anti-Müllerian hormone (granulosa cell tumor)
Estradiol (granulosa cell tumor)
Testosterone (Sertoli-Leydig tumor)
Androstenedione (Sertoli-Leydig tumor)
Dihydroepiandrosterone (Sertoli-Leydig tumor)
Alfa-fetoprotein (yolk sac tumor, immature teratoma, mixed germ cell tumor)
HCG (choriocarcinoma, embryonal, polyembonal, mixed germ cell tumor)
Lactate dehydrogenase (dysgerminoma, yolk sac tumor, immature teratoma, mixed germ cell tumor)

TM for cancer screening are presented in table 2.

Type of Malignancy	What is Analyzed	TM
Breast Cancer	Blood	BRCA 1 CA 15-3 BRCA 2 CA 27-29
Ovarian Cancer	Blood	CA 125 HEY
Brain Cancer	Blood	Glial fibrillary acidic protein (GFAP)
Leukemia	Blood	BCR-ABL fusion gene
Thyroid Cancer	Blood	Thyroid transcription factor 1 Calcitonin Thyroglobulin
Colorectal Cancer	Blood	CEA Tumor M2-PK
Small cell Lung Cancer	Blood	Neuron-specific enolase (NSE)
Neuroblastoma	Urine	Catecholamines: WMA 2 HVA
Colon Cancer, Lung Cancer, Urinary Tract Cancer	Blood	Carcinoembryonic antigen

Recently, a new multi-analyte blood test named CancerSEEK has been introduced to the field of oncology screening [46]. For many adult cancers, it takes 20 to 30 years for incipient neoplastic lesions to progress to a late-stage disease [46]. CancerSEEK uses combined assays for genetic alterations and protein biomarkers. It has the capacity to not only to identify early cancers, but also to localize the organ of origin of these cancers [45]. On the basis of this DNA analysis, the predicted maximum detection capability of circulating tumor DNA (ctDNA) varied by tumor type, ranging from 60% for liver cancer to 100% for ovarian cancer [45]. CancerSEEK's algorithm includes a ctDNA mutation followed by elevations of cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA-19-9), prolactin (PRL), hepatocyte growth factor (HGF), osteopontin (OPN), myeloperoxidase (MPO), and tissue inhibitor of metalloproteinases 1 (TIMP-1)

[45, 46]. The advantage of the combination of protein and genetic biomarkers is the increased sensitivity.

The major problem with TM is that they are products of tumor metabolic pathways while the goal of screening is to detect cancer precursors. The new DETECT test represents a combination of TM with diagnostic PET-CT imaging [47, 49]. The DETECT-A blood test incorporates baseline and confirmation test components that have the potential to detect cancer in many organs. Diagnostic PET-CT is an FDA cleared test that is routinely used to detect tumors. A large body of clinical evidence supports its high sensitivity for early-stage cancers [46, 47]. The most commonly elevated protein biomarkers in participants with cancer were CA15-3 and CEA, followed by CA19-9, CA125, and HGF. Elevated levels of some proteins were sometimes found in patients with cancers not usually associated with those markers, (e.g., CEA in a lung cancer

and CA19-9 in an ovarian cancer) [50].

The analysis of cfDNA has the advantage of identifying alterations that are specific to the tumor [51]. The application of sequencing has allowed ctDNA-based tumor genotyping, which are present in a variety of cancers [50]. TEC-Seq program assessed the plasma specimen in “healthy” individuals (not known to have cancer). Samples were processed within two hours to ensure the collection of cells and cellular debris [51]. TEC-Seq analyses have significantly reduced the sequencing error rate to fewer than one false positive per 3 million bases pairs. Given the different tumors that could be detected, other diagnostic tests will be needed to complement any positive ctDNA mutations analysis to identify the source of occult lesions [57, 58].

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