

Early detection of cancers common in the Eastern Mediterranean Region



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Regional Office for the Eastern Mediterranean

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Acknowledgements

Conceptualization

Dr Ala Alwan, former WHO Regional Director for the Eastern Mediterranean
Dr Rengaswamy Sankaranarayanan, Special Adviser on Cancer Control,
International Agency for Research on Cancer
Dr Ibtihal Fadhil, Regional Adviser, WHO Regional Office for the Eastern
Mediterranean

Project writing and editorial team

Dr Rengaswamy Sankaranarayanan, Special Adviser on Cancer Control,
International Agency for Research on Cancer
Dr Ibtihal Fadhil, Regional Adviser, WHO Regional Office for the Eastern
Mediterranean
Ms Gemma Lyons, Technical Officer, WHO Regional Office for the Eastern
Mediterranean
Dr Slim Slama, Medical Officer, WHO Regional Office for the Eastern
Mediterranean

WHO reviewers

Dr Ala Alwan, former WHO Regional Director for the Eastern Mediterranean
Dr Ibtihal Fadhil, Regional Adviser, WHO Regional Office for the Eastern
Mediterranean
Ms Gemma Lyons, Technical Officer, WHO Regional Office for the Eastern
Mediterranean
Dr Cherian Varghese, Coordinator, WHO headquarters
Professor Ophira Ginsberg, WHO headquarters
Dr André Ilbawi, Technical Officer, WHO headquarters
Dr Marilyns Corbex, Technical Officer, WHO Regional Office for Europe

Other reviewers

Professor Anthony B. Miller, Dr Rola Shaheen, Dr Hussain Khalid, Dr Sherif Omar, Professor Amr Sakr, Professor Mohammad Ismail Akbari, Dr Kazem Zendehtel, Professor Nada Alwan, Dr Nisreen Qatamish, Dr Nagi S. El Saghir, Dr Taha Al Lawati, Dr Samar Alhomoud, Dr Ayda Hussein, Dr Ahmed Mohamed Sulieman, Dr John Flanigan, Dr Marie Ricciardone.

Foreword

The impact of the growing burden of cancer in countries of the WHO Eastern Mediterranean Region is evident, and necessitates implementation of suitable and effective cancer control policies. An important component of cancer control is the early detection of major types of cancer that benefit from effective treatment.

Early detection of cancer aims to detect the disease in its early stages when treatment is simple and affordable, resulting in higher cure rates. Early detection is an umbrella term consisting of two main strategies – early diagnosis and screening. Early diagnosis is universally applicable across all countries, whereas screening programmes require substantial investment and a solid health care infrastructure.

There is a disparity in the level of health care infrastructure across the Region. While some high-income countries have a well-developed and well-financed system, many have a fragmented health infrastructure with limited access for disadvantaged populations. Screening programmes require sustained funding, as a minimum of 10 years is required for the programmes to be of benefit to the population. They also require a solid health care infrastructure to ensure follow-on diagnoses and treatment. Although this is feasible in some of the high-income countries, the biggest gains in early detection across the Region will be seen through the implementation of early diagnosis programmes, ensuring that symptomatic patients are diagnosed as early as possible.

The five priority cancers selected for early detection efforts in the WHO Eastern Mediterranean Region include breast cancer, which is the most common cancer among women and increasing in incidence in all countries of the Region; colorectal and prostate cancers, which are also increasing in incidence; oral cancer, which is common in certain countries due to the high prevalence of tobacco, toombak and qat chewing; and cancer of the uterine cervix, which, although incidence in the Region is low, is one of the most suitable cancers for screening interventions. The low rate of cervical cancer, however, gives the opportunity for the potential reduction of this disease in certain countries in the Region.

Suitable policies for early detection of breast, colorectal, cervical, oral and prostate cancers are discussed in this context. Early detection efforts and strategies within

countries should take into consideration the level of development of existing health systems, future investments in infrastructure and human resources, the epidemiological profile of common cancers and health care financing mechanisms.

I. Introduction

The WHO Eastern Mediterranean Region has a total estimated population of 620 million. The countries within the Region are very diverse in terms of their sociodemographic characteristics, national resources, health care expenditures and health system capabilities (Table A1.1).

WHO has defined three groups of countries in the Region based on population health outcomes, health systems performance and level of health expenditure. Group 1 comprises countries in which socioeconomic development has progressed considerably over the last four decades, supported by high income. Group 2 comprises largely middle-income countries which have developed an extensive public health service delivery infrastructure but that face resource constraints. Group 3 comprises countries which face major constraints in improving population health outcomes as a result of lack of resources for health, political instability, conflicts and other complex development challenges.

Group 1 countries have well-developed, well-financed and secure health care infrastructures, with state-of-the-art diagnostic and treatment facilities; however, they are largely staffed by expatriate human resources. Most of the group 2 countries have health systems that are fragmented, evolving and mainly concentrated in urban areas, with vast regional variations and limited access to health services for rural and socioeconomically disadvantaged populations. Nearly half of the population of the Region live in group 3 countries with poorly developed and financed health care infrastructures, overextended health services, limited health care human resources and poor access to quality health care.

With the changing demography arising from the ongoing epidemiological transition in the Region – such as ageing populations, sedentary lifestyles, dietary changes, physical inactivity, increasing exposure to tobacco and adoption of western lifestyles – the disease pattern is also changing. In group 1 and 2 countries, more than 70% of deaths are due to noncommunicable diseases such as cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. Group 3 countries are struggling with a double burden of disease: while communicable diseases such as malaria and tuberculosis remain a major cause of mortality, the risk and frequency of noncommunicable

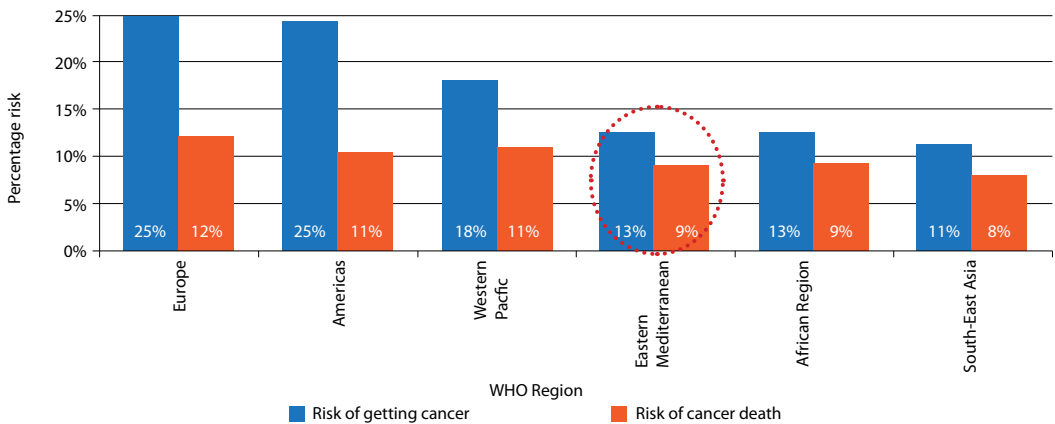
diseases are rising. Even in these countries, nearly half of all deaths are attributable to noncommunicable diseases.

Thus, irrespective of their socioeconomic progress, all the countries in the Region need to invest significantly in health. In particular, they need to improve health care infrastructure, health care human resources and access to health services by introducing universal health coverage and new approaches designed to tackle the formidable challenges posed by the growing burden of noncommunicable diseases, including cancer.

Furthermore, once diagnosed with cancer, the survival rate in the Eastern Mediterranean Region is lower than in regions such as the Americas and Europe. The risk of getting cancer before the age of 75 is 12.9% in the Eastern Mediterranean, whereas the risk is twice as high, at 24.5% and 25.1%, in the Americas and Europe respectively. Despite this, risk of dying prematurely from cancer is similar, at 9.1% and 10.6% in the Eastern Mediterranean and Americas, respectively (Fig. 1).

In October 2012, the WHO Regional Committee for the Eastern Mediterranean endorsed a resolution (EM/RC59/R.3) on health systems strengthening in countries of the Region. The resolution urged Member States to focus on seven strategic priorities for strengthening health systems, which need to be addressed by policy-makers and acted on if strong and resilient national health systems are to be built (Box 1).

Fig. 1. Risk of premature cancer and cancer death (<75 years) by WHO region, Globocon figures, 2012



Box 1. Priorities for health system strengthening in the Eastern Mediterranean Region

- Strengthen leadership and governance in health
- Move towards universal health coverage
- Strengthen health information systems
- Promote a balanced and well-managed health workforce
- Improve access to quality health care services
- Engage with the private health sector
- Ensure access to essential technologies, including medicines

2. Cancer control in the Region

The International Agency for Research on Cancer (IARC) estimates show a total of 262 641 cancer cases were newly diagnosed among men in the Eastern Mediterranean Region in 2012. In the same year, a total of 191 302 men died of the disease (Ferlay et al, 2013). The five most common sites of cancer in men are lung, urinary bladder, liver, prostate and colorectum. In 2012, the estimated numbers of incident cancers and cancer deaths in women was 292 677 and 176 139, respectively. The five most common cancers in women are breast, colorectal, cervical, ovarian and non-Hodgkin's lymphoma. In 2012, breast cancer was the number one cause of cancer mortality (42 228 deaths) in the Region, followed by lung cancer (28 977 deaths).

A cancer control programme is a public health initiative designed to reduce cancer incidence and mortality in the target population and improve the quality of life of cancer patients through systematic and equitable implementation of evidence-based strategies. Comprehensive cancer control aims to reduce the burden of cancer by preventing the identified risk factors and reducing morbidity and mortality from the disease through early diagnosis and prompt treatment. Cancer control programmes should primarily target those cancers most responsible for the high burden of disease, that have major public health implications, and for which there is robust evidence that the systematic application of interventions will lead to mortality reduction in a cost-effective manner, in the context of the available health care resources.

In the Eastern Mediterranean Region, the cancers of significant public health consequence that are amenable to control through specific strategies implemented at the population level are: lung, colorectal, prostate and liver cancers in men; and breast, colorectal, liver and cervical cancers in women. While liver cancer is not amenable to early detection and treatment, it can be effectively prevented by widespread vaccination against hepatitis B infection. Similarly, a large proportion of lung cancers, for which early diagnosis and treatment are also ineffective approaches to control, can be prevented through appropriate tobacco control measures. Breast, colorectal and oral cancers can be controlled through early detection linked to prompt treatment. In regions where cervical cancer is sufficiently common (its incidence is very low in most countries of the Region), vaccination of adolescent girls against persistent infection with high-risk human papillomavirus (HPV) types 16 and 18, the

viruses responsible for around 70% of cervical cancers, is highly likely to prove to be an effective means of prevention. In some countries in the Region, the incidence of oral cancer is high due to the common practice of chewing tobacco in betel quids (e.g. Pakistan), areca nut chewing, qat chewing (e.g. Yemen) and toombak use (e.g. Sudan).

The burden of breast, colorectal, cervical, oral and prostate cancers in the Eastern Mediterranean Region in 2012 and the projected burden of these cancers in 2030 are given in Table A1.2. The burden of breast, colorectal, cervical, oral and prostate cancers in different countries is shown in Table A1.3.

National cancer control programmes in countries of the Region should focus on the five selected cancers through strategies that are feasible, acceptable, ethical and cost-effective. Appropriate strategies for the early detection of these cancers in the three groups of countries in the Region will be discussed in the remainder of this document.

3. Overview of early detection strategies

Key definitions

Early diagnosis aims to detect cancer in its early stages in people with symptoms, when treatment is simple and affordable, resulting in higher cure rates. Early diagnosis is based on improved public and professional awareness of signs and symptoms of cancer. It entails recognizing possible warning signs and taking prompt action, and requires education of the public to improve cancer awareness, training of health care professionals to improve their professional awareness and skills in recognizing early signs and symptoms of common cancers, availability, affordability and good access to diagnostic and staging investigations, treatment services and follow-up care in public health services.

Screening is the process of identifying apparently healthy, asymptomatic people who are at high risk of having clinically undetectable early disease. It involves routine application of a screening test at specified intervals and referring those with “abnormal” (positive) screening tests for further diagnostic investigation and treatment. A screening test may be offered to a large number of asymptomatic people in the population, when it is called population-based screening, or it may be offered by a provider to asymptomatic individuals during routine health care interactions, when it is called opportunistic or spontaneous screening.

Population-based screening programmes are characterized by centralized screening invitations to a well-defined target population; systematic call and recall for screening; timely delivery of test results, diagnostic investigations, treatment and follow-up care; centralized quality assurance; and a programme database with linkages to other information systems (such as cancer and death registration systems) for monitoring and evaluation of the programme.

Opportunistic screening programmes provide unsystematic screening to subjects on request or coincidentally during routine health care interactions. There is no predetermined eligible population or protocol, and no systematic invitation at predefined intervals.

3.1 Early detection of cancer

Early detection of cancer can be achieved in two settings, namely: screening of asymptomatic persons in population-based programmes; and, early diagnosis of symptomatic subjects in clinical settings. These two early detection approaches are distinctly different; they are applied in different contexts and involve different concepts, target groups, acceptance rates, costs and benefit-to-harm equations. Improved population awareness, skilled providers, quality assurance, effective treatment and efficient health services are critical to the success of both approaches;

therefore, they are restricted in their usage to countries or regions where all of these requirements exist.

3.2 Screening programmes

Screening involves testing asymptomatic, apparently healthy persons. A positive screening test implies high probability of disease in the “screen-positive” individual, but is not confirmatory by itself. Further diagnostic investigations are required to confirm or rule out cancer. If the screening test detects a precancerous lesion, a reduction in cancer incidence can be expected (e.g. in colorectal and cervical cancer screening); whereas if the test detects early invasive cancer (as in the case of mammography screening for breast cancer) a reduction in mortality rather than incidence is the anticipated end result.

A screening test may be offered to a large number of asymptomatic people in the population, when it is called population-based screening, or it may be offered by a provider to asymptomatic individuals on demand or during routine health care interactions, when it is called spontaneous or opportunistic screening.

The requirements for an organized screening programme are given in Box 2.

In opportunistic screening programmes, screening tests are provided to subjects on request or coincidentally during routine health care interactions with patients. There is no predetermined eligible population or protocol and no systematic invitation at predefined intervals.

The critical components of a successful screening programme are high coverage of the target population with accurate, quality-assured screening tests and management of screen-positive individuals. These components are most cost-effectively met within organized screening programmes. However, an organized programme is more complex and may take years to roll out successfully, even in more developed countries. Therefore, it may take many years to deliver overall benefits to cancer control programmes in the country(s) involved.

Implementation of population-based screening programmes requires well-developed and well-financed public health services. In the Eastern Mediterranean Region, although a well-developed health care infrastructure exists in group 1 countries, very

Box 2. Requirements for implementing an organized cancer screening programme

- The condition to be screened is a major public health problem in the country or region.
- Adequate health system resources and capacity.
- Availability of affordable, accurate, feasible, safe, acceptable and simple screening tests.
- Organizational resources and capacity to oversee and coordinate gradual roll out of the programme, ensuring quality assurance, high participation, and timely access to treatment.
- Regular monitoring, evaluation, and reporting of programme performance.

few countries have been able to set up sustainable organized screening programmes. In group 2 countries, population-based screening programmes are even more difficult to implement due to significant additional investments in infrastructure and human resources required. In group 3 countries, with even less resources and weaker health systems, early diagnosis would be a more efficient and effective use of resources than screening.

3.3 Early diagnosis

As population-based screening programmes are not feasible in most low- and low-middle-income countries, early diagnosis is an important strategy for all countries to consider in the Region, irrespective of the level of resources and health system development.

Early diagnosis is based on improved public and professional awareness of signs and symptoms associated with cancer. This involves raising awareness among the general public, on cancer symptoms, and training health care providers to recognize early signs of common cancers.

The diagnosis of cancers in advanced stages and lower cancer survival rates observed in low- and middle-income countries in comparison with developed countries are partly due to health system deficiencies. This includes: lack of education, lack of symptom recognition and clinical suspicion in primary care, referral delays, diagnostic delays and inadequacies in availability and access to diagnostic and treatment services. These deficiencies may be addressed by improving clinical suspicion skills of primary care

practitioners, building referral pathways, and investing in health services infrastructure and human resources (Sankaranarayanan 2000; Sankaranarayanan et al, 2010).

Optimizing health systems for timely referrals, diagnostic tests, follow-up and treatment are important for the success of early diagnosis. Referral plans should be accepted by hospital networks. In practice, however, this infrastructure is rarely well established.

High-income countries with well-developed health systems use benchmarks for efficient early diagnosis and prompt treatment initiation. For example, in the United Kingdom, guidelines on suspected cancer specify a maximum of 2 weeks between a referral from primary care provider and a diagnostic test (NHS, 2014). There is also a target for patients to start cancer treatment within 2 months of the suspected cancer referral (Cancer Research UK, 2015). These criteria have been developed in a country whose record on cancer survival is below its expected level of performance and in which the targets are not met in all regions. Delay in diagnosis has been reported as due to lack of knowledge of primary care providers. Given these challenges in a high-income country, it is unlikely that group 2 and 3 countries in the Region will be able to achieve these targets. However, referral guidelines and targets could be a useful lever to improve referral processes in the Region.

4. Early detection of breast cancer

Key messages

- Breast cancer is the most commonly diagnosed malignancy in women in the Region.
- By 2030, the annual number of breast cancer cases and deaths are projected to be around 169 100 and 74 200, respectively, in the Region.
- Early detection and adequate treatment is the only currently feasible control strategy for breast cancer. Screening of asymptomatic women for breast cancer and early diagnosis in symptomatic women should prevent advanced disease and reduce breast cancer mortality.
- While breast self-examination as a screening tool is not recommended, clinical breast examination remains an important diagnostic method, allowing breast cancer as small as 1 cm, thus clinical breast examination skills are critical for primary care practitioners.
- Mammography is the most widely used screening and early diagnosis method in asymptomatic and symptomatic women worldwide.
- All countries in the Region should improve community awareness and primary health care capabilities to detect breast cancer early and for timely referral of suspicious cases through triple diagnostic facilities in health services.
- The key challenges of breast cancer screening experienced by countries in the Region are: a lack of sustained funding; low participation rates; and insufficient oversight of programmes (including quality assurance and regular monitoring and evaluation).
- Countries considering population-based breast screening programmes should assess health system requirements, including capacity, and countries which have already initiated mammography screening must systematically monitor and evaluate these programmes.

4.1 Incidence and mortality

Breast cancer is the most commonly diagnosed malignancy among women the Region. Although breast cancer incidence rates in the Region are substantially lower than rates in high-income countries in Europe and North America, an increasing trend is evident where data are available (Abdel-Razeq et al, 2015; Alghamdi et al, 2013; Hirko et al, 2013; IARC, 2015) (Fig. A1). The estimated number of incident breast cancer cases and deaths in the Region in 2012 were 99 300 and 42 200, respectively (Ferlay et al, 2013). The number of incident breast cancers increased from 61 000 cases in 2008 to 99 300 in 2012; the increase was particularly notable in Bahrain, Egypt, Islamic Republic of Iran, Jordan, Kuwait and Qatar (Ferlay et al, 2013).

The age-specific incidence rates of breast cancer in selected countries in the Region are shown in Fig. A2. The age-specific rates are consistent with the age-specific incidence pattern observed in Asian populations, but differ from those of most developing countries where breast cancer onset is in later age. Peak age-specific incidence rates were observed between the sixth and seventh decades of life in countries from where population-based data are available. IARC has projected that by 2030 the annual number of breast cancer cases and deaths in the Eastern Mediterranean Region will be around 169 100 and 74 200, respectively (Table A1.2).

If breast cancer is detected in stage I and treated, the survival differences between the best prognosis luminal A cancers (5-year survival 98%) and worst prognosis triple-negative cancers (5-year survival 93%) are minimal, whereas in stage II these differences are wider (96% versus 80%) and in stage III wider still (85% versus 50%) (Parise and Caggiano 2014). This indicates the power and benefits of early detection and adequate treatment despite the prognostic implications of the heterogeneous biological nature of breast cancer.

4.2 Early detection of breast cancer

A sensible decision on which early detection strategy should be implemented for breast cancer requires careful consideration of the evidence for different interventions, and availability of the resources required. An overview of the different early detection methods for breast cancer and their role in screening (of asymptomatic women) or early diagnosis (in symptomatic women) are given in Table 1.

4.2.1 Mammography

Mammography is the most widely used early detection test for breast cancer worldwide. Based on the results of randomized controlled trials that demonstrated a reduction in breast cancer mortality, population-based mammography screening was introduced in high-income countries in the late 1980s. Digital mammography is increasingly replacing conventional film-screen mammography in both screening and diagnostic settings. Digital mammography seems to be associated with improved cancer detection, fewer false-positives and lower recall rates.

Table 1. Utility of breast cancer early detection tests

Early detection test	Screening programmes	Early diagnosis
Screen-film mammography	Routinely used (screening mammography)	Routinely used (diagnostic mammography)
Digital mammography	Routinely used (screening mammography)	Routinely used (diagnostic mammography)
Digital breast tomosynthesis	No defined role	In selected situations mostly in high-income countries
Computer-assisted detection	Useful in selected situations	Clinical data absent
Ultrasonography	No defined role	Routinely used
Magnetic resonance imaging	No defined role	Useful in selected situations such as high-risk women with BRCA mutations, >20% lifetime risk
Positron emission tomography	No role	Clinical data absent; not used
Clinical breast examination	Useful adjunctive to mammography/ ultrasonography	Routinely used
Breast self-examination	May facilitate participation in screening programmes	May facilitate early diagnosis
Breast awareness	May facilitate participation in screening programmes	May facilitate early diagnosis

A recent evaluation by the IARC working group, based on observational studies of mammography screening in high-income countries, concluded that mammography screening was associated with a 40% reduction in breast cancer mortality in women aged 50–69 years who attended screening. A lesser benefit was seen among women aged 40–49 years, while the benefit of screening mammography for women over the age of 70 was not clear (Lauby-Secretan et al, 2015).

The challenges associated with mammography screening include difficulty in ensuring consistent high quality mammography, subjectivity in reading and difficulty in interpretation in women with dense breasts (which is common in young women and women with heritable mutations). Hence, mammography screening of asymptomatic women should only be offered in a setting with quality assurance and well-trained competent personnel. The harms associated with mammography screening include false reassurance from false-negative results; false-positive results leading to anxiety and depression, over-diagnosis and overtreatment of non-lethal cancers that would not have been observed clinically in the absence of screening mammography; and

radiation-induced cancer in the long term. As many as three quarters of biopsies following suspicious mammograms are benign. Over-diagnosis refers to detection of small cancers which may never have progressed to symptomatic, life-threatening disease if they had been left undetected and untreated. Having a false-positive mammogram can cause prolonged distress and decrease the likelihood of women participating in the next round of screening (Bond et al, 2013).

At the same time, diagnostic mammography is an important imaging investigation in triaging women with breast lumps and other breast symptoms, and in the early diagnosis of breast cancer among symptomatic women.

4.2.2 Ultrasonography

Ultrasonography of the breasts is another diagnostic modality for breast abnormalities. There is no evidence to justify the use of ultrasound alone in screening of asymptomatic women and it should not be used routinely to screen such women. Routine use of ultrasonography as an adjunctive screening tool along with mammography in women above 49 years with average risk for breast cancer is also not recommended (Gartlehner et al, 2013). A recently published randomized controlled study demonstrated a higher detection rate of breast cancer in Japanese women aged 40–49 years by adjunctive use of ultrasonography with mammography compared to mammography alone (Ohuchi et al, 2016). The most important use of breast ultrasonography is in the diagnostic setting for evaluation of suspicious lesions found by clinical breast examination, particularly in young women; and in women with dense breasts during screening mammography. Ultrasound scan is very useful in differentiating cystic tumours from solid tumours. It has more than 98% accuracy to correctly identify benign and malignant solid breast nodules (Stavros et al, 1995).

4.2.3 Clinical breast examination

Clinical breast examination as an alternative screening tool in resource-limited settings has generated a lot of enthusiasm. To date, there is no evidence from randomized controlled trials or observational studies that clinical breast examination as a standalone primary screening modality for asymptomatic women leads to reduction in breast cancer mortality in population-based screening programmes. A shift towards early stage diagnosis has been observed in two ongoing randomized controlled trials of

clinical breast examination in India, but no breast cancer mortality decline has yet been observed and further follow-up is continuing (Mittra et al, 2010; Sankaranarayanan et al, 2011a). Clinical breast examination as a screening tool leads to referral of around 5% of women for further assessment, which could consume health care resources in low- and middle-income countries. More information is therefore required about its cost–effectiveness.

However, clinical breast examination is an important diagnostic method in investigating symptomatic women at all levels of health service, particularly in primary care settings (Sankaranarayanan et al, 2013a). Clinical breast examination of women with symptoms (such as breast lump, breast asymmetry, skin changes, unilateral nipple retraction, unilateral blood stained nipple discharge, breast skin tethering, ulceration and eczematous changes in nipple and areola) can lead to detection of breast cancer in its early stages. Breast cancers as small as 1 cm may be detected by clinical breast examination, although detection capabilities improve with lumps measuring more than 15 mm. Clinical breast examination skills are critical for every medical and nursing practitioner in primary care settings.

4.2.4 Breast self-examination

Breast self-examination as a screening tool is no longer advocated, as the results from randomized trials and observational studies demonstrate that regular performance of breast self-examination or teaching breast self-examination compared to no breast self-examination is not associated with earlier detection of disease, reduced tumour size or reduction in breast cancer mortality (Baxter 2001; Semiglazov et al, 1992; Thomas et al, 2002). On the other hand, regular practice of breast self-examination might increase the frequency of physician visits and unnecessary biopsies.

4.2.5 Breast awareness

Breast awareness is different from breast self-examination and refers to patients having knowledge of breast cancer signs and symptoms, and recognition of the normal appearance and consistency of their breasts, by periodic inspection and palpation during dressing or bathing (Harmer 2011; Sankaranarayanan et al, 2013a). Breast self-awareness does not involve any regular, systematic examination technique such as breast self-examination. The goal of breast awareness is for women to promptly

recognize any changes in their breasts and thus seek medical care. Breast awareness and empowering women to seek prompt care have far-reaching implications for breast cancer early detection and treatment. This is evident from the fact that frequency of advanced cancers declined, breast cancer survival significantly improved and breast cancer mortality started declining even before the introduction of large-scale mammography screening programmes in developed countries around 1975–1980.

4.3 Mammography-based screening programmes: regional perspective

In high-income countries, breast cancer screening is mostly performed through mammography in either organized or opportunistic programmes. In many such countries, organized screening and opportunistic screening programmes coexist, and mammography may be overused by these two approaches unless strategies involving doctors and the organization of health care services to promote adequate screening aim to reduce the overuse of mammography in the same individual. Despite controversies over its efficacy and concerns regarding over-diagnosis, mammography is the most widely used screening method in asymptomatic women and the most widely used diagnostic procedure in symptomatic women for the early diagnosis of breast cancer. While two views (craniocaudal and mediolateral oblique) are used for screening mammography, multiple views may be used for diagnostic mammography.

The basic infrastructural component of an organized mammography-based screening programme is a breast screening unit, which sends out a screening invitation, screens target women, and investigates screen-positive cases. The composition and number of breast screening units vary in different high-income countries. In the United Kingdom, for example, each breast screening unit is equipped with two digital mammography units, ultrasonography, facilities for fine needle aspiration cytology, core biopsy and excision biopsy, histopathology services and information systems; and are staffed by programme managers, clerical staff, nurses, radiographers, imaging assistants, technicians, pathologists, radiologists and surgeons. The Derby Breast Unit at the Royal Derby Hospital, United Kingdom, has four consultant surgeons, three consultant radiologists, two consultant oncologists, a consultant plastic surgeon and six breast care nurses, and it serves 78 000 target women who are invited for screening every 3 years. The National Health Service breast screening programme

in the United Kingdom has 80 such units that manage screening of all target women (around 5.64 million women aged 50–70 years) over a 3-year period (Screening and Immunisations team, 2015). The 80 breast screening units screened around 4.28 million (7.5.9%) target women in the 3-year period from April 2011 to March 2014. Each breast screening unit can offer screening in hospitals, mobile clinics or in convenient community locations (shopping malls). Each screening unit screens around 16 000 (range: 3900–46 000) women each year; they detect around 120 women with breast cancer (range: 22–310) annually with an average detection rate of 8–9 cancers per 1000 women screened. For instance, in 2013–2014, of the 2.08 million women screened by the 80 breast screening units, 88 700 (4.3%) women were referred for further assessment, 17 961 breast cancers were detected; 21.6% of them were non-invasive or micro-invasive; 39.9% were less than 15 mm in maximum dimension.

The above description is given to show the huge infrastructure and human resource requirements for an efficient mammography-based organized screening programme, which precludes any possibility of introducing organized mammography-based screening programmes in most group 2 and group 3 countries of the Eastern Mediterranean Region. Although the WHO position paper on mammography screening (WHO, 2014) recommends considering population-based mammography screening programmes for women aged 50–69 years if the conditions for implementation of an organized programme (Annex, Box A1) are met in limited resource settings with strong health systems, many group 2 countries in the Region are unable to meet these conditions. If any of the group 1 countries wish to introduce organized mammography-screening programmes targeting women aged 45–70 or 50–70 years with mammography repeated every 2 years (as in most high-income countries) or every 3 years (as in the United Kingdom), they should carefully consider the described infrastructure, information system and human resource requirements, as well as the experience from Bahrain (see Box 3). Considerable organization and inputs are required to run efficient mammography-screening programmes. Countries may have the financial resources for the infrastructure, but national human resources are strikingly lacking since a large proportion health care personnel are expatriates in group 1 countries.

Box 3. Case studies from group 1 countries**Bahrain**

The Ministry of Health and Bahrain Cancer Society jointly organized a population-based mammography screening programme in August 2005, with five health centres providing mammography screening 6 days a week targeting 53 000 national women aged 40 years and above, and a centralized mammography reading and reporting unit with a specialist radiologist. Suspicious cases are referred to Salmaniya Medical Complex, Manama, for diagnostic investigation and treatment. Between August 2005 and April 2007, 11 237 women were screened and 52 were diagnosed with breast cancer (Bahrain Cancer Society, 2010). There has been no comprehensive evaluation of the Bahrain mammography screening programme; however, a recent report indicated that 127 breast cancers were diagnosed in the screening programme from 2005 to 2010. This constituted a fifth of all breast cancers diagnosed during the period, with declining proportions of screen-detected cancers over time, possibly indicating the inconsistent performance and poor coverage of the screening programme and showing the drawbacks and deficiencies of inefficient screening programmes (Al Hajeri 2013; Hamadeh et al, 2014).

Qatar

The Primary Health Care Corporation in Qatar was given the authority under Qatar's National Cancer Programme to implement breast cancer screening services nationwide in late 2015, as outlined in the National Health Strategy 2011–2016. The Primary Health Care Corporation has signed a contract in this regard with international companies (FujiFilm, RadNet and Specialized Medical Solutions) and will leverage these companies' knowledge and expertise in integrated screening programmes; the Primary Health Care Corporation will assume all operational management of the service (Al Raya Newspaper Gulf Times, 2015). There is a strong need to increase awareness of the importance of and participation in breast cancer screening among Qatari women as shown by a recent study (Donnelly et al, 2014). Without this awareness, compliance with the most recent breast cancer screening recommendations in Qatar will remain low.

Saudi Arabia

A recent study in Saudi Arabia reported very low breast awareness and very low rates of breast cancer screening in a country with free health services, calling for culturally sensitive educational campaigns to improve breast cancer screening (El Bcheraoui C et al, 2015).

Among group 1 countries in the Region, the target population (women aged 45–69 years or 50–69 years) in Bahrain, Kuwait, Qatar, Oman and United Arab Emirates is small compared to Saudi Arabia.

4.4 Early diagnosis of breast cancer: regional perspective

Early diagnosis of breast cancer among women with breast lumps and other breast symptoms is the most feasible and highly recommended early detection strategy in all countries of the Region. The health system capabilities in terms of both national human resources and infrastructure should be augmented in all group 2 and 3 countries to ensure that all symptomatic women have access to clinical breast examination by skilled clinicians at primary or secondary levels of care. This will require considerable investment in training primary care physicians and general practitioners in clinical breast examination, organizing referral mechanisms of clinically suspected cases and setting up multidisciplinary breast cancer diagnosis and treatment facilities across the countries.

Clinical breast examination-positive women should be further investigated with triple diagnosis (also known as triple testing or triple evaluation) at secondary or tertiary care facilities, which is a permutation of clinical assessment, diagnostic mammography and/or ultrasonography and fine needle aspiration cytology/biopsy. The tests used in an individual case will be determined by the presenting symptom(s), the clinical findings and the age of the patient. Ultrasound is the imaging modality most commonly used for patients aged less than 50 years, with or without digital mammography. The delayed diagnosis of cancers after triple assessment in women who present with symptoms and are subsequently diagnosed with cancer is less than 0.5% (Britton et al, 2009). Breast magnetic resonance imaging (MRI) does not form part of the initial imaging assessment of patients in the triple diagnosis procedure. Patients with benign or normal results are reassured, and their findings explained; they may be referred back to their primary care doctor.

A 5-year survival rate exceeding 75% can be achieved for breast cancers by ensuring the availability and accessibility of early diagnosis through: improved public and professional awareness of signs and symptoms of early breast cancer, prompt referral of suspicious cases, and access to triple diagnosis and basic treatment facilities (Sankaranarayanan and Swaminathan, 2011).

In all countries in the Region, the universally applicable breast cancer early detection approach to tackle the growing menace of breast cancer is early diagnosis. There are already good examples of breast cancer early diagnosis initiatives in the Eastern Mediterranean

Region: both Jordan and Morocco provide an excellent model for scaling up of breast cancer early detection in low- and middle-income countries worldwide (Box 4).

Box 4. Case studies from group 2 countries

Jordan

There has been good progress in Jordan, where a breast cancer early diagnosis programme, the Jordan Breast Cancer Program, was introduced in 2007 covering the whole country (Abdel-Razeq et al, 2015). It is a national initiative led by King Hussein Cancer Foundation to improve breast cancer awareness and to ensure provision of good-quality early diagnosis, treatment and follow-up care. The programme objective is to downstage breast cancer presentation to stages I and II when the disease is most curable, despite differing biology (Parise and Caggiano, 2014). As part of the programme, there has been intensive educational intervention to improve breast health knowledge among women. A number of qualitative studies have assessed the impact of these breast awareness interventions (Taha et al, 2010; Taha et al, 2014). Breast awareness campaigns involve husbands to capitalize on family support, and a recent study found that Jordanian men perceive themselves as having a vital role in supporting, guiding and encouraging their wives to follow the breast cancer early diagnosis recommendations of the programme (Taha et al, 2013). Emphasizing the good prognosis for women with early-stage breast cancer (virtually 100% 5-year survival in stage I, and more than 85% 5-year survival in stage IIA irrespective of underlying biology of the disease), involving breast cancer survivors in breast awareness campaigns and catalysing family support encouraging women to seek breast health care have been hallmarks of the campaign and useful in addressing women's ambivalence, fear and anxiety towards seeking breast cancer early diagnosis (Taha et al, 2012). In 2009, 26% and 30% of breast cancers were diagnosed in stage I and II, respectively, compared to 7% and 24% in 2005, and stage III cases declined from 56% in 2005 to 23% in 2009 (Taha, 2015). Currently in Jordan, more than two thirds of breast cancers are diagnosed in stage I and II compared to less than 30% 10 years ago, and 5-year survival exceeds 75% (Abdel-Razeq et al, 2015) as compared to 59% for cases diagnosed during 1997–1998 (Arkoob et al, 2010).

Morocco

Morocco has invested substantially in a nationwide breast cancer early diagnosis programme based on augmenting breast cancer awareness through public education; improving access to clinical breast examination for women aged above 30 years at government primary health centres (over 300 centres) by improving infrastructure; and by training primary care doctors, nurse and midwives to provide clinical breast examination (1228 trained providers) and refer women with suspected cancer for triple assessment by experienced staff at 28 centres for the early detection of breast and cervical cancers. The referral centres have diagnostic mammography, diagnostic ultrasonography, fine needle aspiration cytology and counselling facilities. Each centre investigates around

1200–3000 referred women every year and diagnoses around 90–150 breast cancers, with 75% in stages I and II. Those with invasive cancers are referred to one of the 11 cancer treatment facilities, which have pathology facilities, including immunohistochemistry for estrogen, progesterone and HER2/neu receptors, surgery facilities for breast conservation and reconstruction, radiotherapy, chemotherapy, hormone therapy and follow-up care. Access and compliance to treatment has substantially improved in Morocco, partly due to the dormitory facilities provided by the Government that facilitate completion of radiotherapy and chemotherapy courses (Obtel et al, 2015).

Egypt

A recent population-based study in Gharbiah province in Egypt indicated that the proportion of localized breast cancers increased from 14.8% in 1998 to a modest 21.4% in 2008, with an average annual per cent change increase of 5.5% in incidence rate. There was a significant decline in incidence of distant cancers with an average annual per cent change of -4%. This was attributed to awareness campaigns and downstaging efforts in Egypt (Hirko et al, 2013).

5. Early detection of colorectal cancer

Key messages

- Colorectal cancer screening reduces cancer-specific mortality and is cost-effective compared to no screening in middle- and high-income countries with high incidence rates.
- No single screening strategy has been found to be more cost-effective than others.
- Despite evidence that screening can reduce colorectal cancer incidence and mortality, it is underutilized. It is only offered to a small proportion of target populations worldwide and, where offered, widespread differences in implementation exist.
- Introduction of colorectal screening, through an organized programme in a phased manner, is feasible in group 1 and some group 2 countries in the Region.

5.1 Incidence and mortality

Despite comparatively low incidence rates (Table A1.4) compared to highly developed western countries, a rising trend in colorectal cancer incidence has been observed in some countries of the Eastern Mediterranean Region (Fig. A3–4). IARC estimated that 18 105 cases of colorectal cancer were detected in men and 14 664 in women in the Region in 2012 (Table A1.2). In Saudi Arabia, colorectal cancer has been the most common cancer in men and the third most common in women since 2002.

Currently, most colorectal cancers are diagnosed at an advanced stage in countries in the Region. For example, in a recent study in Saudi Arabia, the 5-year survival for colorectal cancer patients was 45%, and 28% of patients were diagnosed with distant metastases (Alsanea et al, 2015).

Furthermore, it is well recognized that more than 95% of colorectal cancers arise from advanced adenomas and thus advanced adenomas are the primary precursor lesions of colorectal cancers (Williams et al, 2013). The criteria for advanced adenoma include a polyp measuring 10 mm or more, a polyp showing severe dysplasia irrespective of size, or a polyp with tubulovillous architecture irrespective of size. There is compelling evidence that removing adenomas from the colon substantially reduces the risk of developing colorectal cancer (Williams et al, 2013).

5.2 Colorectal cancer screening methods

Screening of asymptomatic subjects aged 50–70 years is an important strategy in colorectal cancer early detection and prevention, while early diagnosis in symptomatic persons is an important strategy in downstaging of the disease.

Colorectal cancer may be detected by several early detection tests, such as: guaiac-based faecal occult blood test (gFOBT) and faecal immunochemical test (FIT)/immunochemical-based faecal occult blood test (iFOBT), which detect lesions indirectly by detecting occult blood in the stool; sigmoidoscopy, which examines the distal colon; and total colonoscopy, which detects lesions directly by colonic inspection. The utility of the different early detection tests for colorectal cancer are given in Table 2.

5.2.1 Faecal occult blood tests

Tests to detect occult blood in the stool are the most widely used colorectal cancer screening interventions worldwide. gFOBT involves testing three consecutive rehydrated or non-rehydrated faecal samples for occult blood, following dietary

Table 2. Utility of colorectal cancer early detection tests

Early detection test	Screening programmes	Early diagnosis
Guaic-based fecal occult blood test (gFOBT)	Was used in screening programmes; now increasingly replaced by fecal immunochemical occult blood test (FIT or iFOBT). FIT-positive persons are triaged by colonoscopy	No defined role
FIT or iFOBT	Widely used in population screening programmes targeting 50–69-year-old persons at a frequency of every 2 years	May be used for early diagnosis in symptomatic persons
Sigmoidoscopy	Explores distal colon only; not suitable for colorectal cancer screening	Explores distal colon only; if negative or positive, colonoscopy is indicated. Hence not recommended for early diagnosis
Colonoscopy	Time consuming and cumbersome procedure; widely used in opportunistic screening in the United States of America and Germany targeting 50–69-year-old persons, repeated at 10-year intervals	Recommended for early diagnosis in symptomatic FIT-positive persons

restrictions; it detects both upper and lower gastrointestinal bleeding. It has low sensitivity for detecting advanced adenoma (16–31%) and colorectal cancer (25–38%) and may suffer from interobserver and batch-to-batch variability. The combined results from four randomized controlled trials showed that annual or biennial gFOBT screening was associated with a 16% reduction in the relative risk of mortality from colorectal cancer. When adjusted for screening attendance in the individual trials, there was a modest reduction (25%) in the relative risk of colon cancer in those attending for at least a single round of screening, and a possible reduction in the incidence of colorectal cancer (Hewitson et al, 2007).

The limitations of gFOBT have led to FIT becoming the faecal occult blood test of choice. In high-income countries, FIT has largely replaced gFOBT as the primary colorectal cancer screening test in population-based screening programmes. It is more sensitive than gFOBT, it is specific to lower gastrointestinal bleeding, and haemoglobin (Hb) and faecal sample collection do not require dietary restrictions. FIT is proposed as a screening test based on a single faecal sample at 2-year intervals for persons aged 50–69 years. Increasing the number of faecal samples does not improve the accuracy of FIT. There are qualitative, non-automated FITs with a fixed positivity cut-off of faecal Hb concentration (e.g. 75 ng/mL or 100 ng/mL) giving binary negative and positive results. Quantitative FIT produces a quantifiable result of faecal Hb whose positivity threshold may be adjusted. Testing a single sample with a positivity threshold at 75 ng/mL Hb offers a good trade-off between sensitivity and specificity. A positive test occurs in a small (1–5%) proportion of persons tested, who are then advised to undergo colonoscopy and subsequent management, based on colonoscopy findings (Khuhaprema et al, 2014; Stracci et al, 2014). A single FIT might be positive in 50% of patients with colorectal cancer and 25% of those with advanced adenoma, and thus it is also a useful investigation in the diagnostic pathway of colorectal cancer in symptomatic patients. Excessive temperatures may increase the false-negative rates of FIT.

No randomized controlled trial has yet reported on the impact of FIT-based screening on colorectal cancer mortality. In a nationwide screening programme with FIT targeting 5.5 million subjects aged 50–69 years in Taiwan, China, a 62% reduction in colorectal cancer mortality was observed in 1.2 million participants as compared to nonparticipants. The 21.4% coverage of the population receiving FIT led to a

significant 10% reduction in colorectal cancer mortality (relative rate, 0.90; 95% confidence interval, 0.84–0.95) after adjustments for a self-selection bias (Chiu et al, 2015). Interim results from a recent randomized controlled trial comparing FIT every 2 years in 26 599 subjects with one-time total colonoscopy in 26 703 subjects reported higher participation in the FIT group (34.2% versus 24.6%), similar detection rates of colorectal cancer in both groups (0.1% versus 0.1%) and a 2-fold higher detection of advanced adenoma in the total colonoscopy group (1.9% versus 0.9%). Mortality outcomes from this study are awaited (Castells and Quintero 2015; Quintero et al, 2012; Zorzi et al, 2015).

5.2.2 Sigmoidoscopy

Flexible sigmoidoscopy screening has reduced colorectal cancer mortality by 22–31% and incidence by 18–23% in randomized controlled trials (Brenner et al, 2014; Stracci et al, 2014). The impact of screening with flexible sigmoidoscopy on incidence and mortality rates is limited to the distal colon only. A colonoscopy is still needed if flexible sigmoidoscopy shows a positive finding.

5.2.3 Colonoscopy

Total colonoscopy permits direct visualization of the entire colonic mucosa, biopsy of lesions, and removal of polyps and early stage cancer. The major use of total colonoscopy is for confirmatory diagnosis following a positive gFOBT, FIT and flexible sigmoidoscopy test. Total colonoscopy screening is increasingly used in opportunistic screening of colorectal cancer in a small number of countries (including the United States of America and Germany), and is associated with 31–65% reduction in colorectal cancer mortality in observational studies (Brenner et al, 2011; Zauber et al, 2012). Recommendations for endoscopy screening include flexible sigmoidoscopy every 5 years or total colonoscopy every 10 years beginning at age 50 years (Winawer et al, 2006). However, both endoscopy techniques have limitations as colorectal cancer screening tests: they are time-consuming invasive procedures; they require bowel cleansing; they are expensive, painful and suffer from high inter-operator variation; and most importantly, they require a large number of highly skilled providers.

5.3 Colorectal cancer early detection: regional perspective

Colorectal cancer screening reduces colorectal cancer-specific mortality and is cost-effective compared to no screening in middle- and high-income countries with high incidence rates; however, no single screening strategy has been found to be more cost-effective than others. Despite evidence that screening can reduce colorectal cancer incidence and mortality, it is underutilized, offered to only a small proportion of target populations worldwide and, where offered, implementation is inconsistent. Programmes are still evolving in high-income countries (Schreuders et al, 2015). A recent review of colorectal cancer screening programmes in 12 countries indicated invitation coverage of 30–100% and participation coverage of 7–68% (Klabunde et al, 2015).

Introduction of colorectal cancer screening is feasible in group 1 and some group 2 countries in the Region in a phased manner. However, cost-effectiveness will depend upon the baseline incidence of colorectal cancer in participating countries. All men and women aged 50–69 years may be screened by FIT every 2 years and positive cases should be evaluated by total colonoscopy. This will require setting up of colonoscopy services provided by expert colonoscopists to perform diagnostic and operative colonoscopies. A pilot programme may be useful to assess programmatic feasibility before full-scale national or regional roll out, as in Thailand and other high-income countries (Australian Government, 2005; Khuhaprema et al, 2014; Steele et al, 2009; UK Colorectal Cancer Screening Pilot Group, 2004). Box 5 describes a pilot programme of colorectal cancer screening implemented in Qatar.

Furthermore, countries in the Eastern Mediterranean Region need to invest in creating population awareness about the early symptoms and signs of colorectal cancer. They must also ensure that symptomatic cases are promptly referred for colonoscopy and further management. Therefore, developing adequate colonoscopy and treatment services is critical. All countries in the Region should develop adequate facilities and financing mechanisms for access to early diagnosis in symptomatic persons.

Box 5. Case study: colorectal cancer screening pilot programme in Qatar

In a pilot programme of colorectal cancer screening with FIT in Qatar, 57 (4.5%) of 1242 healthy subjects aged 45–74 years in three primary health care centres were found to be screen-positive and referred for colonoscopy. Of these, 32 (56%) underwent colonoscopy, among whom five were found to have colorectal cancer, three had advanced adenomas and four had adenomatous polyps. These findings indicate that colorectal neoplasms can be detected in primary health centre-based population screening programmes. The yield of positive results of colorectal cancer screening in Qatar is comparable to the yield in other reported studies in high-risk countries (John et al, 2014).

Based on this experience and as outlined in the National Health Strategy 2011–2016, the Primary Health Care Corporation in Qatar was given the authority, under Qatar’s National Cancer Programme, to implement colorectal cancer screening services nationwide in late 2015. The Primary Health Care Corporation has signed a contract in this regard with international companies (FujiFilm, RadNet and Specialized Medical Solutions) and will leverage these companies’ knowledge and expertise in integrated screening programmes. The Primary Health Care Corporation will assume all operational management of the service (Al Raya Newspaper Gulf Times, 2015).

6. Early detection of cervical cancer

Key messages

- Cervical cancer incidence and mortality are generally low in the Region.
- Screening is highly effective in the prevention of cervical cancer in view of its long natural history, easy accessibility of the cervix, availability of suitable screening tests and simple, safe and effective treatments for precancerous lesions.
- Several screening tests are available. WHO recommends HPV testing as the screening test of first choice for women aged above 30 years, provided resources permit and it is sustainable.
- Combined screening and treatment of cervical precancer can improve compliance with diagnostic and treatment investigations, reducing rates of loss-to-follow-up.
- Group 1 countries should vaccinate girls aged 9–13 years through two doses of HPV vaccine (at 6-month or 1-year intervals), as recommended by WHO, and provide HPV screening to women aged 30–49.
- Group 2 and 3 countries with moderately high incidence of cervical cancer should introduce HPV vaccination and visual inspection with acetic acid (VIA)-based screening for women aged 30–49 years once every 5 years.
- Achieving high coverage rates of both of vaccine doses and screening is essential to give adequate protection.

6.1 Incidence and mortality

Cervical cancer incidence and mortality are generally low in the Eastern Mediterranean Region (Table A1.4). IARC estimates show that 14 861 cases of cervical cancer were diagnosed, with 7791 deaths from the disease in the Region in 2012 (Table A1.2). Population-based cancer registry data from most countries in the Region indicate age-standardized incidence rates of less than 6 per 100 000 women, which are similar to rates in high-income countries with successful screening programmes (Table A1.4, Fig. A5). However, slightly higher age-standardized incidence rates (around 10–15 per 100 000) have been reported from some countries, such as Algeria, Morocco and Sudan (Bouchbika et al, 2013; Hamdi Cherif M. et al, 2014; Obtel et al, 2015; Saeed et al, 2014; Tazi et al, 2013)

6.2 Cervical cancer screening tests

Screening is highly effective in the prevention of cervical cancer in view of its long natural history, easy accessibility of the cervix, availability of suitable screening tests and simple, safe and effective treatments for precancerous lesions. Virtually all cervical cancers are related to persistent infection by one of the oncogenic types of HPV (types 16, 18, 31, 35, 39, 45, 51, 52, 56, 59, 66, 68, 69, 73 and 82). It takes over 2–3 decades from infection with HPV to developing cancer, thereby providing a long preclinical detection phase allowing several opportunities for screening.

Early detection tests can detect precancerous cervical lesions in apparently healthy, asymptomatic women, as well as early invasive cancer in symptomatic women. These include conventional cytology (Pap smear), HPV testing and VIA.

6.2.1 Cytology

The most widely used cervical screening test in the world is cytology. High-income countries have integrated cytology screening services into medical and public health services, with high coverage leading to substantial declines in cervical cancer incidence and mortality (IARC, 2005). However, cytology has certain inherent limitations, which make it unsuitable for many low- and middle-income countries. These include moderate sensitivity, stringent quality control requirements and high training needs.

Liquid-based cytology offers improved test specimen collection with a lower frequency of unsatisfactory smears and shorter time needed for interpretation compared to conventional cytology; however, it has more or less equivalent sensitivity (Whitlock et al, 2011).

6.2.2 HPV testing

HPV testing is the most accurate, reproducible and provider-independent cervical screening test. It is much more sensitive than cytology (Arbyn et al, 2012). HPV tests have been widely evaluated in several randomized controlled trials.

In a cluster randomized trial in India of around 135 000 women aged 30–59 years, following even a single round of HPV testing, a significant 53% reduction in the incidence of advanced cancer (stage II and above) and a 48% reduction in cervical cancer mortality were observed (Sankaranarayanan et al, 2009).

Furthermore, HPV-based screening has been shown to provide 60–70% greater protection against invasive cervical carcinomas, compared with cytology-based screening, in four European randomized trials (Ronco et al, 2014). Data from large-scale randomized trials support initiation of HPV-based screening from age 30 years, at intervals of at least 5–10 years. During the interval there is a very low probability of HPV screen-negative women developing high-grade cervical intraepithelial neoplasia or cervical cancer (Ronco et al, 2014; Sankaranarayanan et al, 2009; Schiffman et al, 2011).

WHO recommends HPV testing as the screening test of first choice for women aged above 30 years provided resources permit and it is sustainable (WHO, 2013).

6.2.3 Visual inspection with acetic acid

VIA is a screening test appropriate for resource-limited settings. It involves naked-eye visualization of the cervix 1 minute after the application of 3–5% acetic acid solution under bright light. VIA is a simple, feasible, affordable and real-time point-of-care test. A wide range of health professionals, including doctors, nurses, midwives and primary health care workers can perform the test after a short period of training. Infrastructure needs are minimal and the consumables are universally available. In a randomized trial in South India, VIA screening was associated with a 25% decline in cervical cancer incidence and 35% reduction in mortality (Sankaranarayanan et al, 2007a). VIA provides immediate results enabling diagnosis and/or treatment to be carried out in the same visit for screen-positive women (Mwanahamuntu et al, 2011; Parham et al, 2015; Sankaranarayanan et al, 2007b). However, interpretation of the test is difficult in postmenopausal and older women; VIA is not recommended in women above 50 years of age.

6.3 Cervical cancer early detection: regional perspective

An important and effective additional strategy to prevent the disease is to vaccinate adolescent girls with the efficacious and safe HPV vaccines. Although this is not an early detection strategy, it represents an important element of cervical cancer control. A combined approach of vaccination and screening could result in a significant reduction of cervical cancer, within a few decades, in some countries in the Region.

HPV vaccination should be provided to girls aged 9–13 years, by administering two doses of HPV vaccine (at 6-month or 1-year intervals), as recommended by WHO. HPV screening should be delivered to women aged 30 to 49 years. Achieving a high coverage rate of both vaccination and screening is essential to provide adequate protection. However, a different approach is more suitable for group 2 and 3 countries with moderately high cervical cancer incidence rates, such as Morocco and Sudan. This would be introduction of HPV vaccination and VIA-based screening for women aged 30 to 49 years once every 5 years.

To improve compliance of screen-positive women for further investigations and treatment, the single visit approach to combine screening, diagnosis and treatment may be followed. The WHO expert panel recommendations for screen and treat are described in Box A2 (annex). Screen and treat protocols for cervical cancer can be performed in a primary care facility by visual inspection of the cervix by trained providers (with either acetic acid (VIA) or Lugol's iodine (VILI)). VIA and VILI can be done during one clinic visit. A HPV test can require hours to days for the results to return and can be provided in a one-visit protocol or two-visit protocol as an independent or sequential test.

The rates of false positive results and overtreatment are higher with VIA and VILI as compared to HPV test. The screening modality depends on existing resource services and availability, health system infrastructure and availability/reliability of follow-up services. The cost of a HPV test and the waiting time for the results are becoming more favourable, thus suggesting that HPV can be a preferred approach in resource-appropriate settings. The human and material resource requirements for screen and treat are lower than those needed for other screening modalities that generally require more than one contact with the health system.

Countries need to invest in health infrastructure and human resources required for VIA, colposcopy and treatment of premalignant lesions. The programme should be appropriately planned to ensure high coverage of the targeted female population. However, it is likely that a programme will take some time to be implemented. Until then, primary care practitioners and gynaecologists should utilize routine health care interactions to screen women aged 30 years and above with speculum examination and VIA, and treat screen-positive women (Sankaranarayanan et al, 2013a).

It is also important to ensure early diagnosis of women presenting at any health facility with symptoms such as postcoital bleeding, intermenstrual/postmenopausal bleeding, excessive foul-smelling vaginal discharge and lower abdominal pain. They should receive prompt pelvic examination, biopsy of any suspicious findings and prompt referral to an oncology centre if suspicious for malignancy. All countries in the Region should develop adequate facilities in their public health services, supported by adequate health care financing mechanisms and access for early diagnosis and treatment of cervical cancer in symptomatic women.

Box 6. Case study: early diagnosis of cervical cancer in Morocco

Morocco has invested substantially in organizing an early diagnosis programme for cervical cancer through routine health services. It has invested substantially in training VIA providers in primary care and in developing 28 referral centres where VIA-positive women can be referred and investigated by trained colposcopists, and those found with cervical cancer precursors can be treated by trained doctors. Those found with invasive cancers are referred to one of 11 cancer treatment facilities. Morocco provides a model for scaling up of early detection of cervical cancer in group 2 countries.

7. Early detection of oral cancer

Key messages

- A high risk of oral precancerous lesions and oral cancer has been reported in qat chewers and in toombak users.
- A high incidence of oral cancer has been found in Pakistan, southern Saudi Arabia, Sudan and Yemen.
- Organized oral cancer screening programmes are not feasible in the Region.
- Precancerous lesions can be easily detected and treated through early diagnosis.

7.1 Incidence and mortality

Oral cancer incidence rates are low in most countries in the Eastern Mediterranean Region (Table A1.2), with the exception of Pakistan, southern Saudi Arabia, Somalia, Sudan and Yemen. A high risk of developing oral precancerous lesions and oral cancer has been reported in qat chewers (El-Wajeh and Thornhill 2009) and in toombak users in Sudan (Ahmed 2013; Idris et al, 1995).

7.2 Screening for oral cancer

In addition to early diagnosis, screening for oral cancer is feasible as the oral cavity is an easily accessible site for examination by doctors, nurses and health workers or for self-examination. Early-stage oral cancer patients have a better prognosis than those with advanced disease (Sankaranarayanan et al, 2010). The target population for oral cancer screening are those aged 30 years and above with tobacco and/or alcohol habits.

Oral visual inspection using adequate light, with tactile palpation, is the most widely used and evaluated oral cancer screening test. This is due to its feasibility, safety, acceptability and accuracy to detect oral precancerous lesions and cancer. It is also efficacious and cost-effective in reducing oral cancer mortality (Ramadas et al, 2013; Sankaranarayanan et al, 2013b; Sankaranarayanan et al, 2005).

The test involves systematic physical examination of the oral mucosa under bright light for signs of premalignant lesions or early oral cancer. This is followed by careful

inspection and palpation of the neck for any enlarged lymph node masses (Ramadas et al, 2013).

Evidence was demonstrated in a cluster randomized controlled trial of a high-risk group of tobacco or excessive alcohol users. A significant 34% reduction in oral cancer mortality following three rounds of oral visual screening (Sankaranarayanan et al, 2005). Fifteen-year follow up indicated a sustained reduction in oral cancer mortality, with a larger reduction among those participating in repeated screening rounds. There was an 81% reduction in oral cancer mortality in tobacco and/or alcohol users participating in four screening rounds (Sankaranarayanan et al, 2013b).

7.3 Oral cancer early detection: regional perspective

The countries in the Region with a high incidence of oral cancer (such as Pakistan, southern Saudi Arabia, Sudan and Yemen) have limited resources, with the exception of Saudi Arabia. An organized oral visual screening programme targeting all tobacco, alcohol, qat or toombak users aged 30 years and above every 3 years is not feasible given the limited health care and financial resources in these countries.

Therefore, all countries in the Region with high incidence rates of oral cancer should implement awareness-raising programmes. These must include information on the harmful aspects of tobacco, alcohol, qat and toombak use, in addition to the signs and symptoms of oral precancerous lesions and cancer. Such programmes should encourage those users to seek prompt early diagnosis.

Primary care providers in these countries should be educated in the early detection of oral cancer and precancers using oral visual inspection. They should be encouraged to examine high-risk individuals (i.e. those with a chewing habit) during routine interactions with the health service.

These countries should develop adequate facilities and financing mechanisms for early diagnosis and treatment of oral cancer in high-risk symptomatic persons.

8. Early detection of prostate cancer

Key messages

- Prostate cancer incidence is steadily increasing in the Region and presents a challenge to the existing cancer health care services in all countries.
- Current evidence is insufficient to recommend widespread population-based screening for prostate cancer by prostate-specific antigen (PSA) testing or digital rectal examination.
- Screening of asymptomatic men for prostate cancer is associated with over-diagnosis and overtreatment.

8.1 Incidence and mortality

Although the incidence of prostate cancer in the Region is lower than in western countries (Forman et al, 2013), prostate cancer incidence is steadily increasing. This is evidenced in countries where long-term population-based incidence data are available (Hilal et al, 2015; Shamseddine et al, 2014). This increasing incidence presents a challenge to the existing cancer health care services in all countries.

The age-specific incidence rates of prostate cancer in selected populations are shown in Fig. A6.

8.2 Early detection tests for prostate cancer

The tests used for early detection of prostate cancer are PSA testing, prostate cancer antigen 3 (PCA-3) testing and digital rectal examination. Estimation of PSA levels in the blood and digital rectal examination are the most widely used prostate cancer screening early detection tests. PSA levels above 3 ng/mL, 4 ng/mL or 5 ng/mL in men aged 50–59 years, 60–69 years and 70 years or above, respectively, are considered abnormal. Elevated levels of PSA and/or an abnormal digital rectal examination should prompt further investigation with transrectal ultrasound-guided biopsy to confirm diagnosis.

8.2.1 PSA testing

PSA is a normal protein synthesized in the ductal and acinar epithelium and secreted into the lumina of the prostate. It is abundant in seminal fluid and can enter blood circulation only when the basement membrane is disrupted due to prostatitis, urinary tract infection benign prostatic hyperplasia, prostate biopsy, injury and cancer, among others. Thus, PSA levels may elevate in these conditions with a false-positive rate of up to 50%. A pooled analysis indicated that at a threshold of 4ng/mL, the sensitivity of PSA was 21% to detect any prostatic cancer and 51% to detect high-grade cancers (Gleason score above or equal to 8) (Mistry and Cable, 2003). The specificity of the test was 91% and positive predictive value was 30% to detect any prostatic cancer. Both the specificity and the positive predictive value were reduced significantly to detect aggressive cancers. It is important to note that more than 65% of men with a raised PSA level will not have cancer, as PSA levels rise in all men as they get older.

8.2.2 PCA3 testing

Of the new biomarkers, urine-based PCA3 is reportedly highly specific for prostate cancer and is not affected by prostate volume, previous prostate biopsy and prostatitis. PCA3 is a non-coding RNA and is the most specific biomarker for prostate cancer to date; it is not expressed in any other human tissue or cancer. PCA3 RNA is highly overexpressed in 95% of tumours compared to normal or benign hyperplastic prostate tissue. However, the balance of benefits and harms related to PCA3 testing for diagnosis and management of prostate cancer in the general male population is not yet clear (Bradley et al, 2013; EGAPP Working Group 2014).

8.2.3 Digital rectal examination

Digital rectal examination is complementary to PSA testing and the two are often used together. A digital examination can distinguish between malignancy (hard gland or palpable nodules) and benign enlargement (smooth, firm, enlarged gland). The test is often falsely negative in early prostatic cancer. In a meta-analysis of 47 791 men, the pooled sensitivity, specificity, and positive predictive value for digital rectal examination were 53.2%, 83.6% and 17.8%, respectively, to detect any prostatic cancers (Mistry and Cable, 2003).

8.3 Prostate cancer screening: regional perspective

In a meta-analysis of five randomized controlled trials involving some 341 300 men aged 45–80 years, PSA screening with or without digital rectal examination did not significantly reduce mortality (Ilic et al, 2013). Only one study reported a significant (21%) reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55–69 years. The randomized controlled trials clearly demonstrated that screening can detect large numbers of early stage non-aggressive prostatic cancers; however, early detection and treatment of such cases does not translate into a reduction in mortality. There is no evidence that screening can selectively detect the more aggressive tumours and prevent subsequent metastases. In addition, screening can lead to harms of varying severity such as bleeding, short-term anxiety, unnecessary investigations such as biopsies, over-diagnosis, overtreatment, erectile dysfunction, urinary incontinence and infection.

Current evidence is insufficient to recommend widespread population-based screening for prostate cancer by PSA testing or digital rectal examination in the Region. Screening of asymptomatic men for prostate cancer is associated with over-diagnosis and overtreatment. In a considerable proportion of men, prostate cancer remains asymptomatic and never becomes clinically significant. Asymptomatic persons will receive no benefit from screening, which leads to detection of localized, low-risk, non-lethal cancers. Such screening might lead to long-term harms from treatment, including impaired urinary function and erectile dysfunction.

However, at the individual level, PSA testing along with digital rectal examination may be advised to men after the age of 60 years if they are willing to go for the test, only after appropriate counselling regarding the pros and cons of testing. Men with a life expectancy of less than 10–15 years should be informed that screening for prostate cancer is unlikely to be beneficial and may lead to substantial harms.

8.4 Early diagnosis of prostate cancer: regional perspective

In symptomatic men, a careful digital rectal examination followed by serum PSA estimation and transrectal ultrasound biopsies in patients with high PSA values should

lead to diagnosis. Common symptoms of prostatic enlargement in men aged above 50 years are those of bladder outflow obstruction, including hesitancy, incomplete voiding, nocturia, urinary incontinence, double stream and reduced flow. These are also the symptoms of prostate cancer. Patients with prostate cancer may present with symptoms of metastasis, the most common being acute bone pain with/without fracture.

A careful digital rectal examination can reveal the size of the prostate, indurations and hardness, nodularity and extension of tumour through the capsule and involvement of the seminal vesicles. Serum PSA should be estimated routinely in such patients: the higher the level of PSA, the greater the likelihood of cancer. The risk of prostate cancer in symptomatic men with PSA levels above 10 ng/mL can exceed 60%, especially if associated with enlarged prostate. The PSA level also correlates with the stage and aggressiveness of cancer. Men with positive digital rectal examination and raised/rising PSA level should have transrectal ultrasound-guided biopsies. Multiple core biopsies should be obtained to confirm the diagnosis. Depending on the aggressiveness of the tumour, the patient can be kept under observation, active surveillance or treatment with radical surgery and/or radiation therapy.

All countries in the Region should develop adequate facilities, financing mechanisms and access for early diagnosis and treatment of prostate cancer in symptomatic men.

9. Conclusion

When considering the implementation of a population-level screening programme, it is important to consider both the benefits and harms. Risks include over-diagnosis and overtreatment. There is also controversy regarding the evidence of effectiveness of some screening programmes. Furthermore, most countries in the Region do not have the resources and infrastructure required to implement systematic, high-quality cancer screening programmes. Therefore, although population-level screening programmes may be feasible for some cancers (breast, colorectal and cervical) in high-income countries, it is recommended that countries in the Region focus on developing early diagnosis programmes initially, as these are likely to have the greatest impact.

There is potential to implement early diagnosis programmes for five key cancers in the Eastern Mediterranean Region: breast, colorectal, cervical, oral and prostate cancer. Early diagnosis can be promoted by raising awareness of the signs and symptoms of common cancers among the general public, target population groups and health professionals. Furthermore, prompt referrals to accessible diagnostic services are of vital importance. This will require considerable investment in training of the primary care physicians in examinations, referral mechanisms and setting up multidisciplinary diagnosis and treatment facilities across the countries.

It is important that countries pilot any early detection programmes prior to national roll-out. This is to ensure the programmes are effective and efficient, and to accurately gauge the resource implications. Monitoring and evaluation of early detection programmes is also an essential process, to ensure quality and to continuously improve services. Countries must embed such monitoring processes at the initial stages of programme development.

In summary, all countries in the Region should develop adequate facilities for early diagnosis, referral and diagnostic investigations, including imaging, biomarkers, fine needle aspiration cytology and histopathology in their public health services to support early detection. They should also ensure adequate health care financing mechanisms and access for early diagnosis and treatment of early stage cancers detected by screening or early diagnosis. Furthermore, it is important that countries raise awareness of the signs and symptoms of cancer among the general public and health care professionals to facilitate early stage diagnosis.

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Annex I

Table A1.1. Sociodemographic characteristics and per capita health spending in countries in the Eastern Mediterranean Region

	Population (thousands)	Adult literacy rates (%) (15+ years; both sexes)	GNI per capita (I\$)	Per capita total expenditure on health (US\$)
Afghanistan	28 100	31	2000	51
Bahrain	1200	93.5	Data not available	895
Djibouti	860	Data not available	Data not available	129
Egypt	84 628	70.4	10 850	152
Iran, Islamic Republic of	76 942	82.9	15 600	490
Iraq	35 095	Data not available	15 220	226
Jordan	6530	93.2	11 660	388
Kuwait	3806	95		1428
Lebanon	4168	99.2	17 390	650
Libya	6028	89.5	Data not available	578
Morocco	32 950	67.1	7000	190
Oman	3855	87.8	Data not available	690
Pakistan	184 350	58	4920	34
Palestine	4485	95.9	Data not available	248
Qatar	2003	97.5	123 860	2029
Saudi Arabia	29 994	99.3	53 780	795
Somalia	10 195	Data not available	Data not available	Data not available
Sudan	36 163	50.2	2370	115
Syrian Arab Republic	21 639	85.8	Data not available	105
Tunisia	10 778	97.3	10 960	297
United Arab Emirates	9206	94.3	Data not available	1343
Yemen	25 235	33.6	3820	71

GNI: gross national income; I\$: international dollar; US\$: United States dollar

Source: <http://www.emro.who.int/entity/statistics/statistics.html>

Table A1.2. Estimated and projected numbers of cases and deaths in selected cancers in the Eastern Mediterranean Region, 2012 and 2030

Cancers	2012				2030			
	Men		Women		Men		Women	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Breast	-	-	99 284	42 228	-	-	169 083	74 181
Cervix	-	-	14 861	7791	-	-	25 681	14 113
Prostate	18 585	12 141	-	-	34 500	21 966	-	-
Colorectal	18 105	11 768	14 664	9523	32 148	21 071	25 987	38 249
Oral	11 601	6185	9080	6560	20 234	11 064	15 981	8772

Source: Ferlay et al, 2013.

Table A I.3. Absolute numbers of cases and deaths in selected countries of the Eastern Mediterranean Region, 2012

Population	Breast			Cervix			Prostate			Colorectal			Oral						
	Cases		Deaths	Cases		Deaths	Cases		Deaths	Cases		Deaths	Cases		Deaths				
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women					
Afghanistan	3108	1695	42	5	237	194	570	862	570	237	194	589	474	317	247	612	453	435	318
Bahrain	177	42	22	5	39	15	22	5	39	15	22	57	14	38	14	14	3	4	1
Iran, Islamic Republic of	9795	3304	947	370	4111	2297	3811	2297	3811	2297	3811	3811	2267	3352	1995	763	249	617	200
Iraq	4542	1983	291	142	556	398	291	142	556	398	611	422	655	454	227	107	184	87	
Jordan	1237	426	50	19	285	164	50	19	285	164	561	338	406	245	47	15	27	8	
Kuwait	314	103	30	12	112	24	30	12	112	24	115	48	77	46	16	4	9	4	
Lebanon	1934	599	113	42	807	411	113	42	807	411	407	229	338	190	54	16	37	11	
Oman	195	65	38	15	77	43	38	15	77	43	84	49	51	30	22	7	12	1	
Qatar	148	31	15	4	40	13	15	4	40	13	78	37	37	19	20	5	3	0	
Saudi Arabia	2791	795	241	84	703	321	241	84	703	321	1168	621	879	473	194	53	164	44	
Syrian Arab Republic	4140	1623	210	92	738	484	210	92	738	484	1253	818	1032	676	185	73	116	46	
United Arab Emirates	568	124	93	28	89	26	93	28	89	26	177	80	83	38	59	14	21	5	
Yemen	1963	997	198	117	122	97	198	117	122	97	354	253	222	167	126	81	157	99	
Eastern Mediterranean Region	99284	42228	14861	7791	18585	12141	18105	11768	14664	9523	11601	6185	9080	6560					

Source: Fenay et al, 2013.

Table A1.4. Age-standardized incidence rates of breast, cervix, prostate, colorectal and oral cancers in selected countries of the Eastern Mediterranean Region, 2003–2007

	Breast	Cervix	Prostate	Colorectal		Oral	
				Men	Women	Men	Women
Bahrain	560	5.7	13.7	14.5	11.0	2.4	0.6
Islamic Republic of Iran, Golestan Province	280	5.4	10.6	12.9	10.0	0.6	0.7
Kuwait	460	4.6	13.3	10.5	12.0	0.3	0.7
Qatar	45.7	5.3	10.4	20.2	16.7	0.0	0.5
Saudi Arabia, Riyadh	21.1	2.0	7.9	12.3	10.3	0.5	0.6
Lebanon (2008)*	95.7	5.6	39.2	19.5	18.9	3.9a	2.6a
Oman (1998–2007)**	15.7	5.8	8.4	5.5	4.1	2.2	0.9

*oropharyngeal cancer

Source: Forman D, et al, 2013.

*Source: Shamseddine et al, 2014.

** Source: Gulf Center for Cancer Control and Prevention, 2011.

Box A1. Characteristics of organized screening programme

- A commitment and a policy at the national level to make the services accessible to all of the target population.
- Centralized coordination at national or regional levels.
- A programme protocol that clearly defines:
 - » screening and treatment methodologies;
 - » frequency of screening and target age for screening;
 - » operational aspects of the programme.
- A mechanism of inviting the target men and women systematically to ensure high participation rate.
- Linkage between screening, diagnosis and treatment, and adequate facilities for diagnosis and treatment, without financial barriers to their use.
- Well-functioning health information system linking all the service delivery points and also the cancer registries.
- A robust programme monitoring, supervision and quality-assurance plan.

Box A2. Screen-and-treat strategy summary recommendations

The expert panel suggests:

- Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat. In resource-constrained settings, where screening with an HPV test is not feasible, the panel suggests a strategy of screen with VIA and treat.
- Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. However, in countries where an appropriate/high-quality screening strategy with cytology followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.
- Use a strategy of screen with VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either programme or countries that currently have both programmes available.
- Use a strategy of screen with an HPV test and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.
- Use either a strategy of screen with an HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat.
- Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with VIA and treat.
- Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat.
- Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.

Fig. A1. Trends in breast cancer incidence in selected countries in the Eastern Mediterranean Region

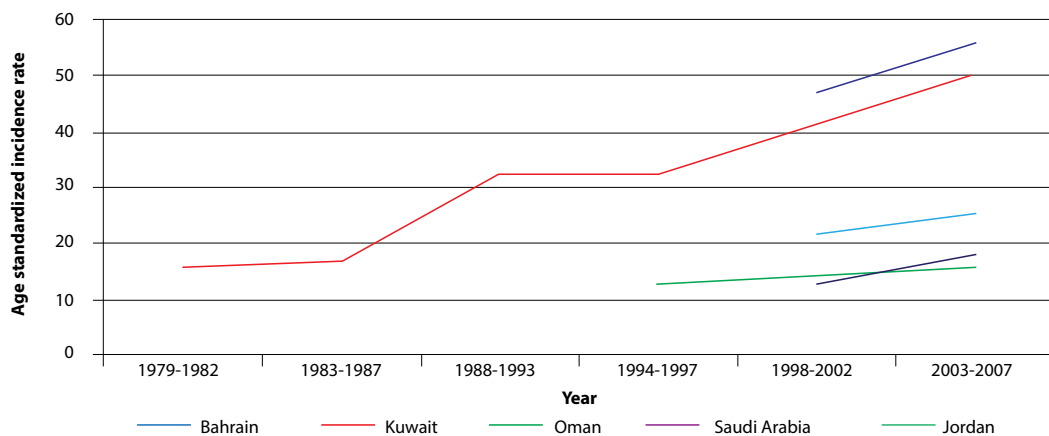


Fig. A2. Age-specific incidence rates of breast cancer in selected countries in the Eastern Mediterranean Region, 2003–2007

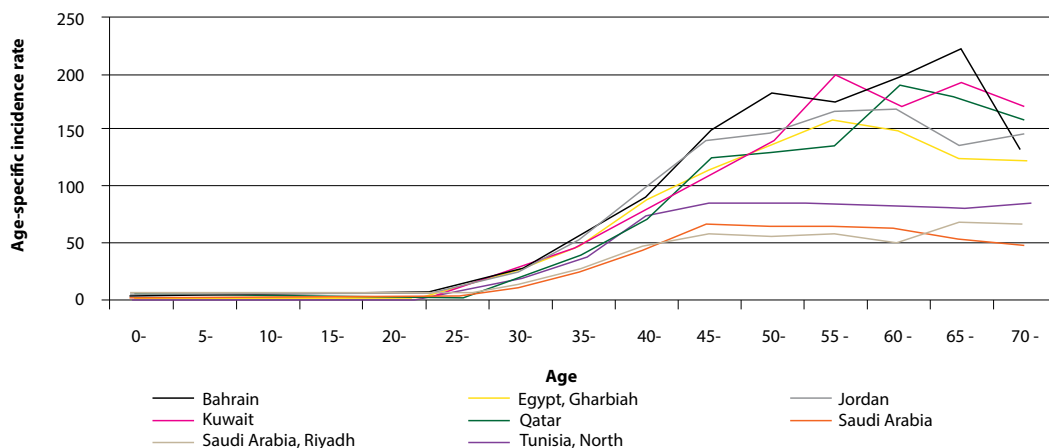


Fig. A3. Trends in colorectal cancer incidence in men in selected countries in the Eastern Mediterranean Region

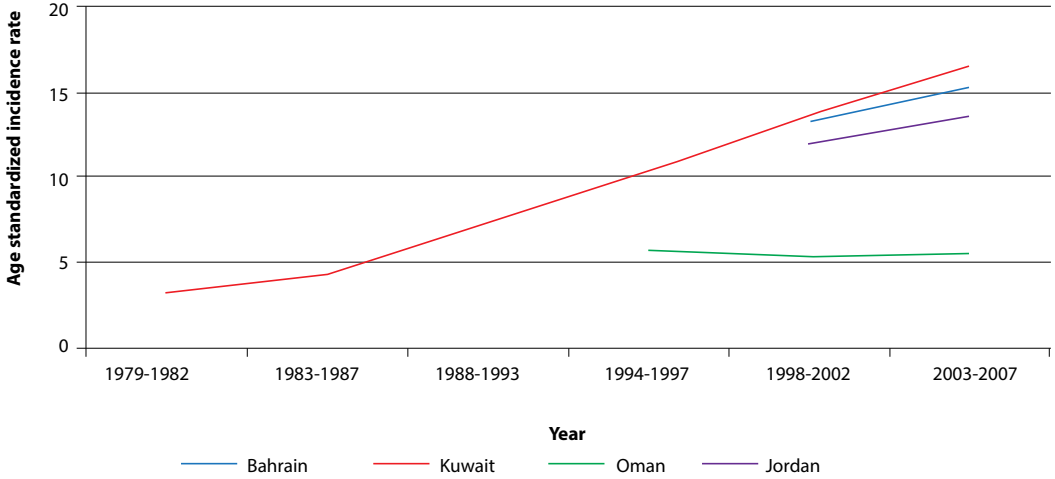
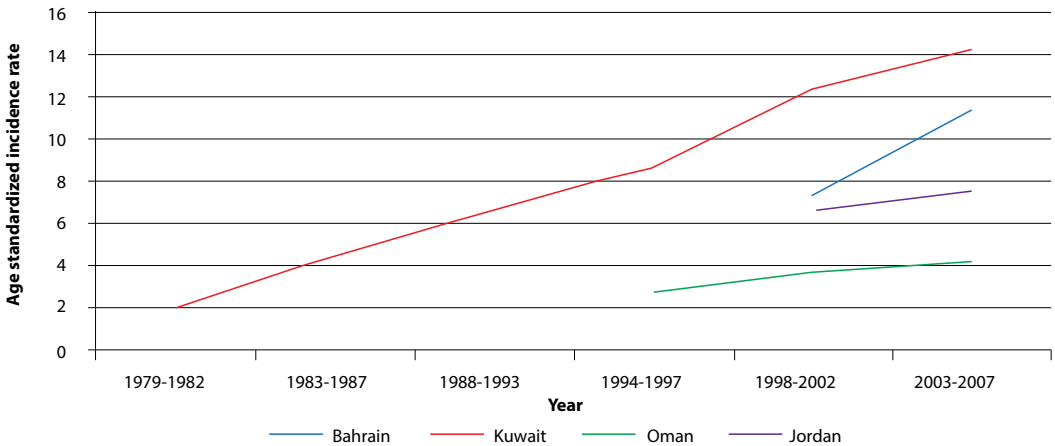
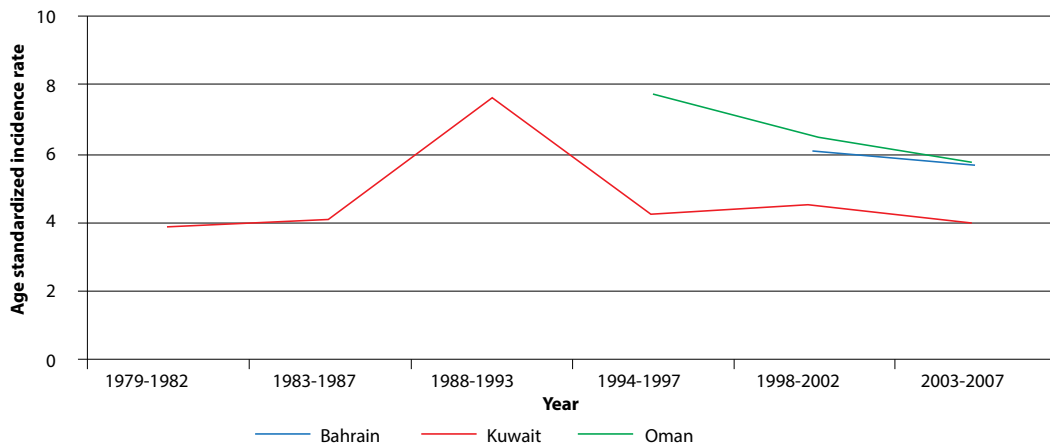


Fig. A4. Trends in colorectal cancer incidence in women in selected countries in the Eastern Mediterranean Region



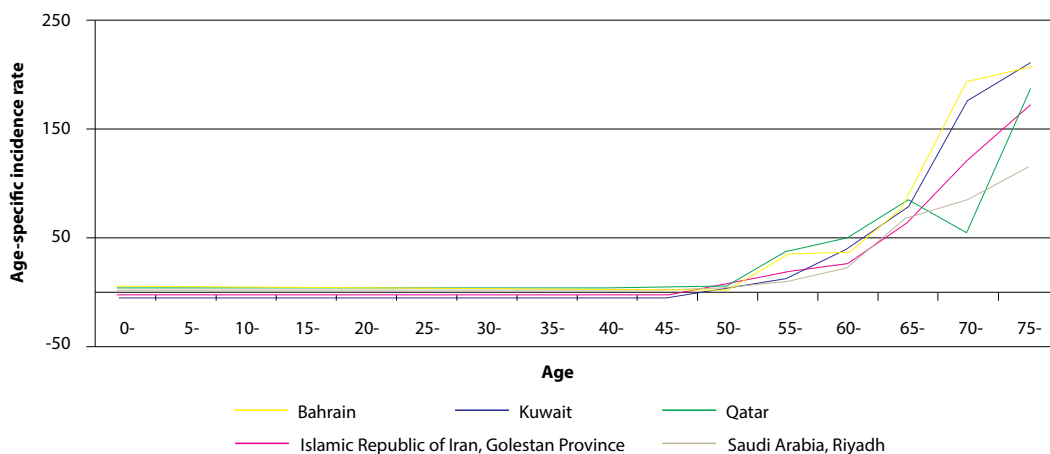
Sources: Forman D, et al, 2013. Gulf Center for Cancer Control and Prevention, 2011. Alghamdi et al, 2013. Jordan Cancer Registry, 2010.

Fig. A5. Trends in cervical cancer incidence in selected countries in the Eastern Mediterranean Region



Sources: Forman D, et al, 2013. Gulf Center for Cancer Control and Prevention, 2011. Alghamdi et al, 2013. Jordan Cancer Registry. Cancer Incidence in Jordan 2010.

Fig. A6. Age-specific incidence rates of prostate cancer in selected countries in the Eastern Mediterranean Region, 2003–2007



Source: Forman D, et al, 2013.

The impact of the growing burden of cancer in countries of the WHO Eastern Mediterranean Region is evident, and necessitates implementation of suitable and effective cancer control policies. Cancer control programmes should primarily target those cancers most responsible for the high burden of disease, that have major public health implications, and for which there is robust evidence that the systematic application of interventions will lead to a reduction in mortality in a cost-effective manner, in the context of the available health care resources. In the Region, national cancer control programmes should focus on five selected cancers – lung, colorectal, prostate and liver cancers in men; and breast, colorectal, liver and cervical cancers in women – that are amenable to control through specific strategies implemented at the population level.