MINISTRY OF HEALTH
SINGAPORE

Cancer Screening

MOH Clinical Practice Guidelines 1/2010

Academy of Medicine, Singapore

College of Family Physicians, Singapore

Chapter of Respiratory Physicians, Chapter of Medical Oncologists, College of Physicians, Singapore

Feb 2010

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Cancer Screening

MOH Clinical Practice Guidelines 1/2010

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

		Page
	Executive summary of recommendations	1
1	Introduction	5
2	Screening for Nasopharyngeal Carcinoma	11
3	Screening for Colorectal Cancer	16
4	Screening for Liver Cancer	30
5	Screening for Lung Cancer	34
6	Screening for Breast Cancer in Women	37
7	Screening for Cervical Cancer	52
8	Screening for Uterine Cancer	59
9	Screening for Ovarian Cancer	62
10	Screening for Prostate Cancer	66
11	Clinical Quality Improvement	78
	References	79
	Self-assessment (MCQs)	104
	Workgroup Members	107

Foreword

Cancer is the leading cause of mortality in Singapore, accounting for approximately 28% of the total number of deaths. Colorectal cancer (Age-standardised rate, ASR 40.2 per 100 000 per year) and breast cancer (ASR 57.1 per 100 000 per year) are the most common cancers among males and females respectively. Guidance on cancer screening was previously covered in the MOH clinical practice guidelines (CPG) on Health Screening published in 2003. As cancer has consistently been a major disease burden, it is appropriate that the updated guidelines are published as a dedicated CPG on cancer screening.

Cancer screening aims to detect disease early in asymptomatic people through the application of examinations or procedures. With the proliferation of cancer screening packages and types of screening tests in the market, there is a need for evidence-based guidelines to help doctors in selecting the appropriate tests for their patients. Screening is not without risks. False positives inevitably generate anxiety and require further tests that introduce additional risks and costs; false negatives may confer a false sense of security. Screening should only be conducted when supported by evidence of improved clinical outcome when a condition is discovered and treated at an earlier stage than was previously the practice.

Major revisions/additions to the previous health screening CPG include a new chapter on screening for nasopharyngeal carcinoma. This CPG also takes into account new evidence and their impact on cancer screening. For example, new recommendations concerning cervical cancer screening for HPV-vaccinated women and the use of computed tomography colonography in colorectal cancer screening have been included in this CPG.

I hope that this publication will assist doctors and patients make appropriate decisions in screening for cancers.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Executive summary of key recommendations

This executive summary contains the key recommendations from the main text of the guidelines. Please refer to the main text for other recommendations.

Screening for nasopharyngeal carcinoma

B Mass screening of general population at normal risk with EBV serology is **not recommended** (pg 13).

Grade B, Level 2++

Screening for colorectal cancer

A For average-risk individuals, screening for colorectal cancer has been shown to improve survival and is recommended (pg 18).

Grade A, Level 1++

B For average-risk individuals, screening for colorectal cancer should begin at age 50 years (pg 18).

Grade B, Level 2++

B **For individuals at increased risk or high risk**, screening by colonoscopy is indicated. (Refer to table 1 for age at which screening should be started) (pg 18).

Grade B, Level 2++

Screening for liver cancer

C Patients with chronic hepatitis B infection and liver cirrhosis from other etiologies are at increased risk of developing hepatocellular carcinoma, and surveillance should be offered to these at-risk individuals with the aim of detecting hepatocellular carcinoma that could be more amenable to therapy, and hence potentially translate to better outcomes (pg 31).

Grade C, Level 2+

Screening for lung cancer

A The use of serial chest X-rays to screen for lung cancer is **not recommended** (pg 35).

Grade A Level 1+

A The use of single or serial sputum cytologic evaluation to screen for lung cancer is **not recommended** (pg 35).

Grade A, Level 1+

C The use of low-dose CT scan to screen for lung cancer outside the context of a clinical trial is **not recommended** (pg 35).

Grade C, Level 2+

Screening for breast cancer in women

A All normal risk, asymptomatic women 50-69 years of age should be screened with mammography only, every two years. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade A, Level l++

C Women at normal risk aged 40-49 years should be informed of the benefits, limitations and potential harms associated with screening mammography so that they can make an informed choice. If screening is to be performed, it should be done annually. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade C, Level 2++

A Normal risk, asymptomatic women under 40 years **should not** undergo breast screening with any imaging modality (pg 47).

Grade A, Level l+

A In Western nations, the evidence supports mammographic screening every 2 years for all normal risk women 70-75 years of age. However, for Singaporean women the lower incidence of breast cancer in this age group suggests that screening mammography may be less beneficial and should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. If individual screening is performed, it should be at two-yearly intervals. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade A, Level I++

C Breast CT, Scintimammography, PET, and other non-conventional techniques such as Thermal imaging, Optical imaging, Electrical Impedence Imaging and Microwave Imaging are experimental techniques. They **should not** be used for routine breast screening (pg 45).

Grade C, Level 2++

Screening for cervical cancer

C All women who have ever had sexual intercourse should undergo screening for cervical cancer from the age of 25 years (pg 54).

Grade C, Level 2+

B Pap smear screening should be performed at least once every 3 years (pg 55).

Grade B, Level 2++

B Screening should be performed using the Papanicolaou (Pap) smear (pg 57).

Grade B, Level 2++

Screening for uterine cancer

B Screening for endometrial cancer is **not recommended** for women with an average or increased risk for endometrial cancer (pg 60).

Grade B, Level 2++

Screening for ovarian cancer

D The use of screening in women at average risk for epithelial ovarian cancer with serum markers and/or ultrasound is **not recommended**. There are currently no effective methods for the routine screening of asymptomatic women at average risk for ovarian cancer. These screening practices are **strongly discouraged** as they invariably lead to unnecessary interventions that ultimately risk the health and well-being of asymptomatic members of the general population (pg 63).

Grade D, Level 2+

Screening for prostate cancer

A At the present time, given the lack of data on whether screening improves disease-free survival, there is a **lack of evidence** to support population-based screening for the early detection of prostate cancer in Singapore (pg 69).

Grade A, Level 1+

1 Introduction

1.1 Guideline objectives and target group

The cancer screening guidelines are intended to assist medical practitioners, especially those in the primary health care sector, to advise their patients on the screening to be conducted for various diseases based on the patient's age, gender and presence of risk factors.

These guidelines provide current evidence-based clinical practice recommendations on screening for the common cancers in Singapore. The individuals for whom these guidelines are recommended are average-risk asymptomatic adults. High-risk individuals have also been identified.

1.2 Guideline development

The cancer screening guidelines were developed by a workgroup appointed by the Ministry of Health. Its members comprised experts in their areas of specialty, family practitioners and patient representatives. The workgroup formulated these guidelines by reviewing published international screening guidelines and current evidence available in the research literature, and taking into consideration the local population's characteristics. Feedback from relevant professional organisations was also sought in the process.

1.3 Principles for screening

Screening people who are apparently well in order to pick up asymptomatic disease can be beneficial to the individual if early treatment is available to improve the prognosis. It is beneficial to society at large if identification leads to primary and secondary prevention. However, there are other considerations for screening. Wilson and Jungner [1] cited the following principles of screening for early disease detection as a public health programme:

a) The condition sought should be an important health problem
b) The natural history of the disease should be adequately understood
c) There should be a recognisable latent or early preclinical stage

d) There should be a suitable and acceptable screening test or examination
e) There should be an accepted treatment or useful intervention for patients with the disease
f) Facilities for diagnosis and treatment should be available
g) There should be an agreed policy on whom to treat as patients
h) 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
i) Case finding should be a continuing process and not a one-off project.

Whether or not a screening policy results in improved health outcomes depends on a number of factors viz. the characteristics of the disease, the screening test, and the target population.

Screening may be considered where there is a high prevalence of the disease with potential serious consequences, the disease condition has a natural history with a latent stage during which symptoms of disease are either not present or early; and when detected and managed, is beneficial in improving the likelihood of favourable health outcomes (viz. reduced disease-specific morbidity or mortality). The screening test should be acceptable to the public, simple, fairly readily applied, and valid. With regard to diagnosis, the condition must be treatable and treatment and care available for those who need it. Early treatment should improve the outcome compared to treating patients when they present with signs and symptoms of the disease.

There is also a need for screening on a continuing basis rather than single-occasion screening. One-off screening is of limited value because only a small proportion, often those at least risk, is likely to be screened, and screening picks up those persons in the population who just happen at that particular time to have that condition being checked for. It therefore does not affect the future incidence of disease. Continuing examinations at stipulated intervals have greater advantage as they cover more of the population at risk including, by re-examination, persons presenting with new disease.

1.4 Screening tests characteristics

Sensitivity and specificity are important characteristics of the validity of a screening test. The validity of a screening test is the ability of the test to separate those who may have the disease condition from those who may not. The result of the screening test is confirmed by an acceptable diagnostic procedure ("gold standard") which distinguishes between "true" or "false" results. Sensitivity is the ability of the test to correctly identify those who truly have the disease. It is the ratio, expressed as a percentage, of the number of individuals with the disease whose screening tests are positive to the total number of individuals with the disease. Specificity is the ability of the test to correctly identify those who do not have the disease. It is the ratio, expressed as a percentage, of the number of individuals without the disease whose screening tests are negative to the total number of individuals without the disease.

A highly sensitive test will have a low proportion of false negative results, that is, there will be few missed cases. Few screened people who have the disease will be told incorrectly that they are free of the disease and have a false sense of security. A highly specific test will have a low proportion of false-positive results, that is, there will be few screened people free of the disease who are incorrectly told that they have the condition. False-positives could generate anxiety and unnecessary additional tests which may have potential adverse effects and cost. Ultimately, the medical practitioner would have to weigh the benefits and disadvantages for screening an individual.

The positive predictive value (PPV) is the screening test's ability to identify those who have the disease (true-positives) among all those whose screening tests are positive. PPV is affected by disease prevalence. For example, PPV increases with increasing prevalence of a disease in a high risk population.

Reliability is the ability of the test when reproduced, to have the same result. A poorly reliable test is likely to have high interobserver variation (e.g. between different laboratories) or intraobserver variation (i.e. between the same observer).

1.5 Assessing the evidence

In assessing the evidence, different study designs were considered including randomised controlled trials, cohort studies, case-control studies and uncontrolled clinical studies. Recommendations to screen average and/or high risk individuals are influenced by multiple factors including scientific evidence of effectiveness, costs and policy decisions.

It is often considered that picking up diseases by screening will be economical for a community as a whole. To diagnose and treat all patients would however, also add considerably to the total screening cost. Hence, only prospective studies which determine if morbidity or mortality has been reduced and life improved when compared to a non-screened population can demonstrate the savings in cost to a community. However, there are often limitations to such studies including the difficulty in practice of randomising people into screened and control groups, ethical issues to conduct randomised trials when using a test that is already regarded as normal practice, and significant losses over time in both the intervention and control groups during the study.

1.6 What's new in the revised guidelines

The Ministry of Health clinical practice guidelines on Health Screening published in July 2003 had included recommendations on cancer screening.

The following is a list of major revisions or additions to the guidelines:

(1) New chapter on screening for nasopharyngeal carcinoma (chapter 2) has been added.

(2) Chapter 3: Screening for Colorectal Cancer
- The table on the recommended screening age for colorectal cancer has been updated.
- More discussion on the screening tools and recommendations on the use of the various tools are provided.

(3) Chapter 4: Screening for Liver Cancer
- Recommendation for surveillance of high-risk individuals and additional recommendations on recommended screening tests.

(4) Chapter 6: Screening for Breast Cancer in Women
    - Recommendations on the benefits of clinical breast examination and breast self-examination are included.
    - For normal risk women aged 40-49 years, the recommendation on mammography has been changed from “screening annually” to “informed choice”.
    - Listed down the conditions in which women should consider genetic evaluation and testing for hereditary breast cancer syndrome.
    - Some discussion on the emerging evidence of the utility of MRI in screening of women who have genetic risk of breast cancer.
(5) Chapter 7: Screening for Cervical Cancer
    - Age to stop screening has been revised to age 69 to be in line with the recommendations for cessation of breast cancer screening.
    - Included a sub-section discussing on women who have had a hysterectomy, immunocompromised women and women vaccinated with HPV Vaccines.
(6) Chapter 9: Screening for Ovarian Cancer
    - Further discussed on screening for women with average risk (women with persistent symptoms and use of contraceptive pills).
    - Addition of a recommendation for women with family histories suspicious for BRCA mutations to screen, and provided a list of risk factors suspicious for BRCA mutations.
(7) Chapter 10: Screening for Prostate Cancer
    - The role of the various screening tests is discussed in greater length.
    - Included recommendations on frequency of screening and when (at what age and condition) should screening be stopped.
    - The current evidence on whether population screening should be done is discussed in greater length.
    - Provided a summary of key points in patient education and counselling for prostate cancer screening.
(8) Chapter 11 provides a list of clinical quality indicators and targets for the national screening programmes. Clinical quality indicators for the general clinic setting are also suggested.

1.7 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Screening for nasopharyngeal carcinoma

Key Recommendation:

B Mass screening of general population at normal risk with EBV serology is **not recommended** (pg 13).

Grade B, Level 2++

2.1 Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Singapore. The age standardized mortality rate for NPC in males is 6.4 per 100,000 population per year for males and 1.7 per 100,000 per year for females (1998-2002). The male and female ratio is 3.8 to 1.[2]

Altogether 92% of cases in Singapore occur in the Chinese population. Incidence rates for nasopharyngeal carcinoma remained stable for 25 years (1968-1992) but subsequently began to decline. In Chinese men the annual age-standardised rate fell from 18.7 in 1988-92 to 12.5 per 100,000 in 2003-2007.[2] The annual age-standardised rate in Chinese women also decreased over the same period, from 7.2 to 4.1 per 100,000.[2] Malays have about 30-50% risk and Indians 6-7% risk compared to that of Chinese.

Among males, the incidence rises in the third decade and peaks between 40-65 years; the plateau is less distinct in females.

Risk factors

Genetic and environmental co-factors particularly the Epstein-Barr virus (EBV) have been implicated in the aetiology.

2.2 Key concepts in NPC screening

Stage I disease still accounts for less than 10 % of all cases. Delay in diagnosis averaging 6-8 months is common. Cervical

lymphadenopathy (stage III) as the presenting feature occurs in more than 60% of patients. Treatment outcome for NPC is very much stage-dependent. The cure rate for stage I disease is up to 88% and less than 50% for stage IV.[3,4,5] Hence in theory early detection should improve overall cure rate.

NPC has not been shown to be associated with any macroscopic or microscopic pre-malignant condition.[6] Early NPC is likely indistinguishable from chronically inflamed lymphoepithelium common in nasopharynx. Biopsy remains the key to diagnosis. Nasopharynx exfoliation smear for EBV nuclear antigen / RNA and other viral components is not reliable for a screening test as normal cells may also contain viral particles. However, screening for Nasopharyngeal Carcinoma by Detection of the Latent Membrane Protein 1 *(LMP-1)* Gene with Nasopharyngeal Swabs is currently being explored.[7]

EBV infection in endemic regions occurs early in life and remains latent in B-lymphocytes for life. EBV genomes are found in all histological types of nasopharyngeal carcinoma. Compared to other head and neck cancers, NPC patients have higher geometric mean titres against EBV antigens namely viral capsid (VCA), early antigen (EA) and nuclear antigen (EBNA). Anti-EBV IgA class antibodies constitute the most frequent seroimmunological index used clinically both in diagnosis and screening and has been observed to rise 2-3 years ahead of clinical diagnosis.[8]

2.3 Who should be screened?

2.3.1 Mass population screening

Notwithstanding the observation that ethnic Chinese from Southern China have a particularly high incidence of nasopharyngeal carcinoma, no studies have demonstrated that mass screening of the general population results in decreased mortality.

A serological survey involving 195,000 adult subjects > 30 years old from three different counties in Southern China was conducted in the late 1970's-80's. The VCA IgA positive population ranged from 0.6 to 10% from which 106 NPC were diagnosed giving a detection rate of 1.6% to 13.6%, mostly in the early stage.[9] The NPC detection rate of screened VCA IgA positive population in various counties was 7 to

80 times annual general population incidence.[10,11] A recent prospective screening study (1996-2002) of over 42,000 adults in a Southern Chinese city with VCA IgA and endoscopy reported an elevated VCA IgA rate of 7.4% (over 3000 cases). 171 NPC patients were diagnosed from the cohort, of which 74 were asymptomatic with 60% having stage I disease.[12]

However it is also a fact that most of the VCA seropositive individuals never develop the cancer in their life time.

B Mass screening of general population with normal risk with EBV serology **is not recommended**.

Grade B, Level 2++

2.3.2 Families with NPC cases

Familial aggregation of NPC is well documented in many epidemiological studies. Between 5.9-15.5% of newly diagnosed NPC patients will give a family history of NPC.[13,14] In many studies and follow-up reports, first degree relatives have increased risk compared to the general population in the same age groups. This magnitude of familial risk in endemic regions is one of the highest among cancers.[15] Family history by itself has no actual clinical effect on the survival, but serves to advance NPC diagnosis among those with diseased relatives.[16]

Hence about 10% of new NPC patients are "familial"[3], while the other 90% are the "spontaneous" type of NPC in which their first degree relatives are at no higher risk of developing NPC than the general population. The value and cost-effectiveness of a formal screening programme for asymptomatic first degree relatives of patients without any other family history of NPC should be further evaluated.

It would be prudent to educate primary care physicians and relatives of all newly diagnosed NPC patients on the presentation and symptomatology of NPC so that they might have an improved awareness and an increased index of suspicion of the disease.

In the absence of large scale prospective studies in the past 30 years, we depend more on ongoing studies and clinical experience to guide our practice.

GPP Families with 2 or more index cases may be screened with EBV IgA and nasoendoscopy.

GPP

2.4 What should be done?

2.4.1 EBV IgA serology tumour marker

i) Biotech kits (ELISA)

Biotechnological kits are available commercially using ELISA methods for measuring IgA to EBV EA, EBNA-1 with different laboratory cut-off points. The variable end-points and lack of large scale seroimmunological clinical trial render its usefulness/ implication in clinical practice less clear.[17]

ii) Indirect immunofluorescence tumour marker

In general 80-90% of NPC patients have elevated IgA to EBV VCA and EA.

The distribution of normal anti-EBV titres in healthy Singapore Chinese general population are as follows:

Anti EBV VCA IgA – 86% below 1:5
10% from 1:5-1:10
4% at 1:40

Anti-EBV EA IgA – less than 1:5

VCA IgA has higher sensitivity but lower specificity than EA IgA; the percentage varies depending on laboratory cut-off points and disease stage of presentation.[15] Based on over five thousand samples done in Hong Kong with 215 NPC patients VCA IgA has sensitivity of about 90% and specificity 80% while EA IgA has sensitivity of about 65% and specificity 97%.[18]

Clinical significance

VCA IgA is affected by viral upper respiratory infection and thereafter remains high for six months or more. It is highly sensitive but a less reliable tumour marker for NPC screening.[19] The titre level of clinical significance is 1:160.

Other malignancies that cause elevated EBV IgA include parotid salivary gland undifferentiated carcinomas, salivary gland lymphoepithelioma, thymoma, lymphoma, bronchial carcinoma and gastric carcinoma.

2.4.2 Radiological scan

Radiological scan is useful in detecting early NPC. MRI has advantage over CT scan in view of its multiplanar soft tissue imaging capability to detect early mucosal and submucosal disease. The value of CT-PET scan in this situation is uncertain and its use in clinical practice is still evolving.

2.4.3 Early Antigen (EA) IgA positive individuals

Early Antigen (EA) IgA is highly specific. Positive individuals are likely to have NPC.

B A head and neck examination should be done with nasoendoscopy in Early Antigen (EA) IgA positive individuals.

Grade B, Level 2++

3 Screening for colorectal cancer

Key Recommendations:

A For average-risk individuals, screening for colorectal cancer has been shown to improve survival and is recommended (pg 18).

Grade A, Level 1++

B For average-risk individuals, screening for colorectal cancer should begin at age 50 years (pg 18).

Grade B, Level 2++

B **For individuals at increased risk or high risk**, screening by colonoscopy is indicated. (Refer to table 1 for age at which screening should be started) (pg 18).

Grade B, Level 2++

3.1 Introduction

Colorectal cancer is now the commonest cancer in Singapore. The average population risk for developing colorectal cancer in Singapore is among the highest in the world. The age-standardised rates for men for the period 2003-2007 was 40.5 per 100,000 per year and for women it was 29.0 per 100,000 per year.[2] Most colorectal cancers develop from adenomatous polyps. The detection and removal of adenomas by colonoscopy reduces the risk of colorectal cancer.[20] The long pre-malignant period of the adenoma-carcinoma sequence makes it ideal to screen for colorectal cancer.

Screening for colorectal cancer has been proven to save lives. Prospective randomized trials have demonstrated mortality reduction by the detection of early cancer as well as removal of adenomatous

polyps.[21-23] In the United States and northern European countries, colorectal cancer mortality has been falling, and this has been attributed to screening, early detection, prevention by polypectomy, and improved treatment.[24]

However despite strong evidence that screening for colorectal cancer saves lives, the actual uptake and practice of screening has been limited. This may be due to sub-optimal population awareness, insufficient advocacy by doctors, and unfamiliarity with screening tests or concerns over costs.

Since the first edition of the guidelines published in 2003, more studies on new tests such as the faecal immunochemical tests (FIT), stool DNA tests and computer tomography colography (CTC) have become available, and this information has been incorporated into the current guidelines and recommendations.

3.2 Who should be screened?

Individuals in the general population have varying risks of developing colorectal cancer and can be stratified into the following risk categories:

Average-risk individuals
The lifetime probability of an individual developing colorectal cancer is approximately 5%.[25] The risk rises with age, occurring sporadically among younger individuals and rising sharply after the age of 50[2] years. This would include asymptomatic individuals and individuals who do not have a family history of colorectal cancer, as well as those with family history confined to non-first degree relatives or relatives older than 60 years old.

Increased-risk individuals
Patients at high risk for colorectal cancer include those who have one or more first-degree relatives with colorectal cancer[26] or a personal history of colorectal neoplasia. Patients with prior endometrial, ovarian or breast cancer and those who have had pelvic radiation may have a slightly higher than average risk of colorectal cancer.

High-risk individuals
Patients at very high risk for developing colorectal cancer are those with a hereditary or genetic predisposition for colorectal cancer, that

is, a family history of familial adenomatous polyposis, other hereditary gastrointestinal polyposis syndromes or hereditary non-polyposis colorectal cancer. Also at high-risk are patients with a long history of extensive inflammatory bowel disease.

3.3 Recommendations for screening

A For average-risk individuals, screening for colorectal cancer has been shown to improve survival and is recommended.[21-23]

Grade A, Level 1++

B For average-risk individuals, screening for colorectal cancer should begin at age 50 years.[24]

Grade B, Level 2++

B **For individuals at increased risk or high risk**, screening by colonoscopy is indicated. (Refer to table 1 for age at which screening should be started).[24]

Grade B, Level 2++

3.4 Screening tests

Various screening tests are available and individuals should make an informed decision on choosing one of the options. Individuals at average risk have an option of choosing from several tests.

Screening tools currently available in current practice include

- Faecal occult blood test (FOBT)
- Colonoscopy
- Flexible sigmoidoscopy
- Computed Tomographic Colonography
- Double Contrast Barium Enema

These tests have different performance characteristics and evidence base. The current screening tests of choice for population based screening are faecal occult blood testing or colonoscopy.

Faecal occult blood tests (FOBT)

Stool blood tests are known as faecal occult blood tests (FOBT) and are designed to test for the presence of minute amounts of blood in the stool. There are 2 types of FOBT kits; the guaiac FOBT (gFOBT) and the faecal immunochemical test (FIT).[24,27] The earlier studies which demonstrated that annual or biennial FOBT reduced colorectal cancer mortality were performed with the gFOBT,[21-23] while FIT is a newer test using the more specific immunological detection of human hemoglobin which gives superior sensitivity and specificity. The present evidence indicates that FIT is a more sensitive screening tool than gFOBT.[28]

FIT has advantages compared to gFOBT. FIT detects human globin and is thus more specific for human blood than guaiac based tests, which rely on detection of peroxidase in human blood and also react to the peroxidase that is present in dietary constituents such as red meat, vegetables and some fruits. Unlike gFOBT, FIT is not subject to false-negative results in the presence of high-dose vitamin C supplements, which block the peroxidase reaction.

Whenever a FOBT test is positive, a diagnostic colonoscopy is necessary to examine the entire colon to rule out the presence of cancer or advanced neoplasia.

A Annual faecal occult blood test reduces mortality from colorectal cancer and is recommended as one of the screening test options.[21-23]

Grade A, Level 1+

C A positive faecal occult blood test requires a diagnostic workup with colonoscopy to examine the entire colon in order to rule out the presence of cancer or advanced neoplasia.[24]

Grade C, Level 2+

C Faecal immunochemical testing is more sensitive than guaiac tests in the detection of colorectal cancer, and is the recommended type of stool testing.[28]

Grade C, Level 2+

C For guaiac faecal occult blood tests, 3 specimens on consecutive days is recommended for **screening** of average risk individuals.[7]

Grade C, Level 2++

C For faecal immunochemical test, 2 specimens on 2 separate days is recommended for **screening** of average risk individuals.[24]

Grade C, Level 2+

Colonoscopy

Colonoscopy is a direct visualization of the entire colon and rectum using an endoscope inserted via the anus. It is considered the most accurate assessment of the colon and is the gold standard for diagnosis. It requires good bowel preparation and may require sedation. There are associated risks of complications including perforation (0.03-0.17%), and bleeding (0.03-0.09%). If polypectomy is performed, this increases to 0.3% and 1.4% respectively.[29,30]

Colonoscopy allows detection and removal of polyps which is not possible with other modalities. Regular survey and removal of polyps has been shown to prevent mortality in the National Polyp Study.[31,32] The incidence of colorectal cancer was reduced by 76% compared with a control population without colonoscopy.

There has been no prospective randomized studies on colonoscopy for screening of the general population, and evidence to support use of colonoscopy in screening is based on the studies on the surveillance and removal of colonic polyps and cohort studies employing colonoscopy and flexible sigmoidoscopy.

Colonoscopy has several limitations. It requires bowel preparation to ensure a good examination. Although it is the best available test for detection of polyps, it is recognised that there is an inherent miss rate for polyp detection.[33,34] Missed rates of 6-12% for large adenomas (≥ 10mm) and for cancer, about 5% have been reported.[35,36] Withdrawal time after complete insertion of the colonoscope is related to polyp detection rates. Polyps that are often missed are mainly low risk or insignificant hyperplastic polyps. The entity of flat or depressed polyps may be elusive to detection without the use of adjuncts like chromoscopy.[37]

B Colonoscopy is one of the recommended screening tests for the average risk asymptomatic population, from age 50 years.

Grade B, Level 2++

Frequency of colonoscopy

If an index colonoscopy is normal, extrapolated evidence from the National Polyp Study and the VA Cooperative Health Study[38] support a 10-yearly policy.

B For screening the general population at risk, colonoscopy should be performed at an interval of no more than 10 years.[38]

Grade B, Level 2++

If an index colonoscopy showed low risk polyps, colonoscopy surveillance may be considered in 5 to 10 years.[20] Patients having high risk polyps (those that show features of severe dysplasia, focal malignancy, sessile, more than 10 mm, multiple $\geq$3) should undergo colonoscopy within 3 years after the initial polypectomy. Patients with more than 10 polyps should consider rescope within 3 years. In uncertain removal, colonoscopy is to be repeated in 2-6 months to ascertain complete removal. Following resection of colon cancer, provided synchronous disease has been excluded, surveillance colonoscopy should be performed in 1 year to look for metachronous lesions.[39]

In individuals with a history of colorectal polyps, follow-up surveillance is indicated at intervals determined by the risk profile according to the type of polyp.

B Individuals with high risk polyps should undergo follow-up colonoscopy within 3 years. Individuals with low risk polyps should have follow-up colonoscopy within 5 years.

Grade B, Level 2++

In very high risk individuals where the clinical history suggests hereditary non-polyposis colorectal cancer syndrome (HNPCC), colonoscopy is the method of choice. More frequent screening intervals of 1-2 years may need to be considered.

In individuals with a strong family history defined as multiple first degree relatives with colorectal cancer or adenomas or an individual

in the family less than 60 years old, colonoscopy is the screening method of choice and should start at 40 years old or 10 years younger than the youngest diagnosed individual in the family, whichever is earlier.

In individuals with a single first degree relative diagnosed with colorectal cancer at age greater than 60 years old, screening should start at 50 years old or 10 years younger than the age of onset and colonoscopy is the method of choice.

C Colonoscopy is the only screening test that combines detection with prevention by polypectomy, and is recommended as one of the screening test options.[24]

Grade C, Level 2+

Flexible sigmoidoscopy

Flexible sigmoidoscopy is an endoscopic procedure that examines the lower half of the colon. The effectiveness of flexible sigmoidoscopy is based on the assumption that two-thirds of colorectal cancers and polyps are within reach of the scope (defined as examination up to at least 40 cm or to the splenic flexure). It has the significant advantage of simpler preparation for the patient as it requires only an enema beforehand, as well as lower risk of complications like perforation and bleeding. The patient must however be prepared to undergo further colonoscopy if polyps are detected.

Evidence for its use is supported by case control and cohort studies that showed 60-80% reduction in colorectal cancer mortality for the area of the colon within its reach.[2] In the NCI PLCO randomized trial, at least one polyp or mass was detected in 23% of the subjects who underwent screening by flexible sigmoidoscopy.[40]

Data supporting the use of flexible sigmoidoscopy all face the same limitation that is derived mainly from controlled trials that use colonoscopy to determine potential miss-rates of proximal polyps. Such studies that include the large VA Cooperative Study Group[41,42] have shown high detection rates of proximal lesions if an index polyp is detected distally. However, as high as 62% of advanced proximal lesions are not associated with distal adenomas.[43,44] Results are still awaited from large scale randomized trials in US and Europe.

Combined FOBT and flexible sigmoidoscopy confer better detection rates than if either one of the two modalities is used alone.[45,46]

It is recommended that the interval of screening remains at 5-years in view of the high variability in the quality of bowel preparation and the depth of scope insertion. A more frequent interval has not shown increase in polyp detection rates.[47]

The main limitation of flexible sigmoidoscopy is that it is unable to examine the proximal half of the colon, and therefore the test is unable to detect cancers or polyps in the proximal half of the colon. In addition proximal neoplasia has become more common after the age of 65 years, and up to 62% of proximal neoplasia are not associated with distal adenomas.

B Flexible sigmoidoscopy is recommended as one of the screening test options for colorectal cancer.[24]

Grade B, Level 2++

B Combined flexible sigmoidoscopy and faecal occult blood test (or faecal immunochemical test) has superior sensitivity compared to either test alone. The combination of these two tests is recommended over either test singly.[45,46]

Grade B, Level 2++

Computed Tomographic Colonography (Virtual Colonoscopy)

Computed tomographic colonography (CTC), also known as virtual colonoscopy, is a minimally invasive imaging examination of the colon and rectum, using CT scan to acquire images and computer software to process the images for interpretation. There have been rapid advancements in this technology, including multi-detector CT, thin slices, software improvements and techniques such as stool tagging with barium or contrast agents. It is the best available imaging test if optical colonoscopy is contraindicated or incomplete, and in this regard is superior to barium enema. The main concern over CTC is the risk of cumulative radiation, if used repetitively for surveillance.

C CT Colonography is a new test for colorectal imaging, and has been shown to be effective in detecting neoplasms ≥ 10 mm, and is recommended as one of the screening test options for colorectal cancer.[24]

Grade C, Level 2++

GPP If the initial screening study with computed tomographic colonography is negative, a screening interval of 5 years is recommended.[24]

GPP

Double contrast barium enema

Double contrast barium enema (DCBE) is a radiographic procedure which evaluates the colon by instillation of barium and then distending the colon with air introduced through a flexible catheter inserted into the rectum. Prior colon preparation with a dietary and laxative regimen is necessary for an optimal examination. There have been no randomised trials or case-control studies evaluating the efficacy of double contrast barium enema as a primary screening test in average-risk people.

C Double contrast barium enema is not the preferred first line screening modality for asymptomatic individuals. It is acceptable as second line if optical colonoscopy is contraindicated or fails.

Grade C, Level 2++

D If the initial screening study with barium enema is negative, a screening interval of 5 years for the next test is recommended.[24]

Grade D, Level 2+

Stool DNA Tests

Stool DNA tests aim to detect known mutations that occur during the formation of colorectal cancer. Common targets for assay include Kras, p53, APC, BAT 26 and long DNA. The sensitivity of such tests based on multi-target assays is between 62% to 91% for cancer and between 27 to 82% for advanced adenoma. The specificity for negative colonoscopy is 93 to 96%.[48] A randomized controlled trial has shown that stool DNA testing detected more advanced colorectal neoplasia than did Hemoccult II.[49]

The current limitation to stool DNA tests is the current lack of standardized laboratory protocols, the high costs of tests, and the lack of data on appropriate intervals between negative stool DNA examinations. It is anticipated in future that standardized protocols will be adopted and costs will decrease, allowing its adoption as a screening test in future.

GPP Stool DNA tests are presently **not recommended** for population screening.

GPP

Genetic Testing

Genetic testing is clinically available for hereditary non-polyposis colorectal cancer syndrome (HNPCC) and familial adenomatous polyposis. Individuals or families suspected to have these hereditary cancer syndromes should be referred to a tertiary centre, such as a cancer genetics clinic, for genetic risk evaluation and testing. The identification of a causative mutation in an index patient may facilitate predictive testing of family members to identify pre-symptomatic carriers for early surveillance. First-degree relatives of an index patient confirmed to have familial adenomatosis polyposis or hereditary non-polyposis colorectal cancer syndrome should be managed as at-risk individuals and enrolled in early surveillance programmes unless genetic testing confirms them to be non-carriers. Individuals whose personal or family history fulfill the Amsterdam I/II or revised Bethesda criteria should be evaluated for hereditary non-polyposis colorectal cancer syndrome.[50] A diagnosis of familial adenomatous polyposis is usually made clinically by the presence of >100 adenomatous polyps in the colorectum.

GPP High-risk individuals suspected of hereditary colorectal cancer syndrome should be referred to a cancer genetics clinic for evaluation.

GPP

Use of carcinoembryonic antigen for screening

Carcinoembryonic antigen is a blood test used to monitor tumour burden in patients with established colorectal cancer. However, it is not recommended for use in the screening of asymptomatic, average-risk patients. It can be elevated in other malignant conditions, benign

conditions such as ulcerative colitis and liver cirrhosis and among smokers. The low specificity and sensitivity of the plasma carcinoembryonic antigen in the diagnosis of colorectal cancer makes it a poor screening tool.[51]

GPP Carcinoembryonic antigen is **not recommended** as a screening test for colorectal cancer.

GPP

3.5 Cost-effectiveness

Any form of screening for colorectal cancer has been demonstrated to be cost-effective compared to no screening.[52,53] However, the best method of screening has remained controversial. Issues of effectiveness, risks, costs, compliance and patient choice have been debated.

There has been no trial directly comparing screening methods for colorectal cancer. The approach taken has been to use decision models to determine cost-effectiveness based on the natural history of colorectal cancer as well as local data for cancer incidence, costs of treatment, costs of screening and the sensitivity and specificity of various screening tools. In most models, the incremental costs of one or more screening methods versus no screening are assessed. No cost-effectiveness ratios comparing each screening method to the next most effective option were assessed. The latter approach is generally recommended in order to support choices between different strategies.[54]

Mathematical modeling using Singapore data has shown that screening can increase the life expectancy of the Singapore population between the ages of 50 years and 70 years.[55]

The same study showed that faecal occult blood testing was the most cost-effective population screening method when compared to sigmoidoscopy, barium enema and colonoscopy. However, if compliance to screening recommendations is taken into account, colonoscopy qualifies as a more cost-effective method.[38] Once or twice in a life-time colonoscopy appears to have a higher compliance rate than annual faecal occult blood testing.

The cost-effectiveness of CT colonography has also been compared with colonoscopy with the conclusion that the former is not suitable for population screening.[56]

In the absence of a clear choice for a specific screening method, patient choice based on information regarding the effectiveness, risks and costs is the current approach to be used for individual screening.

3.6 Other relevant information

Choice of screening test

Of the screening tests available, the screening test of choice for population-based screening is the faecal occult blood test, with preference for the immunochemical test. This is inexpensive, safe, non-invasive and effective. Some individuals may prefer colonoscopy since the latter combines detection with prevention by polypectomy,

There is less evidence for the other tests. CT colonography is the best available imaging test if optical colonoscopy is contraindicated or incomplete, and in this regard is superior to barium enema. The main concern over CT colonography is the risk of cumulative radiation. There is sufficient evidence that flexible sigmoidoscopy confers benefit as a screening test compared to no screening, but it is suboptimal in that the proximal half of the colon is not assessed.

Individual preference (informed choice)

When possible, clinicians should educate patients on the screening test options. This would empower individuals to exercise their choice based on individual preferences.

Compliance

Most patients find stool collection for FOBT a challenge with the need for appropriate diet before test, avoidance of red meat and Vitamin C. In some testing methods, it is necessary to avoid red meat, cauliflower and broccoli. There is also a need for a fair amount of stool handling with some collection methods which may prove to be unacceptable or manually difficult.

The FIT kit addresess some of these issues and the current method of collection requires minimum stool handling. The storage means allows the patient to collect the stools in the privacy of their homes, store for a period of time at room temperate and return the kits to the laboratory for test. There is also no need for diet restriction and is thus very acceptable and suitable for the Chinese population as the diet is high in peroxidase which might interfere with the gFOBT kits.[57] It has been noted that patients undergoing FOBT who were required to observe dietary restrictions prior to sample collection were less likely to return the test kits (like in the gFOBT).

Its has also been shown that intensive one to one education of patient on the FOBT increases the chances of the patient returning the FOBT kits compared to the handing out of education materials that are written down.[58] Time spent explaining to the patient on the need for FOBT and how to collect the stool samples by healthcare providers would certainly increase compliance to this screening method in the community.

Screening advocacy in primary care

Primary healthcare providers should advocate colorectal cancer prevention through proper risk stratification of our patients and offering the most appropriate and cost effective screening methods.

Those who are offered FOBT screening should be advised on the limitations of such a method, the need for a full examination of the colon should a stool test be found positive and the need for regular testing.

Summary

Colorectal cancer is the most common cancer in Singapore according to incidence. Screening for colorectal cancer should be offered by care providers since there is good evidence that screening for colorectal cancer will lead to reduction of mortality from the disease in all risk groups.

Based on the foregoing discussion and review of international practice parameters and guidelines[24,59,60], the following recommendations are made for the screening of colorectal cancer (see Table 1).

Table 1 Recommendations for the screening of colorectal cancer

RISK GROUP	SCREENING TOOL	ONSET (Age)	FREQUENCY	GRADE OF RECOMMENDATION	LEVEL OF EVIDENCE
A. Average risk Asymptomatic or family history limited to non-first degree relatives (screening tool alternatives in order of supporting evidence)	Faecal occult blood testing	50 years	Annually	A	1++
	Colonoscopy	50 years	Every 10 years	B	1+
	CT Colonography	50 years	Every 5 years	C	2+
B. Increased risk					
1. Colorectal cancer in first degree relative age 60 years or younger or two or more first degree relatives	Colonoscopy	10 years prior to youngest case in the family or age 40 years, whichever is earlier	Every 5 years	B	2++
2. Colorectal cancer in first degree relative over the age of 60 years	Colonoscopy	10 years prior to youngest case in the family or age 50 years, whichever is earlier	Every 10 years	B	2+
3. Personal history of colorectal polyps	Colonoscopy	3 years after polypectomy in the presence of high risk features (>1 cm, multiple, villous architecture); otherwise, 5 years after polypectomy for low risk polyps	-	B	2++
4. Personal history of colorectal malignancy	Colonoscopy	One year after resection	Every 3 years	B	2++
5. Personal history of ovarian or endometrial cancer	Colonoscopy	One year after resection	-	C	4
C. High risk					
1. Family history of familial adenomatous polyposis	Flexible sigmoidoscopy (switch to colonoscopy if adenomas identified); consider genetic counselling and testing	10 to 12 years (from puberty)	Annually	B	2+
2. Family history of hereditary non-polyposis colorectal cancer	Colonoscopy; consider genetic counselling and testing	20-25 years	Every 1-2 years	B	2+
3. Inflammatory bowel disease a. left-sided colitis b. pan-colitis	 Colonoscopy Colonoscopy	 From 15th year of diagnosis onwards From 8th year of diagnosis onwards	 Every 1-2 years Every 1-2 years	 B B	 2+ 2+

4 Screening for liver cancer

Key Recommendation:

C Patients with chronic hepatitis B infection and liver cirrhosis from other etiologies are at increased risk of developing hepatocellular carcinoma, and surveillance should be offered to these at-risk individuals with the aim of detecting hepatocellular carcinoma that could be more amenable to therapy, and hence potentially translate to better outcomes (pg 31).

Grade C, Level 2+

4.1 Introduction

Liver cancer, of which 85% were hepatocellular carcinoma, is the fourth commonest cancer among Singaporean males, with a male to female ratio of 4.1:1.[2] Overall, the incidence rates seem to have remained stable over the last 15 years.[61]

4.2 Risk factors

The main risk factors for development of hepatocellular carcinoma are (1) chronic hepatitis B infection and (2) liver cirrhosis from various etiologies (hepatitis C, alcohol, non-alcoholic steatohepatitis and other chronic liver diseases).

4.3 Definition

The recommendations here are for hepatocellular carcinoma only and do not apply to other forms of liver tumours.

4.4 Who should be screened?

a) General asymptomatic population

There is no data to support screening for hepatocellular carcinoma in the general population.

b) At-risk population

C Patients with chronic hepatitis B infection and liver cirrhosis from other etiologies are at increased risk of developing hepatocellular carcinoma, and surveillance should be offered to these at-risk individuals with the aim of detecting hepatocellular carcinoma that could be more amenable to therapy, and hence potentially translate to better outcomes.

Grade C, Level 2+

Within this at-risk group, a recognized sub-set of high-risk group include those with
(1) chronic HBV,
(2) male,
(3) >45 years,
(4) family history of hepatocellular carcinoma,
(5) presence of liver cirrhosis, and
(6) co-infection with hepatitis C.[62-67]

Several population-based screening studies have been published[11-13] and some show better median survival compared to those not screened.[68-70]

The optimal age to initiate hepatocellular carcinoma surveillance is currently not defined. However, in our local population, hepatocellular carcinoma incidence rises dramatically after 30 years of age in males, and 35 years of age in females.[61]

C Screening for liver cancer may be done at an interval of 6 months for high risk groups and 1 year for other groups.

Grade C, Level 2+

The ideal screening interval is not known, but based on median tumour doubling time of 117 (range: 29-398) days in most cases, a

suggested interval of 6 months for high risk groups and 1 year for the remainder is reasonable. An interval of 6 months is reasonable because most hepatomas would have at least one doubling time between surveillance interval and ample time to detect the tumours before they reach 5 cm in size.

4.5 What should be done?

C An ultrasound of the hepatobiliary system and serum alpha feto-protein level are recommended screening tests.[68,71-75]

Grade C, Level 2+

4.5.1 Serum alpha feto-protein levels

Both hepatoma cells and regenerating hepatocytes secrete alpha feto-protein, and serum levels can be raised to the thousands in liver inflammation. A rise in alpha feto-protein level (>20 ng/ml) in the absence of significant liver inflammation suggests hepatocellular carcinoma with a negative predictive value of 99% and a positive predictive value of up to 30% in non-cirrhotics and 60% in cirrhotics.[68] A rising trend strongly suggests the presence of hepatocellular carcinoma[71], although alpha feto-protein should never be used alone to diagnose hepatocellular carcinoma.

4.5.2 Ultrasonography of the liver

The sensitivity of ultrasonography of the liver ranges from 58-87% in cirrhotics to 71-90% in non-cirrhotics[68] with a false positive rate of 28-82%.[72-75] Regenerating and/or dysplastic nodules in cirrhosis are the leading cause of false-positive ultrasonography of the liver.

GPP Abnormalities in alpha feto-protein and/or ultrasound that raise suspicion for hepatocellular carcinoma are best referred to a specialist centre for assessment and management. The combination of alpha feto-protein and ultrasound is superior to either test alone.[76]

GPP

4.5.3 Others

Liver function test

GPP The liver function test is not performed for hepatocellular carcinoma surveillance. However, a low serum albumin associated with a high serum alkaline phosphatase is suggestive of a liver lesion and warrants further investigation.[77]

GPP

4.6 Conclusion

GPP Hepatocellular carcinoma surveillance should be offered to at-risk individuals with (1) chronic hepatitis B infection or (2) liver cirrhosis from other etiologies. Surveillance should be performed with ultrasound of the liver and αFP at 6 monthly intervals for high-risk and yearly for low-risk individuals. There is no definite recommended age to start surveillance although local statistics show that hepatocellular carcinoma incidence increases from the age of 30 years in males and 35 years in females.

GPP

5 Screening for lung cancer

Key Recommendations:

A The use of serial chest X-rays to screen for lung cancer is **not recommended** (pg 35).

Grade A Level 1+

A The use of single or serial sputum cytologic evaluation to screen for lung cancer is **not recommended** (pg 35).

Grade A, Level 1+

C The use of low-dose CT scan to screen for lung cancer outside the context of a clinical trial is **not recommended** (pg 35).

Grade C, Level 2+

5.1 Introduction

Lung cancer remains an important cancer in Singaporean males and it is the leading cause of cancer death in Singapore. The main risk factor for lung cancer is a history of smoking. Although the risk of lung cancer is attenuated by cessation of smoking, the risk is not eliminated. Lung cancer now occurs just as commonly in current and former smokers. Increasingly, lung cancers are also occurring in people who have never smoked.

Non-small cell lung cancer (NSCLC) accounts for over 75% of all lung cancers. It is typically diagnosed when the disease is locally advanced or when systemic metastasis is already present. The overall 5 year survival of NSCLC is 15%. In contrast, the 5-year survival of surgically resected early stage NSCLC approaches 75%.

Plain chest radiography (CXR) and sputum cytology have been investigated in randomized controlled trials in the 1960s and 1970s.

Screening using computed tomography (CT) has been studied in multiple single-arm observational studies and a few randomized trials since the 1990s. To date, only preliminary results have been published from the randomized trials.

5.2 Who should be screened?

Although most will regard current or former smokers as being high risk, there is no universally accepted subset of individuals in which screening has been found to reduce mortality.

5.3 What should (or should not) be done?

5.3.1 Chest x ray

A The use of serial chest X-rays to screen for lung cancer is **not recommended.**[78]

Grade A Level 1+

5.3.2 Sputum cytology

A The use of single or serial sputum cytologic evaluation to screen for lung cancer is **not recommended**.[78]

Grade A, Level 1+

5.3.3 Low-dose spiral CT scan

C The use of low-dose CT scan to screen for lung cancer outside the context of a clinical trial is **not recommended**.[79-86]

Grade C, Level 2+

5.4 The evidence for lung cancer screening

Randomized controlled trials in the 1960s and 1970s with chest radiograph and sputum cytology found that screening increased detection rate of early lung cancers, with no evidence of a reduction in lung cancer mortality. Despite the screened subjects having a higher likelihood of receiving an early lung cancer diagnosis, the frequency of advanced cancer diagnosis and deaths were similar in the intervention and control arms.[78]

These results raised the possibility that the cancers that were found through screening may not actually be the cancers that would have progressed to cause advanced disease.

The results of early trials found that low-dose CT detects two to four times more lung cancers than CXR. CT detects smaller lung cancers than are normally visible on CXR. The average size of CT-detected prevalence cancers has ranged from 9 to 16.5 mm. It is noteworthy that over 90% of CT-detected nodules are benign, even in a targeted, high-risk population.[79-86] There was concern that CT screening may be detecting biologically favourable lesions, leading to unnecessary diagnostic and treatment interventions.[87] Because the early trials did not contain a control group, the impact of CT screening on the absolute number of late-stage cancers and lung cancer mortality remains unknown.

There are currently two on-going randomised controlled trials. The National Lung Cancer Screening Trial (NLST) by the National Institute in the USA which had more than 50,000 participants[88,89] and NELSON trial in Netherlands, Belgium and Denmark which had 15,000 participants.[90] The results of these trials are expected in 2 to 3 years.

Lung cancers have multiple genetic aberrations, some of which are also present in premalignant lesions. The use of biomarkers in the sputum and blood as a screening tool is under intensive investigation and holds promise for the future.[91,92] Autofluorescence bronchoscopy is another technique that is able to detect and differentiate premalignant from malignant bronchial epithelium. Its role in lung cancer screening or surveillance of high-risk patients for lung cancer has not been established and is therefore not recommended for routine screening.[93,94]

5.5 Summary

There is no proven evidence for the efficacy of lung cancer screening at present. The screening utility of low-dose spiral CT is unknown and is currently being studied in ongoing trials. At-risk individuals who seek low-dose spiral CT examination outside of a clinical trial should be informed of the limitations and risks of such a procedure.

6 Screening for breast cancer in women

Key Recommendations:

A All normal risk, asymptomatic women 50-69 years of age should be screened with mammography only, every two years. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade A, Level 1++

C Women at normal risk aged 40-49 years should be informed of the benefits, limitations and potential harms associated with screening mammography so that they can make an informed choice. If screening is to be performed, it should be done annually. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade C, Level 2++

A Normal risk, asymptomatic women under 40 years **should not** undergo breast screening with any imaging modality (pg 47).

Grade A, Level 1+

Key Recommendations (continued):

A In Western nations, the evidence supports mammographic screening every 2 years for all normal risk women 70-75 years of age. However, for Singaporean women the lower incidence of breast cancer in this age group suggests that screening mammography may be less beneficial and should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. If individual screening is performed, it should be at two-yearly intervals. Ultrasound and clinical breast examination are **not routinely required** (pg 47).

Grade A, Level 1++

C Breast CT, Scintimammography, PET, and other non-conventional techniques such as Thermal imaging, Optical imaging, Electrical Impedence Imaging and Microwave Imaging are experimental techniques. They **should not** be used for routine breast screening (pg 45).

Grade C, Level 2++

6.1 Introduction

Breast cancer remains the most frequent cancer among women in Singapore, and approximately 6% of all women will be diagnosed with invasive disease in their lifetime.[61] Between the years 1998 and 2002, breast cancer accounted for 28% of all cancers diagnosed in women, 16% of cancer deaths, and 4.1% of all deaths among women. The incidence rate has continued to rise at approximately 4% per year, and the age-standardized incidence rate for Singapore women (59.9

per 100,000 per year in 2003-2007)[2] is slightly lower than two-thirds of the rates recorded for women in northern Europe and the US.[95] While the peak incidence of breast cancer occurs in the 55-59 age group, it is worth noting that 40%[1] of the cases are diagnosed in women below the age of 50.

6.2 Risk factors

Factors that modestly increase the risk of breast cancer by 1.5 to 2.5 fold include early age at menarche, late age at menopause, late age at first live-birth, and prolonged use of hormone replacement therapy. Also, certain benign or pre-malignant breast conditions, e.g. atypical ductal hyperplasia, atypical lobular hyperplasia or lobular carcinoma in-situ can increase breast cancer risk by up to 5-10 fold. Family history may increase breast cancer risk by 1.5-2.5 fold in those with one first- or second-degree relative diagnosed with breast cancer age >50, to up to 10-15 fold in those with strong family history of breast cancer and/or ovarian cancer suggestive of hereditary predisposition.[96]

Women suspected to have genetic risk for breast cancer (see section 6.5.3) should undergo formal genetic risk assessment in a specialist facility, ideally in a cancer genetics clinic. Women who are proven BRCA mutation carriers, untested first-degree relatives of known BRCA mutation carriers, and those with strong family history and estimated to have at least 20-25% lifetime breast cancer risk by risk assessment models are considered to have genetic risk for developing breast cancer. These women have a 5-10 times increased risk of breast cancer compared to women without these risk factors. They frequently present before the age of 40.

Women without genetic risk factors or previous breast conditions are considered to have normal risk of developing breast cancer.

6.3 What should be done?

6.3.1 Clinical breast examination

The New York Health Insurance Plan trial[97] and the Canadian National Breast Screening trials[98,99] included clinical breast examination in their studies. Both failed to show any mortality benefit from clinical breast examination. Although cancer detection rate by

[1] Data on cancer incidence in Singapore, 2003-2007, National Registry of Diseases Office.

clinical breast examination appears to be low, it was noted that some cancers detected by clinical breast examination were not detected on mammography.[97] Furthermore, clinical breast examination provides the occasion for doctors to educate women about breast cancer.[100]

D Although clinical breast examination has been shown to confer no mortality benefit in a screened population, it is good practice to advise women to consult their doctor for clinical breast examination whenever there is any noticeable change in their breast.

Grade D, Level 4

6.3.2 Breast self-examination

Breast self-examination has been studied in a high quality large-scale RCT as a screening test for breast cancer in Chinese women.[101] This trial showed no mortality benefit from breast self-examination when used for screening. Nevertheless, breast self-examination is felt to improve women's awareness of their own breasts and breast cancer. In Singapore, the breast cancer incidence starts to rise significantly only for women over the age of 30. It can be argued that routine breast self-examination for Singapore women should start after 30.

D Despite evidence that it has no survival benefits, monthly breast self-examination is recommended as it is felt to improve women's awareness of their own breasts and breast cancer. Breast self-examination is recommended from the age of 30 for normal risk women.

Grade D, Level 4

6.3.3 Mammography

6.3.3.1 Rationale

The underlying premise for breast cancer screening is that it allows for the detection of breast cancers before they become palpable. Small tumours are more likely to be early stage disease, having better prognosis, and are more successfully treated.[102-104]

Breast cancer screening may be sporadic (or opportunistic), where an individual woman chooses to have intermittent screening mammography at her discretion, or mass (or population-based screening), where women are systematically invited to have screening mammography at predetermined intervals such as in BreastScreen Singapore.

The goal of breast screening on a mass, or population basis is to produce a shift in cancer detection towards pre-invasive cancers, and to eventually reduce the mortality from breast cancer. However, a significant reduction in mortality at the population level is expected only after 7-10 years with 70% of the target population receiving mammography.[105] In Singapore, about 57.7% of women aged 40-69 years have had a screening mammogram, although only 41% of women aged 50-69 had been screened within the previous 2 years, in accordance with the recommended frequency.[106]

Mammography based screening is widely accepted as appropriate and beneficial for women above the age of 50. Eight randomized controlled trials of screening with mammography have been conducted to date.[97-99,107,108] While there is variation in the observed mortality reductions, a meta-analysis of the most recent results showed a 24% mortality reduction associated with an invitation to screening.[100]

Although recent controversy was raised about the actual impact of mammographic screening,[109,110] it is generally agreed that the trials, although by no means perfect, give valid evidence for the efficacy of mammographic screening.[111,112] The pooled estimate from all the trials and all ages show overall a significant 20% reduction in breast cancer mortality with invitation to screening in women aged 40 to 74. Subgroup analysis reveals that the magnitude of mortality reduction is greater for women more than 50 years old compared to women in the 40-49 age group.[113] Meta-analyses of randomized controlled trials also demonstrated a 7 to 23% reduction in breast cancer mortality in women 40 to 49 years of age.[114]

The potential survival benefit of breast screening has been calculated to be much higher for younger than for older women, with a high screening frequency resulting in more lifetime gained. However, the

cost of saving years of life in this age group would be at least twice as much for each cancer detected as for women from 50-69 years.[115]

There is great variation in recommendations for mammographic screening for women aged 40-49. Therefore, recommendations for Singapore are based on a balance between international guidelines and practice, and the relatively high incidence of breast cancer for Singaporean women in this age group (40% of cases are diagnosed in women below 50 years)[61], while taking into account the weaker evidence, higher costs and higher false positive rate of detecting breast cancer in this age group using screening mammography.

Clinicians should inform women 40 to 49 years of age about the potential benefits and harms of screening mammography. They should base screening mammography decisions on benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile.[114,116-118]

There is limited data on the efficacy of screening mammography in women over the age of 69. Only one randomised control trial included women older than 69.[119,120] Published screening studies have concluded that the performance and effectiveness of mammography is at least as good if not better in women aged 70 and older compared with younger women.[121,122]

Mammographic screening in older women should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography. However, if she has an estimated life expectancy of less than three to five years, severe functional limitations, and/or multiple or severe co-morbidities likely to limit life expectancy, it may be appropriate to consider cessation of screening.[100]

6.3.3.2 Facts about mammography

Film screen mammography

For routine screening, examination films are taken in medio-lateral oblique and cranio-caudal projections. Two-view examinations decrease the recall rate compared with single-view examinations by

eliminating concern about abnormalities due to superimposition of normal breast structures, significantly improves both sensitivity, particularly for small breast cancers, and specificity.[123-125]

The sensitivity of mammography in women aged over 50 has been estimated to range from 68% to over 90%, with most trials and programmes achieving sensitivities of around 85%. In women aged 40-49 the sensitivity has been reported to be lower, with estimates between 62% and 76%.[126]

Mammography is less effective in identifying cancers in women under 50 because breast tissue tends to be denser in pre-menopausal women. The sensitivity of mammography is much lower in women with dense breasts than those with predominantly fatty breasts.[126] Furthermore, cancers found in younger women tend to be more aggressive and grow faster.[128,129]

The specificity of breast screening by mammography ranges between 82% and 97%.[126]

It is recognised that the interval cancer rate (cancers that appear between routine screening episodes) will be about 10% of all the cancers detected, typically at a level of about 10 per 10,000 screens at 2 years, only about one-third of these will be detectable on retrospective review.[130-133] Therefore, about 7% of breast cancers cannot be detected by screening mammography, even in retrospect.[134]

For breast screening, the optimal screening interval has empirically been determined through analysis of breast screening trial data[135] to be 2 years for women aged 50 to 70 and shorter screening intervals of 1 year is recommended for women aged 40 to 49.

Potential risks of mammography include false-positive results[136], diagnosis and treatment for cancer that would not have become clinically evident during the patient's lifetime, radiation exposure[137,138] false reassurance, and procedure-associated pain. False-positive mammography can lead to increased anxiety and to feelings of increased susceptibility to breast cancer, but most studies found that anxiety resolved quickly after the evaluation.[139-141] Women with false negative mammograms may be given false assurance. Up to one-fourth of all invasive breast cancers are not detected by mammography in 40- to 49- years olds, compared with one-tenth of

breast cancers in 50 to 69 year olds. The diagnosis and treatment of breast cancer may be delayed because of a normal mammogram.[142]

Full field digital mammography (FFDM)

FFDM has been shown to have similar sensitivity but higher specificity than film screen mammography for breast cancer screening.[143,144] In women under 50 years, pre or peri-menopausal women, and women with radiographically dense breasts, FFDM is more sensitive in detecting cancer.[145] In FFDM, mammographic images are acquired and displayed digitally, allowing easier consultation between clinicians and radiologists within the computer network. FFDM systems also come with viewing software for improved analysis of mammographic images. This allows better evaluation of the dense breast and reduces the need for repeat images.

6.3.4 Breast ultrasound

Ultrasound is a useful modality for further assessment of mammographic abnormalities and for image-guided breast biopsy. It can identify cancers that are mammographically occult. However, there is no scientific evidence as yet to support the use of ultrasound alone as a screening test for breast cancer, nor is there any evidence that it reduces cancer mortality. Furthermore routine use of sonography is likely to increase the number of false positive findings leading to increased anxiety, unnecessary recalls, additional evaluation including biopsies or short term follow up. Biopsy rates from ultrasound screening range from 2.5 to 7.4% compared to the rate for screening mammography of 1 to 3%.[146-150]

D Breast ultrasound should not be used for routine breast screening. It has a definite role in the further assessment of a mammographic abnormality.

Grade D, Level 4

6.3.5 Breast MRI

Although MRI is highly sensitive for detecting invasive breast cancer[151,152], its specificity is significantly lower than mammography. MRI should not be used as a screening tool for women at normal risk.

In women with high genetic risk for breast cancer, studies have shown that MRI detects more cancers (with a sensitivity of 71% to 100%) compared to mammography (sensitivity 25% to 40%).[151-153] MRI cannot replace mammographic screening in these women as some cancers may manifest as microcalcifications which may not be shown on MRI.

In all screening studies to date, the specificity of MRI is significantly lower than mammography and results in a higher recall rate (from 8 to 17%) and biopsy rates ranging from 3 to 15%.[151-156] Breast MRI is significantly more costly than "conventional" breast imaging.

D Women who are at high genetic risk for breast cancer will benefit from annual screening mammography and MRI. Breast MRI should not be used for routine breast screening of women who are at normal risk of developing breast cancer. [151-156]

Grade D, Level 4

6.3.6 Other imaging techniques

Dedicated breast CT – Early experience showed dedicated breast CT to be equal to mammography in the detection of breast masses. However there are significant limitations in breast CT for the detection of microcalcifications.[157]

Nuclear medicine techniques such as scintimammography[158,159] and Positron Emission Tomography (PET)[160] are useful adjunct techniques when used together with mammography for evaluation of the symptomatic breast. However, there is no proven benefit when employed in the screening setting.

Non-conventional techniques such as Thermal imaging, Optical imaging, Electrical Impedence Imaging and Microwave Imaging rely on the alteration of physical properties of heat, absorption of light or electrical conductivity in the diseased breast.[161] These techniques are experimental and their efficacy in routine clinical practice is unproven.

C Breast CT, Scintimammography, PET, and other non-conventional techniques such as Thermal imaging, Optical imaging, Electrical Impedence Imaging and Microwave Imaging are experimental techniques. They **should not** be used for routine breast screening.[157-161]

Grade C, Level 2++

6.4 Cost-effectiveness

Cost-effectiveness results from different studies show a broad range of cost-effectiveness ratios for the screening of breast cancer, using mammography. However, for women over the age of 49, comparable studies yield cost-effectiveness estimates that fall within a range, that, by conventional standards, would be considered as cost-effective.[162] Furthermore, a study comparing different screening programmes in the UK concluded that extending the age of invitation to a final screen from 64 to 69 and shortening the interval from three to two years is cost-effective.[163]

Intuitively, screening women under 50 would seem to offer greater benefits, since more life-years should be gained. However, the cost-effectiveness of breast cancer screening in 40 to 49 year old women is lower than that for women over 50, due to the lower breast cancer incidence and the poorer performance of the screening test due to denser breast tissue in the younger age group. It has been estimated that screening women aged 40-49 years costs approximately five times as much per life year saved as screening older women (aged over 50).[164,165]

For older women, results are inconclusive. Current estimates suggest that breast cancer screening after age 65 years reduces mortality at reasonable costs for women without clinically significant comorbid conditions. However, more data are needed on disease biology and preferences for benefits and harms in older women.[166]

Finally, we have to be aware that the above conclusions were based on studies in western developed populations. Those results may not apply to Singapore women, who have a slightly lower incidence rate than two-thirds of the rates recorded for women in northern Europe and US. Therefore, cost-effectiveness ratios might be less favourable for Singapore.

6.5 Recommendations for breast screening

6.5.1 Normal risk, asymptomatic women

Asymptomatic women 50-69 years

A All normal risk, asymptomatic women 50-69 years of age should be screened with mammography only, every two years. Ultrasound and clinical breast examination **are not routinely required**.

Grade A, Level l++

Asymptomatic women 40-49 years

C Women at normal risk aged 40-49 years should be informed of the benefits, limitations and potential harms associated with screening mammography so that they can make an informed choice. If screening is to be performed, it should be done annually. Ultrasound and clinical breast examination **are not routinely required**.

Grade C, Level 2++

Asymptomatic women <40 years

There is no evidence that women under the age of 40 with no risk factors for developing breast cancer will derive any mortality benefit from screening mammography or any other imaging test, even if they occasionally detect an early breast cancer.

A Normal risk, asymptomatic women under 40 years **should not** undergo breast screening with any imaging modality.

Grade A, Level l+

Asymptomatic women >70 years

A In Western nations, the evidence supports mammographic screening every 2 years for all normal risk women 70-75 years of age. However, for Singaporean women the lower incidence of breast cancer in this age group suggests that screening mammography may be less beneficial and should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. If individual screening is

performed, it should be at two-yearly intervals. Ultrasound and clinical breast examination **are not routinely required**.

Grade A, Level l++

6.5.2 Women on hormone replacement therapy

It is now accepted that there is a small but definite increase in risk of breast cancer with prolonged use of hormone replacement therapy (HRT), resulting in a net increase in breast cancer of 0.2% at 5 years, 0.6% at 10 years and 1.2% at 15 years of continuous HRT. This very small absolute increase in risk appears to disappear within 5 years of ceasing HRT.[167] There is no evidence that this slight increase in breast cancer increases patient mortality.

It is reasonable to perform screening mammography regularly for these women. Studies have shown that HRT increases mammographic breast density, leading to lower specificity and higher false positive recalls.[168-170] However, no randomized controlled trials have been carried out in these women and there is no consensus on the ideal screening interval. Therefore, women on HRT should continue to have regular screening. There is no evidence that mammographic screening frequency should be increased based on current evidence.

D Women on conventional hormone replacement therapy have a very slightly increased risk of breast cancer. They should have regular screening mammography. Those aged 40-49 years should be screened annually, and those aged 50-69 biannually.[167]

Grade D, Level 4

6.5.3 Women who have genetic risk for cancers

Women with the following conditions[171] should consider genetic evaluation and testing for hereditary breast cancer syndrome:

1. Breast cancer diagnosed ≤40 years
2. Personal history of breast cancer and ovarian cancer
3. Personal history of breast cancer and a close male blood relative with breast cancer
4. Personal history of breast cancer diagnosed ≤50 years or 2 breast primaries, and ≥1 close blood relative with breast cancer ≤50 years and/or ≥1 close blood relative with epithelial ovarian cancer

5. Personal history of breast cancer diagnosed at any age, with ≥2 close blood relatives with breast and/or epithelial ovarian cancer at any age
6. Individual from a family with a known BRCA1/BRCA2 mutation

Three elements of breast surveillance recommended to these women include self-examination, clinical examination, and radiographic examinations with mammography and magnetic resonance imaging (MRI). These recommendations are of presumed, but unproven, efficacy.[172] Emerging data have supported the role for MRI and have led to the recommendation of inclusion of MRI in the routine management of women with BRCA mutations and those deemed at very high risk for breast cancer.[173]

D Women who are at high genetic risk for breast cancer should perform monthly breast self-examination, 6 monthly clinical breast examination, annual mammogram and MRI. Screening should start at age 25-30 years for BRCA mutation carriers and their untested first-degree relatives, or as early as 5-10 years before the age of onset of breast cancer in the youngest family member in those with family history of breast cancer but no proven mutation.

Grade D, Level 4

GPP Women suspected to be at high genetic risk for breast cancer should be referred to tertiary centres for risk assessment and consideration of genetic testing.

GPP

Some experts recommend staggering MRI screening and mammography screening every 6 months with a view to reducing the rate of interval cancers; others recommend performing both studies at the same time so that the studies can be interpreted together. There is no evidence to support one approach over the other.[173]

D In women with radiographically dense breasts and in women under 50 years, digital mammography is recommended over film screen mammography to increase cancer detection rate.[145]

Grade D, Level 4

6.5.4 Women with prior breast cancer or premalignant conditions

Women with prior breast cancer (including ductal carcinoma-in-situ) have an increased risk of tumour recurrence. They should have annual mammography of the remnant breast (if breast conservation has been performed) and the contralateral breast. The baseline post-treatment mammogram should be performed 1 year after the time of diagnosis but no earlier than 6 months after definitive radiotherapy.

Similar strategies would apply to women with lobular carcinoma in situ and atypical hyperplasia who have 8-10 fold and 4-5 fold increase risk respectively of developing breast cancer.[174,175]

On top of the annual mammography, the American Society of Clinical Oncology recommends monthly breast self-examination and at least 6-monthly clinical breast examination.[174]

Risk reduction strategies can be used and these include tamoxifen, raloxifene, surgery, decisions on hormone replacement therapy, alcohol intake, exercise and weight reduction.[175,176]

D Women with prior breast cancer or pre-malignant conditions should receive annual screening mammography of the remnant and contralateral breasts. At 5 years disease-free post-surgery, they may return to the standard screening interval for asymptomatic women of the same age.[174,175]

Grade D, Level 4

6.5.5 Women with breast implants

There is no evidence that women with breast implants have increased risk of breast cancer compared to age-matched women. Regular mammography remains the most reliable tool for early diagnosis of breast cancer. MRI and ultrasound may be useful as adjuncts and used in selected cases.[177]

A Women with breast implants are recommended to have routine screening mammography once every 1-2 years, depending on their age.[177]

Grade A, Level 1++

6.5.6 Women with silicone breast injections

Screening of breast cancer remains a challenge in these women. On mammography the dense silicone oil may prevent detection of cancer. On ultrasound evaluation, the oil combines with breast tissue to produce dense shadowing from virtually all the breast parenchyma, again obscuring visualization. MRI is a potentially valuable tool to be used in addition to physical examination. However its limitations and drawbacks (false positive diagnosis due to silicone granulomas) need to be understood and each patient should be assessed on a case-by-case basis.[178]

GPP Women with free silicone or paraffin oil injections in their breasts should be clinically examined and counselled as to the futility of screening using any currently available test. MRI may be useful in highly selected cases where there is a strong suspicion of breast cancer.

GPP

6.6 Summary

Mammographic screening once every 2 years is beneficial for women at normal risk of breast cancer over the age of 50 years. There is some evidence to support annual screening mammography for women from 40-49 years. There is also emerging evidence of the utility of MRI in screening of women who have genetic risk of breast cancer. Other non-conventional imaging technologies are not recommended for screening. Breast self-examination and clinical breast examination do not affect survival but is recommended from age 30 years as it increases awareness of breast disease. Hormone replacement therapy is associated with minimal increase in risk of developing breast cancer, and does not warrant more frequent mammographic screening than for other women of similar age.

7 Screening for cervical cancer

Key Recommendations:

C All women who have ever had sexual intercourse should undergo screening for cervical cancer from the age of 25 years (pg 54).

Grade C, Level 2+

B Pap smear screening should be performed at least once every 3 years (pg 55).

Grade B, Level 2++

B Screening should be performed using the Papanicolaou (Pap) smear (pg 57).

Grade B, Level 2++

7.1 Introduction

Cervical cancer is the 6th most common cancer among Singapore women.[2] The age-standardized rate has declined steadily from 18 per 100,000 population per year (1968-1972)[61] to 8.8 per 100,000 population per year (2003-2007)[2]. The age-standardized mortality rate for cervical cancer is 3.4 per 100,000 population per year (2003-2007).[2]

The majority of cervical cancers go through a pre-malignant phase known as cervical intraepithelial neoplasia (CIN). The aim of screening is to detect these pre-malignant lesions before they become cancers. In Singapore the highest number of cases of CIN occurs between 35-44 years of age[61] and the peak incidence of invasive cervical cancer is around ten years later between 45-54 years of age.

The number of women aged 15-19 with significant CIN is very low, with only 4 cases detected in the period between 1998-2002 (0.3%). Women between 20-29 years of age make up 10.0% of the total number with CIN3 while that in women over 70 years of age is 1.5%.[61]

For invasive cervical cancers between 1998-2002, only 5 cases occurred in women under 25 years of age (0.5%). A total of 214 cases occurred in women over 70 years of age (21.3%).[3]

Risk factors

Infection with certain types of Human Papillomavirus (HPV) is a necessary cause of cervical cancer.[179,180] Recently vaccines have been developed against the two most carcinogenic HPV types (HPV-16 & HPV-18) which account for 70% of all squamous carcinomas of the cervix.[181,182]

Risk factors for cervical cancer include:[183-187]

1. Infection with HPV
2. Human Immunodeficiency Virus infection
3. Immunosuppression
4. Multiple sexual partners (in either partner)
5. Onset of sexual intercourse at an early age
6. History of sexually transmitted infections
7. Long term consumption of combined oral contraceptive pills
8. Cigarette smoking

The following groups of women are considered to be at low risk for cervical cancer:

1. Women who have never had sexual intercourse[188]
2. Women who have had a hysterectomy in which the cervix was removed, unless the hysterectomy was performed because of cervical cancer or its precursors[189,190]

7.2 Who should be screened?

7.2.1 Age to start screening

C All women who have ever had sexual intercourse should undergo screening for cervical cancer from the age of 25 years.[191]

Grade C, Level 2+

The rationale for the initiation of screening is that HPV is a sexually transmissible virus and that significant cervical precursor lesions are not likely to be detected until 3-5 years after exposure, and that invasive squamous cervical cancer takes several years to develop. The IARC recommends that screening should not commence until women are 25 years old, stating that "there is minimum benefit and substantial harm in screening below age 25".[191] The choice of 25 years to initiate screening is supported by local data which shows that in the years 1998-2002, women under 25 years of age accounted for only 1.7% (27/1585) of all cases of carcinoma in situ (CIN3). In that same period, there were only 4 cases of invasive cervical cancer in women under the age of 25 years (0.4% of total cases).[61]

GPP Women under the age of 25 years who are considered high risk, or who deem themselves to be high risk may have Pap smears performed if clinically appropriate.

GPP

7.2.2 Age to stop screening

GPP A woman can be discharged from screening at 69 years of age if the smear taken at 69 years is negative and she has had 2 previous consecutive negative smears within the last 10 years.

GPP

However, women over 69 years who have had sexual intercourse and have never had a Pap smear should be screened.

The previous recommendation in MOH Clinical Practice Guidelines 6/2003: Health Screening, was to stop screening at age 65 years. This has been revised to age 69 years to be in line with the recommendations for cessation of breast cancer screening. In addition, local data shows that the percentage of cases of CIN3 detected in

women aged 65-69 years increased from 1.4% (21/1532) in the years 1988-1992, to 2.6% (41/1585) in the years 1998-2002.[61]

7.2.3 Frequency of screening

B Pap smear screening should be performed at least once every 3 years.[192,193]

Grade B, Level 2++

This recommendation does not apply to women with previous abnormal Pap smears who are on follow up with a gynaecologist.

Screening interval benefits are dependant on the age of women screened. A case control study calculated the relative risk of cervical cancer according to screening interval in three age categories: 20-39 years, 40-54 years, and 55-69 years.[193] In the 20-39 age group, annual screening would prevent 76% of incidences of cervical cancer, compared with 61% for 3 yearly screening, and 30% for 5 yearly screening. For the women aged 40-54, annual screening would prevent 88% of cancers compared with 84% for 3 yearly screening. In the 55-69 age group, annual screening would prevent 87% compared with 83% for 5 yearly screening.

7.2.4 Special circumstances

A) Women who have had a hysterectomy

C Women who have had a hysterectomy in which the cervix was removed for benign causes do not need to be screened, unless there is a history of previous cervical intraepithelial neoplasia.[189,190,194]

Grade C, Level 2+

The recommendation to discontinue screening after a total hysterectomy for benign disease is appropriate given the low yield of screening and the potential harm from false positive results.

GPP The absence of a cervix should be confirmed by clinical records or clinical examination. If the indications for hysterectomy are uncertain, screening may be performed at the discretion of the clinician.

GPP

B) Immunocompromised women

There is evidence to show that immunocompromised and HIV positive women are at higher risk of cervical cancer and therefore should be screened more frequently.[183,195,196]

B Immunocompromised or HIV positive women should have annual screening and may be screened earlier.

Grade B, Level 2++

C) Women vaccinated with HPV Vaccines

GPP Women who have been vaccinated with HPV vaccines should continue to have screening at the same intervals.

GPP

The HPV vaccines do not completely prevent cervical cancer as they are targeted primarily at the two most common oncogenic HPV types (Types 16 & 18).[181,182] Women who have been vaccinated remain at risk from infection from the other oncogenic types and therefore should continue to be screened.

7.3 What should be done?

The Papanicolaou (Pap) smear fulfills the criteria for an effective screening test (World Health Organization Criteria).[197] It has been largely responsible for the dramatic decline in incidence of cervical cancer in countries that have implemented comprehensive screening programmes. Two forms of the Pap smear are presently available. The conventional Pap smear involves smearing cervical cells directly onto a glass slide and fixation with alcohol before sending the slide to a laboratory. In liquid based cytology (LBC), the broom type-collecting device is rinsed in the fixative or the head is detached into the fixative, and sent to the laboratory where the final slide is produced. In terms of clinical performance, the Pap smear is relatively insensitive for the detection of CIN or cancer, and must be repeated at frequent intervals to achieve effectiveness. In a meta-analysis, the pooled sensitivity of the Pap smear for detecting CIN2-3 was 51% (95%CI, 37-66%) and the specificity was 98% (95%CI, 97-99%).[198,199]

Liquid based cytology results in a more complete sample without cell clumping and obscuring by blood, mucus or inflammatory cells. In addition, the residual cells from the sample can be used for ancillary tests, such as for HPV and Chlamydia, without the need to collect a further specimen. Most studies show an increased sensitivity of LBC over conventional cytology with no difference in specificity. LBC also results in a reduction in the number or inadequate (unsatisfactory) samples.[199-202] However LBC is a costlier test but this is offset by less frequent need to repeat unsatisfactory smears and for laboratories, a substantial benefit is a gain in productivity due to a shorter time to examine each smear.

Another screening test that has been used is HPV DNA testing (Hybrid Capture II). It has been shown to be more sensitive, but less specific than conventional cytology.[200,203] The role of routine use of HPV DNA screening test is being investigated in a number of on-going clinical trials. At the present time, primary screening with HPV DNA testing is not recommended.

B Screening should be performed using the Papanicolaou (Pap) smear.[198,199]

Grade B, Level 2++

GPP Either conventional cytology or liquid-based cytology may be used.

GPP

7.4 Effectiveness of screening

B A nationwide population-based cervical screening programme that collects data from all Pap smears performed should be implemented.

Grade B, Level 2++

An organised population based cervical screening programme with good coverage and recall mechanisms reduces the incidence of and mortality due to cervical cancer, compared to spontaneous (opportunistic) screening.[204-208]

At present, screening in Singapore is largely opportunistic (MOH National Household Survey 2004 reported that 84% of women had at least one Pap smear). The Health Promotion Board runs a screening

programme (CervicalScreen Singapore) with a recall mechanism to remind women to attend for screening every three years. However, this is limited only to women who consent to register with the programme and who have their Pap smears performed at polyclinics.

7.5 Cost-effectiveness of screening

An organised population based cervical screening programme reduces not only mortality due to cervical cancer, but also costs. A recent study, comparing alternative screening strategies for Hong Kong, showed that for all cytology-based screening strategies, opportunistic screening was more costly and less effective than an organised programme of screening every 3, 4 and 5 years.[209]

8 Screening for uterine cancer

Key Recommendation:

B Screening for endometrial cancer is **not recommended** for women with an average or increased risk for endometrial cancer (pg 60).

Grade B, Level 2++

8.1 Introduction

Uterine cancer is the 4th most common female cancer in Singapore.[2] In Singapore, the incidence has shown an increase over time, from an age-standardized incidence rate of 7.8 per 100,000 population in 1993 to 1997 to 11.7 per 100,000 population in 2003 to 2007. [2]

8.2 Definitions

Average Risk: Women with no identified risk factors.

Increased Risk:

- History of unopposed estrogen therapy
- Late menopause
- Tamoxifen therapy
- Nulliparity
- Infertility or failure to ovulate
- Obesity
- Diabetes
- Hypertension

High Risk: Women with or at risk of hereditary non-polyposis colorectal cancer (HNPCC).

8.3 What should (or should not) be done?

1. There is insufficient evidence to establish whether a decrease in mortality from endometrial cancer occurs with screening by endometrial sampling or transvaginal ultrasound.[210,211]

2. The use of the Pap smear for screening for endometrial cancer has been evaluated and found to be insensitive.[212]

3. B Screening for endometrial cancer is **not recommended** for women with an average or increased risk for endometrial cancer.[211-213]

   Grade B, Level 2++

4. C Hereditary non-polyposis colorectal cancer syndrome (HNPCC) is associated with an increased risk for endometrial cancer, with an estimated lifetime risk between 27-71%.[214] Women with or at risk for hereditary non-polyposis colorectal cancer (HNPCC - Table 2)[215] should be offered annual screening for endometrial cancer with transvaginal ultrasound and endometrial biopsy by age 30-35.[216]

   Grade C, Level 2+

Women in this high risk group should be informed about the risks and symptoms of endometrial cancer, and should be informed about the potential benefits, risks, and limitations of testing for early endometrial cancer, preferable by tertiary centres.

8.4 Other relevant information

Women with endometrial cancer tend to present with symptoms at an early favourable stage so they should be informed about the symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding to their physicians. Although screening is inappropriate for the general population, early evaluation of postmenopausal bleeding with judicious use of hysteroscopy and endometrial biopsy is important for the early detection of endometrial cancer.[217]

8.5 Summary

There is insufficient evidence to screen for uterine cancers other than in women with or at high risk for hereditary non-polyposis colorectal cancer.

Table 2 International Collaborative Group Clinical Criteria for diagnosing hereditary non-polyposis colorectal cancer syndrome (Amsterdam II)[215]

1)	There should be at least 3 relatives with an hereditary non-polyposis colorectal cancer syndrome-associated cancer (cancer of colorectum, endometrium, small bowel, ureter or renal pelvis).
2)	One relative should be a first degree relative of the other two.
3)	At least two successive generations should be affected.
4)	At least one case should have been diagnosed before age 50 years.
5)	Familial adenomatosis polyposis should be excluded in the colorectal cancer cases if any.

9 Screening for ovarian cancer

Key Recommendation:

D The use of screening in women at average risk for epithelial ovarian cancer with serum markers and/or ultrasound is **not recommended**. There are currently no effective methods for the routine screening of asymptomatic women at average risk for ovarian cancer. These screening practices are **strongly discouraged** as they invariably lead to unnecessary interventions that ultimately risk the health and well-being of asymptomatic members of the general population (pg 63).

Grade D, Level 2+

9.1 Introduction

Ovarian cancer is the fifth most common cancer among Singapore women. The age-standardized rate is 12.0 per 100,000 population per year (2003-2007).[2] The age-standardized mortality rate is 4.1 per 100,000 population per year (2002-2006).[2]

9.2 Definitions

Women at Average Risk for Ovarian Cancer: Any woman with no identifiable risk factors.

Women at Increased Risk for Ovarian Cancer: Defined as individuals with any of the following risk factors:

1. Confirmed BRCA1/2 mutation carriers or untested first degree relatives of known BRCA1/2 mutation carriers.

2. Two or more first degree relatives with ovarian cancer.

3. Family history of breast and/or ovarian cancer suspicious of BRCA mutation.

9.3 What should (or should not) be done?

9.3.1 Women at average risk

D The use of screening in women at average risk for epithelial ovarian cancer with serum markers and/or ultrasound is **not recommended**. There are currently no effective methods for the routine screening of asymptomatic women at average risk for ovarian cancer. These screening practices are **strongly discouraged** as they invariably lead to unnecessary interventions that ultimately risk the health and well-being of asymptomatic members of the general population.[218-223]

Grade D, Level 2+

D The most useful strategy at present is for both the medical practitioner and patient to have a high index of suspicion for persistent symptoms of increase in abdominal size, abdominal bloating, fatigue, abdominal pain, indigestion, inability to eat normally, urinary frequency, pelvic pain, constipation, back pain, urinary incontinence of recent onset, or unexplained weight loss.[218]

Grade D, Level 2-

B The use of oral contraceptive pills has been shown to decrease a woman's lifetime risk of developing epithelial ovarian cancer. A regimen of continuous use for as little as one year has been shown to have significant protective effect for epithelial ovarian cancer for up to nineteen years after discontinuation. As such, in the absence of obvious contraindications to oral contraceptive pill use, women may be counseled about its use and its non-contraceptive benefits of decreasing one's lifetime risk of epithelial ovarian cancer.[224,225]

Grade B, Level 2++

9.3.2 Women at increased risk

GPP There is insufficient evidence to recommend for or against the screening of asymptomatic women at increased risk of developing ovarian cancer. Such women should be referred to tertiary centres. Annual pelvic examination, transvaginal ultrasound with or without CA125 serum testing is recommended in women with or at high risk for BRCA mutations based on expert consensus, although there is currently insufficient evidence to ascertain the effectiveness of screening.[172,214,226,227]

GPP

GPP Women with family histories suspicious for BRCA mutations (see Familial risk factors suspicious for BRCA mutations) should be referred to tertiary centres for genetic risk assessment.[172,214,226,227]

GPP

Familial risk factors suspicious for BRCA mutations

1. First-degree relative diagnosed with ovarian cancer before age 40 years.
2. First-degree relative diagnosed with breast and ovarian cancer (one cancer diagnosis before age 50 years).
3. Two or more first- and second-degree relatives (of same lineage) with ovarian cancer.
4. Two or more first- and second-degree relatives (of same lineage) with breast cancer and one relative with ovarian cancer.
5. One first- or second-degree relative with breast cancer before age 40 years and one first- or second-degree relative with ovarian cancer before age 50 years (of same lineage).
6. Two or more first- and second-degree relatives (of same lineage) diagnosed with breast cancer, one before age 40 years.

Source: Adapted from Burke et al.[226]

9.4 Summary

There is insufficient evidence to support routine ovarian cancer screening in women at average risk with CA125 serum testing with or without pelvic ultrasound. Women at increased risk for ovarian cancer should be referred to a tertiary centre.

10 Screening for prostate cancer

Key Recommendation:

A At the present time, given the lack of data on whether screening improves disease-free survival, there is a **lack of evidence** to support population-based screening for the early detection of prostate cancer in Singapore (pg 69).

Grade A, Level 1+

10.1 Introduction

Prostate cancer is the third most common cancer amongst men in Singapore, with an incidence of 23.9 cases per 100,000 per year. It is the sixth leading cause of cancer deaths in Singaporean men.[2]

Prostate cancer incidence increases with age, and men with a family history of prostate cancer and African-American men are at higher risk of both developing and dying from prostate cancer.

The natural history of prostate cancer varies from indolent low grade disease with mortality occurring more than 10 years after diagnosis to aggressive high grade disease which commonly presents with locally advanced disease or metastases with a median survival of 2 years. Autopsy studies clearly indicate that the vast majority of prostate cancers will not manifest clinically. It has been estimated that a healthy 50-yr-old man has a 42% risk of developing a microscopic focus of cancer by the time he is 75 yr old; within that same time frame he has a 9.5% risk of developing clinically evident disease and only a 2.9% risk of dying from prostate cancer.[228]

10.2 Benefits and risks of prostate cancer screening

Benefits of prostate cancer screening

Prostate cancer survival is related to many factors, especially the extent of tumour at the time of diagnosis. The 5-year relative survival

among men with cancer confined to the prostate (localized) or with just regional spread is 100 percent, compared with 31.9 percent among those diagnosed with distant metastases.[249] While men with advanced stage disease may benefit from palliative treatment, their tumours are generally not curable.

Thus, a screening programme that could identify asymptomatic men with aggressive localized tumours might be expected to substantially reduce prostate cancer morbidity, including urinary obstruction and painful metastases, and mortality.

Risks of prostate cancer screening

Although prostate biopsies rarely (<1%)[250] cause complications serious enough to require hospitalization, screening is not an entirely benign process and may be associated with discomfort and possible complications of biopsy, such as pain, hematospermia, hematuria, or infection.[250]

In addition, false-positive results have a psychological cost. Chronic anxiety can follow a negative prostate biopsy because this apparently favourable result cannot completely rule out prostate cancer given the relatively high false-negative biopsy rate.[251] Thus screening may cause undesirable mental health consequences.[251]

Overdiagnosis refers to the detection by screening of conditions that would not have become clinically significant. These patients are subject to the risks of screening, confirmatory diagnosis, and treatment from radical prostatectomy or radiation therapy which may include urinary incontinence, bowel dysfunction, sexual dysfunction and operative mortality. This is an important issue to consider since even in the absence of treatment, many men found to have prostate cancer as a result of screening will have a lengthy period of time without clinical problems.

Current evidence on whether population screening should be done

There is currently no convincing data from randomised controlled trials of screening that show benefits on morbidity and mortality.

In the USA, there has been a reduction in prostate cancer mortality which is often attributed to the widely adopted aggressive screening

policy. However, there is still no absolute proof that the use of prostate-specific antigen (PSA) screening is the cause for reduced mortality due to prostate cancer.

A non-randomized screening project in Tyrol (Austria) [252] may support the hypothesis that screening can be effective in reducing prostate cancer mortality. The early detection programme in combination with the availability of free treatment was used as an explanation for the 33% decrease in the prostate cancer mortality rate seen in Tyrol as compared with the rest of Austria.

Other studies have contradicted the positive findings attributed to screening, with a comparative study between the Seattle area (highly screened population) and Connecticut (seldom screened population) showing no difference in the reduction in the rate of prostate cancer mortality.[253]

In order to really evaluate the efficacy of prostate cancer screening, prospective, population-based, randomized trials are needed. To date, there have been only two published randomized controlled trials of screening by DRE and PSA, the Quebec[254] and Norkoping[255] studies.

The Quebac trial based on 46,193 men reported positive findings, but the data analysis was flawed. When the data was evaluated by a more appropriate intention-to-screen analysis, there was no mortality differences between the screened and non-screen groups.

In the Norkoping trial, after a 15 year followup, prostate cancer diagnosis was more common in the screened group. However, there was no difference in prostate cancer mortality between the screened and unscreened groups.

A pooled analysis of the above two studies also showed no difference in mortality between the screened and nonscreened groups.

Two large randomized screening trials are currently underway, the American Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial[256] and the European Randomized Study of Screening for Prostate Cancer (ERSPC)[257]. These studies, which plan to pool results, should have sufficient power and follow-up duration to determine the efficacy of screening. Results from both trials will not be available for several more years.

A At the present time, given the lack of data on whether screening improves disease-free survival, there is a **lack of evidence** to support population-based screening for the early detection of prostate cancer in Singapore.[254,255]

Grade A, Level 1+

10.3 Who should be screened?

Health professionals should adopt a shared approach to decision making for men who express an interest in prostate cancer testing and discuss both the potential benefits and harms associated with prostate cancer screening.

D Men who are between 50 and 75 years of age, with an estimated life expectancy of more than 10 years, may be offered screening for prostate cancer after a discussion of both the potential benefits and harms associated with prostate cancer screening.[229,230]

Grade D, Level 4

D High-risk men, such as African-American men and men with a strong family history of prostate cancer, i.e. one or more first-degree relatives [father, brothers] diagnosed before age 65 years, may be offered screening at an earlier age.

Grade D, Level 4

D In the absence of a strong family history, routine prostate cancer screening **should not** be offered to men younger than 50 years of age. Men who have a life expectancy less then approximately 10-15 years (either due to age or co-morbid conditions) should be informed that testing and treatment is unlikely to be beneficial.[231]

Grade D, Level 4

10.4 Screening tests

10.4.1 Prostate Specific Antigen (PSA)

PSA is a glycoprotein produced by the prostate gland and found in low concentration in the serum of normal men. It is the most established tumour marker available for diagnosis of prostate cancer.

Reference range

The upper limit of the normal range for serum PSA is generally accepted as 4 ng/ml. Prostate biopsy is generally performed for men with PSA exceeding 4 ng/ml.[232]

However there appears to be a continuum of prostate cancer risk at all values of PSA.[233,234] Men with PSA below the normal cutoff of 4 ng/ml may also have prostate cancer, albeit at a much lower risk. Lowering the PSA cutoff[234] below 4 ng/ml will increase the sensitivity of detecting prostate cancer, but at the cost of more unnecessary biopsies with added morbidity and increased detection of clinically insignificant cancers. Data among Asian men in this aspect is lacking.

Age specific reference ranges

PSA levels increase with age, largely due to a higher prevalence of benign prostatic hyperplasia. Age-specific reference ranges have been developed from normal populations to improve the discriminating power of PSA. Raising the PSA biopsy threshold in older men improves specificity, reducing the number of unnecessary biopsies. Conversely, lowering the threshold in younger men improves sensitivity and increases detection of early-stage tumours. A retrospective analysis of a large screening cohort[235] reported that applying age-specific reference standards would miss 47% of clinically localized cancers in men 70 and older[235] and lead to a 45% increase in unnecessary biopsies for men in their 50s.

The clinical utility of age-specific reference ranges remains uncertain, and they are not recommended by the US Food and Drug Administration (FDA) or PSA assay manufacturers.[236]

D Patients with serum prostate specific antigen exceeding 4 ng/ml should be offered prostate biopsy by a urologist. There is insufficient evidence to support the use of lower prostate specific antigen cutoffs for biopsy, or the use of age-specific reference ranges for prostate specific antigen.[235,236]

Grade D, Level 4

Test performance

Meta-analysis of PSA ≥ 4ng/ml showed the positive predictive value was 25.1%, with a range of 17.0% to 57.0%; sensitivity of PSA in detecting prostate carcinoma was 72.1%, with a range of 66.7% to 100.0%; and specificity of PSA in the detection of prostate carcinoma was 93.2%, with a range of 63.1% to 100.0%.[237]

Pitfalls

PSA is organ specific but not cancer specific. PSA levels are elevated in the presence of benign prostatic hyperplasia (BPH), prostatitis, urinary retention and recent ejaculation. Digital rectal examination does not cause a clinically significant rise in PSA. PSA levels are artificially lowered in patients taking 5∝ reductase inhibitors for BPH or alopecia.

PSA derivatives

PSA Velocity (PSAV)

PSAV is the absolute rate of change in PSA over time. Carter *et al.*[238] differentiated between men subsequently diagnosed with prostate cancer who had a PSAV of ≥ 0.75 ng/mL/year, and those who had BPH or no appreciable prostatic disease (PSAV < 0.75 ng/mL/year). This threshold of 0.75 ng/mL/year was 95% specific and 72% sensitive for a subsequent diagnosis of prostate cancer.

Free: Total PSA ratio

Men with prostate cancer have a greater fraction of serum PSA that is complexed to protease inhibitors i.e lower percentage of total PSA that is free, than men without prostate cancer.[239]

The free:total PSA ratio appears to be most useful in distinguishing between those with and without prostate cancer when total PSA is between 4 to 10ng/ml.[240]

PSA derivatives such as free:total ratios and PSA velocity are adjuncts that may be used to reduce the risk of unnecessary prostate biopsy. However there is also increased risk that prostate cancers might be

missed as a result of withholding biopsy. There is no consensus on the optimal strategy for their use.

GPP Prostate specific antigen derivatives such as free:total ratios and prostate specific antigen velocity **should not** be used for screening in the primary care setting.

GPP

10.4.2 Digital Rectal Examination (DRE)

The accuracy of DRE in diagnosing prostate cancer is highly dependent on the experience of the examiner. A meta-analysis of DRE estimated a sensitivity for detecting prostate cancer of 59% and a specificity of 94%, and positive predictive value of 28%.[241]

A randomized trial of prostate cancer screening showed that DRE alone resulted in detection of 56% of 473 cancers, and 17% of the 473 cancers would have been missed by PSA-based screening.[242]

In screening studies a combination of DRE and PSA has been shown to be superior for detection of prostate cancer than either test alone.[243]

C The use of digital rectal examination and prostate specific antigen are currently the recommended tests for screening for prostate cancer because of the risk of prostate cancer among men with an abnormal digital rectal examination and a normal prostate specific antigen.

Grade C, Level 2+

10.4.3 Transrectal ultrasonography

Ultrasonographic appearance of prostatic nodules is neither specific nor sensitive in the diagnosis of prostate cancer. In a study of 4000 patients, it has been shown that the hypoechoic lesion found on ultrasonography was not associated with increased cancer prevalence compared with biopsy cores from isoechoic areas.[244]

C Transrectal ultrasonography is **not recommended** for the screening or diagnosis of prostate cancer. [244]

Grade C, Level 2+

10.4.4 Novel biomarkers and screening tests

A wide range of novel biomarkers are being developed for prostate cancer. They include various PSA isoforms, TMPRSS2-ERG fusion protein, GSTP1 methylated DNA, EPCA, PCA3, AMACR, autoantibody signatures, amongst others. The source of biospecimens that have been analysed for biomarkers ranged from serum, urine, to prostate biopsy tissue. Most of these novel markers have shown promise in pilot studies but require further validation studies.

GPP There is currently no role for biomarkers other than prostate specific antigen for primary screening.

GPP

10.5 Frequency of screening

The optimal screening interval has yet to be determined. Investigators have studied intervals ranging from 6 months to 5 years.[245] Proponents of a longer screening interval cite the benefits of lower screening costs and reduced incidence of unnecessary prostate biopsies.[246,247] Opponents express concern that patients harboring aggressive but curable cancers are being missed by the longer screening interval.

GPP In general, prostate specific antigen screening is done on an annual basis. However, this screening may be performed once every 2 years in low risk men with baseline prostate specific antigen less than 1.0 ng/ml.

GPP

10.6 Stopping screening

Screening for prostate cancer is unlikely to benefit men with less than a 10-year life expectancy given the generally indolent course of the disease. While most agree with stopping screening of men who develop substantial comorbidities, applying an upper age limit to screening has less of a consensus.

Actuarial tables suggest that only men ages 75 and younger have a 10-year life expectancy, and guidelines recommend against screening older men.

An analysis of data from the Baltimore Longitudinal Aging Study[248] found that discontinuing PSA testing at age 65 for men with PSA levels 0.5 ng/mL or less would still identify all cancers that would have been detected by age 75. If screening were discontinued for men with PSA levels of 1.0 ng/mL or less at age 65, then 94 percent of the cancers would still be detected.

D We suggest that screening be performed until comorbidities or age (75 years) limit life expectancy to less than 10 years or the patient decides against further screening. Stopping screening at age 65 years may be appropriate if the prostate specific antigen level is less than 1.0 ng/mL.[248]

Grade D, Level 3

10.7 Cost-effectiveness of prostate cancer screening

There are a broad range of estimates on the cost of prostate cancer screening, ranging from USD 14,000 to 66,000 per quality-adjusted life-year.[258,259]

Possible strategies to maximise cost-effectiveness of screening include individualisation of re-screening intervals according to baseline or according to age.

Currently there is insufficient evidence on the cost-effectiveness of population based prostate cancer screening.

10.8 Counselling patients about prostate cancer screening

Currently, physicians are still faced with the same question of whether prostate cancer screening improves outcomes. Physicians should continue to provide men with information about the risks and benefits of screening for prostate cancer, allowing patients to give informed consent before undergoing the tests. Routine PSA screening without counselling regarding the potential benefits and harm of PSA testing should be discouraged.

Summary of key points in patient education and counselling for prostate cancer screening[260]

(I) Prostate Cancer

1. Prostate cancer is rare in men under the age of 50 years.
2. The risk is greater in those with a family history.
3. Prostate cancers range from slow growing to aggressive cancers. Slow growing cancers are common and may not cause any symptoms or shorten life. Most men with prostate cancer will not die from it.

(II) Prostate Specific Antigen (PSA)

1. PSA is a substance made by the prostate gland. The PSA test is a blood test measuring the level of PSA in the blood. A raised PSA can be an early indication of prostate cancer. However, there are other conditions which can cause a rise in PSA, for example, prostate enlargement, prostatitis, urinary infection.
2. Approximately 2/3 of men with a raised PSA level will not have prostate cancer.
3. The higher the PSA level, the more likely it is to be cancer.
4. The PSA test can also miss prostate cancer.
5. There is no conclusive evidence that PSA screening in asymptomatic men will improve the mortality of men with prostate cancer.

(III) Further tests when PSA level is raised

1. A prostate biopsy is required to determine if cancer is present.
2. Prostate biopsy is generally safe. However there is a small risk of complications such as bleeding and urinary tract infection.
3. Approximately 2/3 of men who have a biopsy will not have prostate cancer.

ADDENDUM TO PROSTATE CANCER SCREENING GUIDELINES

Results from 2 randomized controlled trials of Prostate Cancer Screening

Results from the long-awaited Prostate, Lung, Colorectal and Ovarian Cancer Screening (PCLO) study and the European Randomized Study of Screening for Prostate Cancer (ERSPC) were published in the March 2009 issue of the The New England Journal of Medicine.

The first paper reported findings from the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PCLO) study, which is a large multicentre randomized trial in the United States.[261] The aim of the prostate part was to determine the effect of annual PSA screening and DRE on prostate-cancer-specific mortality. 76,693 men enrolled between 1993 and 2001 were randomized to undergo annual screening or usual care. After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. The results of this study should be reviewed with some caution as acknowledged by the authors. Many men (approximately 44%) in the experimental and control groups had undergone PSA testing previously, before entry into the trial. Such prescreening could have eliminated some cancers, and importantly, screening in the *control* group (52% in the sixth year) could have masked a modest impact of screening on mortality.

The second paper reported the results of the ERSPC study.[262] The European Randomized Study of Screening for Prostate Cancer (ERSPC) was conducted in several countries starting in the early 1990s. It reported on a core group of 162,000 men, aged 55-69 who were randomized either to receive a PSA evaluation, on average, once every 4 years (with or without a DRE), or to a control group. The cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. There was a 20 percent relative reduction in prostate cancer deaths among those screened when compared to those that were not, during a median follow-up of 9 years. The authors concluded that PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. It was estimated that 1410 men would need to be screened and 48 men treated for prevention of one prostate cancer death over 10 years.

Follow-up for both trials may not be long enough to detect a benefit for screening given the protracted natural history of many prostate cancers.

The AUA Prostate-Specific Antigen Best Practice Statement: 2009 Update

The American Urological Association released the Prostate Specific Antigen Best Practice Statement: 2009 Update at their annual meeting in Chicago (from 24th – 30th April 2009). The report is an update of the previous AUA PSA Best Practice Policy 2000.

There are 2 notable differences in the current policy. First, the age for obtaining a baseline PSA has been lowered to 40 years. Secondly, the current policy no longer recommends a single, threshold value of PSA which should prompt prostate biopsy. With regard to prostate cancer screening the following excerpts are taken from the section on "*The Use of PSA for Early Detection of Prostate Cancer*."

Based on a randomized trial of prostate cancer screening, there appears to be a modest reduction in prostate cancer mortality among those screened when compared to those that are not.[262] In another screening study, there was no difference in prostate cancer mortality when comparing men that were and were not screened.[261] However, there is a large amount of overdiagnosis and overtreatment associated with screening[261,262] and at this point it is not possible to state that screening is associated with more benefit than harm.

Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. The decision to use PSA for the early detection of prostate cancer should be individualized. Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion. Because there is now evidence from a randomized, controlled trial regarding a mortality decrease associated with PSA screening, the AUA is recommending PSA screening for *well-informed* men who wish to pursue early diagnosis.

11 Clinical quality improvement

A) Indicators at the national level

	Indicator	Long-term target
1.	Proportion of women aged 50-69 years screened for breast cancer using mammogram in the last 2 years	>70%
2.	Proportion of women aged 25-69 years screened for cervical cancer with a Pap smear in the last 3 years	>70%
3.	Proportion of people aged 50-69 years screened for colorectal cancer (FOBT in the last year or colonoscopy in the last 10 years)	>70%

B) Indicators for general practitioners at the clinic level

	Indicator	Target
1.	Proportion of regular female clinic patients aged 50-69 years screened for breast cancer using mammogram in the last 2 years	>90%
2.	Proportion of regular female clinic patients aged 25-69 years screened for cervical cancer with a Pap smear in the last 3 years	>90%
3.	Proportion of regular clinic patients aged 50-69 years screened for colorectal cancer (FOBT in the last year or colonoscopy in the last 10 years)	>90%
4.	Number of patients under 50 years offered PSA test for prostate cancer screening	0
5.	Number of patients offered CA-125 test for ovarian cancer screening	0
6.	Number of patients offered CEA test for colorectal cancer screening	0
7.	Number of patients offered lung cancer screening	0

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://smj.sma.org.sg. The answers will be published in the SMJ April 2010 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Choose "True" or "False.

		True	False
1.	The following are important principles for screening:		
	A) Screening is always beneficial and the more tests are done the better.	☐	☐
	B) There should be a recognisable latent or early preclinical stage.	☐	☐
	C) There should be an accepted treatment or useful intervention for patients with the disease.	☐	☐
	D) 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.	☐	☐
2.	Population screening with EBV IgA serology		
	A) Mass population screening detects subclinical NPC in early stage.	☐	☐
	B) EBV IgA positive individuals on follow-up may develop NPC hence mass screening is cost-effective.	☐	☐
	C) EA IgA being highly specific is the more important index than VCA IgA.	☐	☐
	D) Negative EA IgA excludes NPC.	☐	☐
3.	Regarding screening for colorectal cancer		
	A) screening is recommended for all subjects at average risk at age 50 years and above.	☐	☐
	B) faecal occult blood test and colonoscopy are recommended screening tests.	☐	☐
	C) magnetic resonance scan is a recommended screening test.	☐	☐
	D) for a person with a family history of a parent diagnosed to have colorectal cancer at age 50 years, screening would be recommended from the age of 40 years.	☐	☐

		True	False
4.	The following apply to screening for HCC		
	A) There is no data to support general population screening.	☐	☐
	B) Serum alpha feto-protein (∝FP) and ultrasound of the hepatobiliary system (US HBS) are accepted screening methods.	☐	☐
	C) Ideal screening interval is 6 months.	☐	☐
	D) Liver function test is an important part of HCC screening.	☐	☐
5.	The following diagnostic modalities have been shown to reduce lung cancer mortality when used for screening in heavy smokers:		
	A) sputum cytology	☐	☐
	B) chest x-ray	☐	☐
	C) plasma carcinoembryonic antigen assay	☐	☐
	D) Autofluorescence Bronchoscopy	☐	☐
6.	Mammography is appropriate for		
	A) Screening of asymptomatic women aged 50-69.	☐	☐
	B) Screening of asymptomatic women aged 40-49.	☐	☐
	C) Screening of women who had free silicone breast injection.	☐	☐
	D) Screening of women with breast implant.	☐	☐
7.	Use of ancillary imaging modalities:		
	A) Breast ultrasound is helpful in evaluation of mammographic abnormality.	☐	☐
	B) Routine use of ultrasound for breast cancer screening increases the number of false positive findings.	☐	☐
	C) Breast MRI is helpful in screening of normal risk asymptomatic women.	☐	☐
	D) Women at high genetic risk for breast cancer will benefit from annual screening with mammography and MRI.	☐	☐

		True	False
8.	With regards to uterine cancer screening:		
	A) The Pap smear is an acceptable tool for screening uterine cancer.	☐	☐
	B) All women above 45 years should undergo regular screening for uterine cancer.	☐	☐
	C) Women with or at risk for hereditary non-polyposis colorectal cancer (HNPCC) should be offered annual screening for endometrial cancer with transvaginal ultrasound and endometrial biopsy.	☐	☐
	D) The incidence of endometrial cancer has shown an increase over time.	☐	☐
9.	With regards to ovarian cancer screening:		
	A) Family history of ovarian cancer is one of the most important high risk factor for developing ovarian cancer.	☐	☐
	B) Oral contraceptives INCREASE the risk of ovarian cancer.	☐	☐
	C) CA 125 should be done routinely in all women.	☐	☐
	D) Transvaginal ultraound accompanied with CA 125 estimation may be useful in selected women to detect early ovarian cancer.	☐	☐
10.	Screening for prostate cancer revolves around the measurement of serum Prostate Specific Antigen (PSA)		
	A) Although the PSA range 0-4ng/ml is generally accepted as normal there is continuum of cancer risk for all values of PSA	☐	☐
	B) Screening for prostate cancer improves disease free survival.	☐	☐
	C) PSA derivatives (Free: Total PSA ratio and PSA velocity) are useful for prostate cancer screening in the primary care setting.	☐	☐
	D) The combination of digital rectal examination (DRE) and PSA is superior for the detection of prostate cancer than either test alone.	☐	☐

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