Report on the

Regional consultation on establishing guidelines on the prevention and early detection of the most common cancers in the Eastern Mediterranean Region: lung cancer and mesothelioma

Cairo, Egypt
25–27 June 2006
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1. INTRODUCTION

A regional consultation on establishing guidelines on the prevention and early detection of the most common forms of cancer in the Eastern Mediterranean Region—lung cancer and mesothelioma—was held at WHO Regional Office for the Eastern Mediterranean, Cairo, from the 25–27 June, 2006. The objectives of the consultation were to:

- address the possible prevention and early detection interventions for these two cancers in the Region;
- assess the magnitude of lung cancer and mesothelioma in the Region;
- assess the magnitude of tobacco and asbestos exposure in the Region;
- assess social, economic and legislative barriers to efficient prevention of tobacco use and asbestos exposure;
- review possible interventions to reduce tobacco use and asbestos exposure;
- review early detection possibilities for lung cancer and mesothelioma;
- prepare recommendations for Member States on the prevention and early detection of lung cancer and mesothelioma.

Dr Mohamed Abdi Jama, WHO Deputy Regional Director for the Eastern Mediterranean, delivered the opening address of the Regional Director, Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean. Dr Gezairy indicated that the incidence of lung cancer was rising in the entire Eastern Mediterranean Region, and in most countries of the Region, was the predominant form of cancer among men. Its increase was parallel to the increase of tobacco consumption among the population. On a different scale, the incidence of mesothelioma was also rising due to the unsafe use of asbestos.

Professor Rabab Gaafar was elected chairperson and Professor Anthony Miller as Rapporteur. The programme and list of participants are included as Annexes 1 and 2, respectively.

2. TECHNICAL PRESENTATIONS

2.1 Magnitude of the problem of lung cancer in the Region

Dr Ossama Khatib, WHO/EMRO

Lung cancer is responsible for more deaths than any other cancer and results in approximately 1.18 million deaths annually, representing 17.6% of global mortality. Half of these deaths occur in developing countries. In the Region, 35% of males and an increasing percentage of females are smokers. This fact, in addition to economic transition and success in controlling communicable diseases, is leading to an increased incidence of lung cancer. Unsafe use of asbestos is also contributing to the increased incidence of lung cancer and mesothelioma in the Region. Sixty percent (60%) of the population have one or more risk factors for noncommunicable diseases and 8% have six risk factors. The types of cancer responsible for the highest mortality rates are lung cancer, breast cancer, stomach cancer, oral cavity cancer and lymphomas and myeloma. Cancer is the fourth highest cause of mortality in the Region, after cardiovascular diseases, infectious and parasitic diseases and injuries.
Approximately 30% of the population in the Region live in areas of low child mortality but high adult mortality, and the remaining 70% live in areas of both high child and adult mortality.

Cancer rates in the Region are expected to increase by 180% over the next 20 years, a much higher rate than that predicted for other WHO Regions. Bahrain has the highest incidence of lung cancer, followed by Pakistan. Saudi Arabia has the lowest rates. Data on survival rates are lacking in the Region but it is expected that survival is lower than the 6% rate recorded for Europe. The mortality rate in relation to the incidence rate is estimated to be 93% in the Region compared to 87% in Europe and 76% in the United States of America (USA). WHO estimates that approximately 4.2 million deaths a year globally are caused from tobacco use, and this figure is expected to increase to 7 million a year between 2025 and 2030 if present trends continue.

Asbestos is still widely used in the Region and is imported from Canada and Russia. Exposure to asbestos has a very negative effect on public health, causing lung cancer, mesothelioma and asbestosis. Its use in the Region has proliferated following aggressive marketing with few controls. Currently, over 100 000 deaths globally are estimated to be caused by asbestos, 62 000 of which are due to long-term exposure. Even after asbestos use is stopped in the Region, it will be a long time before the number of deaths is reduced, particularly as a result of mesothelioma. More work is needed to promote primary prevention, particularly in relation to smoking and advocating for healthy choices. For asbestos there is no safe threshold, its use should be ceased immediately and replaced with a safer option.

Discussion

Many doctors in the Region smoke and although that number has decreased over recent years, it was agreed that more work needs to be done to stop people smoking in hospitals and to enforce a no-smoking ban in public places. The fact that smoking is highly prevalent among the poor was discussed as was the low taxation on cigarettes and tobacco products, despite the fact that high taxation is known to be the most effective control measure. Measures for control also include education on the dangers of smoking and banning smoking in public places. The difficulty in applying international guidelines was acknowledged and the lack of commitment of governments in addressing this issue.

2.2 The magnitude of the problem of lung cancer in Egypt

Professor Hussein Khaled, National Cancer Institute

The control of lung cancer in Egypt is promoted through a network of eight national cancer control centres. Accurate data on the incidence of cancer in the country are not available, however, estimates from the Gharbiah population-based cancer registry and the National Cancer Institute hospital-based registry suggest about 100 000 cases a year are being diagnosed. Due the age structure of the population, the mean age is lower than in Western countries and lower among females than males, as the lung cancer epidemic is at an earlier stage among women—lung cancer is not yet one of the top ten diseases causing mortality among females. Most diagnosed cases are advanced and the commonest type is
adenocarcinoma followed by common squamous-cell carcinoma. Lung cancer is the fifth most common cancer among males presenting at the National cancer Institute in Egypt after bladder cancer, lymphoma, liver cancer and leukaemia. Data from the Gharbiah registry give very comparable results.

Smoking among females is increasing and women’s attitudes towards smoking are also changing. The use of *shisha* or water pipes which use flavoured tobacco is spreading among the young and its use is falsely believed to be safe. There is also increasing air pollution in big cities and the continuing unsafe use of asbestos in industry.

### 2.3 Risk factors for lung cancer

*Dr M Corbex, WHO/EMRO*

Tobacco use causes 90% of lung cancers, and smokers have an estimated fifteenfold increase in contracting the disease compared to non-smokers. Tobacco-related deaths are expected to more than triple over the next 30 years in developing countries, although countries are at different stages of the tobacco epidemic, and in the Region, the epidemic of lung cancer is only just beginning. Linked to the risk of lung cancer is the length of time an individual has smoked, and so the absolute risk is reduced substantially the earlier an individual ceases to smoke. Contrary to the belief of some, low tar cigarettes are also unsafe as people tend to smoke more intensively, and exposure to passive smoke increases the risk of lung cancer.

Flavoured tobacco was introduced for water pipe use in the 1990s. During a one-hour *shisha*-smoking session, it has been estimated that an individual smokes the tobacco equivalent of 70-100 cigarettes; the water does not filter out carcinogens. In addition, charcoals used to burn the tobacco produce their own toxicants, and the social aspects related to the use of *shisha* also increase the risk of communicable diseases. Nicotine dependency through the use of *shisha* was also increased, and yet the tobacco used in smoking *shisha* is not taxed in the same way as cigarette tobacco. Specific research is needed to identify methods to decrease its use.

Radon slightly increases the risk of contracting lung cancer in both occupational and environmental exposure (including homes built on radon-bearing rocks), but fortunately, high radon levels are not found in the Region.

Occupational exposure to a number of lung carcinogens has been reduced in the West, but exposure may be higher in this Region. There is multiplicative interaction of many industrially encountered carcinogens with tobacco use.

Air pollution increases the risk of contracting lung cancer in many developing countries although outdoor pollution may be less of a problem than indoor pollution caused by cooking and heating stoves. The use of solid fuel indoors has been shown to increase the risk of contracting lung cancer, even among non-smokers.
Treatment for certain malignancies, such as Hodgkin Disease increases the risk of lung cancer, particularly if a patient smokes. Also, repeated X-ray examinations of the thorax may multiply by two the risk of developing lung cancer and there seems to be an additive effect with tobacco use.

There are also some genes which increase susceptibility to lung cancer, again there is interaction with the use of tobacco. Gene–gene interactions have yet to be elucidated and it is still not possible to predict an individual’s risk of lung cancer based on genetic information. There is some protection offered from the high consumption of fruit and vegetables although beta-carotene supplementation is harmful for smokers.

2.4 The Framework Convention on Tobacco Control in the Region: Past, present and future

Dr Fatimah Al Awa, WHO/EMRO

The Framework Convention on Tobacco Control (FCTC) was initiated by WHO in 1995, and in 1999, the Tobacco-Free Initiative was declared a priority programme of WHO. The FCTC negotiations were concluded in 2003. The treaty requires countries to impose restrictions on tobacco advertising, sponsorship and promotion, establish new packaging and labelling for tobacco products, establish clean air controls and to take measures against tobacco smuggling. One hundred and thirty-one countries are party to the treaty, including 18 countries in the Region. The treaty has pushed forward the tobacco control agenda at regional and national levels, and this is evident at the national capacity-building level and the tobacco industry level.

As a consequence of the negotiation process in which Member States were heavily involved, 18 countries in the Region signed the treaty with the exception of Bahrain, Oman and Somalia. To speed up the process in countries, the Ministry of Health should take the necessary steps to involve other ministries to clear up any confusion concerning ratification and the accession process in consultation with WHO.

The FCTC is a continuing process and it is important for countries to be as involved in its future as in its past. Countries need to build on existing alliances and avoid the barriers from the past to implement the treaty and to make it a reality on the ground. WHO is providing guidelines and support in the form of regional workshops, etc. in this respect. Some countries are already using the Framework Convention to strengthen tobacco control and nongovernmental organizations and civil society groups are becoming increasingly involved in tobacco control efforts.

It is now vital for countries which have not ratified the Framework Convention to do so as soon as possible, and countries that are party to it need to review their national situation, align national legislation with the treaty and ensure that legislation is implemented.
Discussion

Participants discussed the need for greater advocacy to discourage the use of *shisha*, particularly as a result of its increased use and prevalence among youth and women who often do not relate its use to tobacco smoking.

2.5 Creating a social movement—tobacco control as an example

*Dr Hisham El Rouby, Youth Association for Population and Development*

Youth are defined as those between the ages of 15 and 35, and are a group which perceive themselves as needing support. Social development requires community organization and youth need to be encouraged to form organized groups. They also need to be able to understand their capabilities as agents of change, and this can be encouraged through dialogue between all sectors of the community. It is important to work with existing youth centres but also to establish informal groups for specific purposes. The cornerstone of working with a community is in building partnerships, utilizing locally available assets and involving all relevant institutions. Needs assessment studies are also required. Community mobilization starts with informed knowledge on community resources and following analyses of problems. When youth adopt an issue, even one which is not primarily theirs, they gain confidence. In one village, tobacco control was recognized as a priority first among the youth. Tobacco use is not an isolated issue but part of a package relating to health and economic and social issues. Tobacco control will be supported by youth if, and when, they recognize the value of tobacco cessation for themselves and for society as a whole. Although the Youth Association has 20 000 volunteers (all non-smokers) in 20 governorates, technical support may be needed from WHO for training and for funding potential studies and interventions.

2.6 The role of the community in cancer control: Experience of a rural centre (Fakkous)

*Professor Sherif Omar, National Cancer Institute*

The Fakkous Cancer Centre, which was established in 1990, is attempting to care for cancer patients in a rural area in a comprehensive way. Previously, patients had to go to the NCI for treatment in Cairo as the centre was initially an outpatient unit and was then expanded. The initial donation toward the centre was US$ 1 million and since then additional funds have been donated. The team at the centre now number 45 and they deliver all forms of cancer care. There are 52 beds and the centre has all necessary diagnostic facilities. Pathology is supervised by a consultant from the NCI in Cairo, and biochemistry by specialists from Cairo University. There are chemotherapy units where treatment is given according to national guidelines and a paediatric oncology unit for 2% of cases. There is also a hospital-based cancer registry. Through an outreach programme teams are able to follow up on patients in the community and early detection is being promoted for downstaging, in particular, for breast cancer. A mammography unit was installed in 2003, and in 2005, 41 mammograms were performed. Much attention is paid to the wider environment, including the disposal of hospital waste. The training of junior doctors, technicians and nurses is sponsored by and conducted in the NCI. Visitors from abroad are encouraged and courses are held for them in the centre. Some patients are now coming from other parts of Egypt for treatment.
Since its establishment, the centre has treated 20 000 inpatients and conducted 14 000 surgical operations. The most common site treated is the breast followed by the bladder. Blood collection and a transfusion service are running and these services are also offered for hepatitis C prevention. A study of smoking in the Fakkous district revealed a prevalence of tobacco use of 29%, with increasing numbers of women now smoking shisha. Cigarette smoking, which is more costly than smoking shisha, has made the use of shisha more appealing to people of this low-income rural region.

2.7 Chemoprevention of lung cancer

Professor Paul Baas, Netherlands Cancer Institute

Chronic tobacco exposure leads to chronic DNA injury. Chemoprevention is intended to delay, retard or reverse the process of carcinogenesis. Chemoprevention can be primary among those at risk; secondary among those with pre-malignant conditions; or tertiary among those who have already been treated for a tobacco-related cancer. In any case, it is not a surrogate for smoking cessation. Sputum atypia has been demonstrated as a predictor of the incidence of lung cancer, particularly among heavy smokers who have had chronic obstructive lung disease over the age of 60. Tyrosine receptor inhibitors, cox inhibition, promotor methylation and local delivery of retinoids are currently being considered as potential chemopreventive agents. The Finnish alpha-tocopherol, beta-carotene prevention study and the beta-carotene and retinol efficacy trial identified an increase in the incidence of lung cancer smokers treated with beta-carotene, although the physicians health study did not, although this may be explained by the fact that there were fewer current smokers in the physicians study. Beta-carotene in other trials was also observed to increase the risk among smokers. Also, so far, no secondary small prevention trials were able to show any protective effect with a variety of agents. There has, however, been some indication of the benefit in some small tertiary trials. In a larger trial, there was no benefit of N-acetylcysteine or retinol. Higher fruit and vegetable intake has been shown to have a possible protective effect in cohort studies, although the International Agency for Research on Cancer (IARC) has assessed the evidence as limited. In one study, statins appeared to reduce the risk of lung cancer but there was some suggestion of bias in selection. In another study, phytoestrogens seemed to have a protective effect.

Discussion

It was agreed that further work was necessary in the area of identifying people at high risk and in planning interventions at the correct stage of the natural history. However, at present, there is no role for chemoprevention in lung cancer control.
2.8 The role of early detection and screening for lung cancer in cancer control

Professor A.B. Miller, University of Toronto

There is currently no evidence that the early detection of lung cancer through awareness of symptoms (e.g. onset of cough, haemoptysis), can reduce mortality from the disease. Therefore, there is interest in screening, especially with low-dose spiral computerized tomography (CT) as the trials of chest X-ray or sputum cytology screening in the past have demonstrated no evidence of effectiveness. However, these trials were small and of limited value. Recently, single arm studies, in effect an observational study of a defined cohort without a concurrent (randomized) control group, have reported good detection rates of small resectable lung cancers with CT, superior to previous experience of chest X-rays. However, such studies which implicitly depend on historical controls cannot prove that reduction in lung cancer will follow such screening. Furthermore, low-dose CT seems to preferentially detect peripheral adenocarcinomas but does not detect more malignant (squamous or small cell) central cancers.

In screening for lung cancer, the outcome evaluated has to be the level of reduction in lung cancer mortality (the numbers of deaths arising from lung cancer, with the population screened as the denominator), not improvement in survival rates among detected lung cancer cases compared to expected rates. Screening is associated with earlier diagnosis so survival of cases is a biased estimator of effect, due to lead time, length bias, selection bias and over-diagnosis bias and the detection of cancers that were not destined to present in the lifetime of an individual. Over-diagnosis has been identified by prolonged follow-up in the Mayo Lung Trial. It is inevitable for screening by CT as the lead time gained is prolonged and competing causes of death caused by smoking are occurring so that death will occur among many subjects with screen-detected cancers before their lung cancer kills them. It is also important to recognize that over-diagnosis confounds any attempt to evaluate screening by CT in a single arm study.

There are three ongoing screening trials incorporating lung cancer screening, the results of which are not reported yet. The US prostate, lung, colon and ovary trial (PLCO) is a large-scale, randomized trial to determine whether screening will reduce the number of deaths from cancers of the prostate, lung, colon and ovary and involves over 150 000 men and women aged between 55 and 74 enrolled at ten centres across the United States. The end date for recruitment was September 2000. Screening in the trial ceases this year and each participant will be followed for at least 13 years. The lung screen is a chest X-ray given on three annual occasions to all, and to smokers for another (fourth) screen. The trial has a 90% ability to detect a 10% reduction in lung cancer mortality, substantially greater than previous chest X-ray trials.

The US national lung screening trial was designed to build upon the PLCO trial. Participants aged between aged 55 and 74 defined as current or ex-smokers with at least a 30 pack a year smoking history were randomized as current or ex-smokers with at least a 30 pack a year smoking history were randomized to annual chest X-ray or low-dose spiral CT screening. Commencing after pilot studies in September 2002, the enrolment of 52 000 participants was completed in April 2004. All will have three annual screenings, due to be completed in September 2006 and will be followed up at least until 2008.
A multicountry CT trial started more recently in Europe and to date the majority of the 16,000 participants are from the Netherlands, although participants are also being recruited in Denmark and Italy and probably soon in Germany. This trial compares CT screening with no screening, again among smokers and ex-smokers. Those who smoke will be counselled to encourage them to stop.

Although screening trials are expensive, they are essential to evaluate the efficacy of lung screening, as there is no other easy or cheap way. Each of the new US trials should have adequate power to detect a reduction in lung cancer mortality about 5 years after accrual is completed. According to current knowledge, there is no evidence that early detection or screening contributes to lung cancer control.

Discussion

The question was raised as to the possible benefit of screening high-risk groups, especially asbestos-exposed workers. Currently, there is no evidence that such screening is beneficial. It is unlikely that screening would be effective among those at higher risk from occupational exposure and could not be demonstrated to be effective among smokers.

2.9 Early diagnosis of lung cancer

Professor Jan Van Meerbeeck, University Hospital, Belgium

Lung cancer is a significant public health problem, and therefore, one of the principle criteria for supporting screening is fulfilled. Potential imaging tools are chest X-ray, conventional and low-dose CT scan, chest MRI and PET scan. Resolution for chest X-ray is a lesion of 6–10 mm, for low-dose CT it is 1–3 mm, but the higher the sensitivity, the lower the specificity. There has been one meta-analysis of the evidence, with a total of 245,610 subjects, and several of the trials have been found to suffer from contamination and a lack of compliance. Several studies, such as the Mayo Lung Project, found higher numbers of people with stage 1 cancer with greater survival confirmed in the meta-analysis, but for all studies combined there was no difference for all causes of mortality, or for lung cancer mortality.

In low-dose CT, the beam rotates around the patient in a helical fashion with four or more detectors, a reduction in slice thickness, improvements in resolution, the radiation dose (less than mammography) and a lower scan time of 12 seconds (one breath hold). The sensitivity for detection of nodules has substantially improved. For every cancer detected on average there will be 10 more nodules detected. Also, 40%–50% of subjects have benign nodules. The likelihood of malignancy increases with the size of the nodule (8–20 mm represents a 19% likelihood and > 20 mm represents a 50% likelihood). In an Italian study of 5,202 people aged 50+ who were current or former smokers, CTs were repeated at three months for those with nodules of 5.1–8 mm. Nodules were found in 53% of participants. There were 55 cancers detected, 73% in stage 1–2, 73% were adenocarcinomas and 12% had thoracotomy with no cancer detected. Other series showed similar results. Therefore, CT is of greater sensitivity than chest X-ray but has a much lower specificity and although survival will be improved there is no evidence yet for this in relation to lung cancer mortality. Further improvements in CT technology are expected with increases in sensitivity but with poorer
specificity. Studies are ongoing on markers in sputum. PET scan resolution currently is poorer than CT although it will improve.

It is important to distinguish between patients who are symptomatic, patients who may need diagnostic evaluation and patients who are asymptomatic (ex-) smokers, even if they are at high risk from smoking or from other factors. There is no justification at present for offering screening to such people because of the risks without any evidence of reduction in lung cancer mortality. This is just as true for opportunistic screening as for organized screening.

2.10 The emerging epidemic of mesothelioma in Egypt

Professor Nelly Ali El Din, WHO/EMRO

Malignant mesothelioma is an aggressive tumour, the principle cause of which is asbestos exposure. It is highly fatal, with a median survival time of 6–15 months. The incidence globally is 10–20 per million for males and 2 per million for females, although incidence is increasing. Few countries appear to have yet passed the peak; in Europe the peak will be passed by 2020. In Egypt, mesothelioma is an increasing problem and rates are expected to increase as asbestos use continues with aggressive marketing by chrysotile producers in Canada and Russia. The use of asbestos began in Egypt 5000 years ago, and in 2004 there were 14 asbestos-using factories in Egypt. Use is now limited to chrysotile (previously, mixtures with crocidolite and amosite were used). Many thousands of employees work in asbestos plants. Asbestos workers, their family members and those living next to asbestos factories suffer the effects of fibre inhalation, which affects a circular area of between 5 k and 7 k from the factory.

From 1989–1999, 148 cases of malignant melanoma were diagnosed and/or treated in the NCI. Residential exposure was identified clearly in 82% of cases and occupational exposure in 13% of cases. Data from the hospital-based registry showed that the relative frequency of malignant mesothelioma increased from 0.47 in 2001 to 1.35 in 2004. This is much higher than the figures recorded in other countries of the Region. The median age of individuals with malignant melanoma was 48 years with a male-to-female ratio of 1:7.

Between 2000 and 2004, 832 cases of malignant melanoma were diagnosed at the NCI and Abbassia Chest Hospital in Cairo. The male-to-female ratio dropped to 1:5, residential exposure was confirmed at 65% and clear links to the major areas where asbestos had been used for some time were identified. Twenty percent (20%) of individuals affected were younger than 40 years old. This and the high proportion of residentially-associated cases suggest exposure commenced in childhood.

A field study was undertaken to assess the sources of asbestos exposure in one area of Cairo. Asbestos waste had been improperly disposed of and was found close to fences separating residential areas from factories, and even schools. Air samples were collected in a neighbourhood of factories, with the highest concentration adjacent to a school (3.02 fibres/cc—higher than the USA Occupational Safety and Health Administration standards for occupational exposure). Broken fibres of chrysotile were found on microscopy.
There is no compensation scheme in Egypt for asbestos-related diseases. A parliamentary committee has recommended that asbestos imports should be banned and the use of asbestos should be phased out. One of the 14 factories in Egypt in 2004 has been investigated and was closed. In another factory, substitutes for asbestos are now being used. Some employees have been compensated by their employers. A pension of 100% is available for occupationally-associated asbestos disease. Experience elsewhere has shown that evidence of fibre exposure is important in securing compensation.

2.11 Risk factors for mesothelioma

Professor Rabab Gaafar, National Cancer Institute

Asbestos was used in Egypt at the time of the pharaohs to embalm bodies. Asbestos is cheap and is used in many industries in Egypt in cement products, insulation in construction, brake linings, etc. and yet the principle risk factor for mesothelioma is exposure to asbestos. It is characterized by a long latency period from the onset of exposure to diagnosis of an asbestos-related disease suggesting that multiple genetic events are necessary in its pathogenesis. There is no threshold dose of asbestos below which the risk of developing mesothelioma does not exist. Risk does relate to the intensity and duration of exposure, the shape of the fibre, the amphiboles being most dangerous although chrysotile does increase risk. The carcinogenic effect is not only due to its physical properties but also from chemical effects. It is often preceded by pleural plaques. In the case studies from the NCI, 12% of sufferers had a family history and 44% were smokers. In eastern Turkey, there are three villages where 50% of deaths are caused by malignant mesothelioma as a result of environmental exposure to erionite, although genetic studies of these cases suggested a dominant genetic susceptibility. Mesotheliomas have been suggested to be associated with the simian virus SV40 (a contaminant of the polio vaccine from 1954–1966) which could also be a co-carcinogen with asbestos. This virus causes mesothelioma in hamsters and has been detected in mesothelioma specimens in some countries, but not in others. There is a plausible mechanism for its activation.

2.12 Clinico-pathological features of malignant mesothelioma: Studies from the NCI

Professor Rabab Gaafar, National Cancer Institute

Among mesothelioma cases presenting at the NCI between 2000 and 2002, asbestos exposure was documented in 67% of cases. The median time of exposure was 36 years and 75% of all exposures were residential. Individuals complained of dyspnoea, chest pain and cough and were often found to have pleural effusion. The median survival was 14.4 months; for stage 1 to 2 it was 19 months with better performance status. SV-40 was detected among 60% of cases, 83% of which had experienced exposure to asbestos. Survival did not vary by SV-40 status, nor by p53 and was poor for cases having an altered retinoblastoma gene. Seventy percent (70%) of cases over-expressed the marker epidemal growth factor receptor (EGFR); those who did not express this marker did better clinically. Glutathione positivity appeared to potentiate the effect of EFGR on survival.

Multimodality therapy (pleuropneumonectomy, chemotherapy, radiotherapy) for 22 patients appeared to prolong survival in the early stages of the disease (the median survival
was 28 months). In more advanced cases there are potentially active chemotherapy agents and more are anticipated in the future. To date, trials show marginal increases in survival with available agents. Studies of other markers suggest that antiangiogenesis agents may have a role in the treatment of malignant mesothelioma.

2.13 Early detection of mesothelioma

Professor Jan Van Meerbeeck, University Hospital, Belgium

The cumulative lifetime risk of mesothelioma among asbestos-exposed populations in the west is 1%. If there is asbestosis, the risk of mesothelioma increases sixtyfold, if there are pleural changes, the risk is increased sixteenfold. Chest X-ray gives numerous false positives in exposure to asbestos and so has been abandoned.

One study of low-dose CT found one case of mesothelioma per 602 people. In another study nodules were found in 76% of a group of 519 people. Following investigation, nine malignancies, seven lung cancers, one malignant mesothelioma and one thymic carcinoma were diagnosed. The low detection rates of malignant mesothelioma do not justify separate randomized trials of CT among asbestos-exposed individuals.

An ideal biomarker should have diagnostic value, i.e. predict the disease among asbestos-exposed subjects but also reflect the disease extent and its prognosis. However, previous experience suggests the chance of finding such a marker for mesothelioma is low. Also, new tests tend to be used in high-prevalence populations with sensitivity often based on relatively advanced cases and with over-estimation of specificity. Currently, osteopontin and mesothelin are being considered. Osteopontin is over-expressed in many cancers, including mesothelioma. In a small retrospective study in the US including many low-stage mesotheliomas, together with asbestos-exposed subjects and controls, it was necessary to raise the cut-off level to achieve reasonable specificity; sensitivity was reasonable. Mesothelin tends to be positive in mesothelioma, but also in adenocarcinomas. Soluble mesothelin-related protein (SMRP) is also being evaluated using monoclonal antibodies, but is not yet approved by the Food and Drug Administration (FDA). So far, four studies have been conducted with prevalences of mesothelioma (34%), healthy controls (18%) and other cancers (19%). In one study, sensitivity was 65% and specificity was 91%, in another, it was 80% and 83%, respectively. In other studies, there was little elevation among subjects with benign lesions but some elevation among those with other cancers. Overall, in these studies the performances of the tests were not encouraging, although there were some data to suggest some correlation with response. In one study using retrospective assessment of prospectively collected blood samples, 25%–37% of patients had increased levels of SMRP one year before diagnosis. Further validation of these markers is required before they can be recommended for routine use for early diagnosis.

2.14 Asbestos: Truth and consequences

Mrs Laurie Kazan, International Ban Asbestos

One American expert has estimated that asbestos may cause 10 million deaths and may account for 1% of all deaths among the worst affected age groups. Calculations by Finnish
scientists show that for every 170 tonnes of asbestos used in a country one death from mesothelioma will occur and the national incidence of asbestos-related lung cancer will increase. Between 1995 and 2029, 500 000 people will die in Western Europe from asbestos-related cancer. In the Region, the Islamic Republic of Iran and the United Arab Emirates are the biggest users of asbestos and in the past, Egypt was also a major asbestos consumer but a national ban was adopted in 2005. There is doubt, however, as to whether the necessary regulations are being implemented.

In Australia, asbestos was widely used in asbestos-cement products in the construction of residential properties, and to date, the Australian national mesothelioma register has recorded 6129 cases of mesothelioma. Belgium had the highest national mesothelioma incidence in Europe (29:1 000 000), which can be linked to large-scale asbestos use in the production of asbestos-cement building products. Compensation for some Belgian asbestos victims began in 1982 but the Belgian Asbestos Victims’ Group believes it is inadequate and leaves many victims with no compensation. In the United Kingdom (UK), men born in the 1940s are at greatest risk of dying from malignant mesothelioma; 1% of these men will die from mesothelioma.

In developing countries, such as Brazil, India, Pakistan and the Philippines, asbestos is used without precautions. In the Philippines, more than 30 000 workers experience direct or indirect exposure to asbestos. In India, lung impairment and radiological abnormalities are found among high proportions of asbestos-exposed workers. Asbestos dumps in Pakistan are common and there is virtually no protection for at-risk workers who often work in circumstances that expose others, even children, to hazardous asbestos dust. Asbestos is also often milled in close proximity to wheat. Action has been taken in Saudi Arabia to ban asbestos imports by Royal Decree.

The World Trade Organization (WTO) has stated that the controlled use of asbestos is particularly questionable for the building industry and DIY enthusiasts, the most important users of cement-based products containing chrysotile asbestos. In 2006, the International Labour Organization (ILO) adopted a resolution supporting the elimination of the future use of asbestos and the identification and proper management of asbestos currently in place.

Discussion

In the discussion it was pointed out that other cancers, which are probably caused by prolonged asbestos exposure, include larynx, stomach and colorectal cancers. There is a problem in the Region as workers with asbestos-related disease can not obtain confirmation from the medical system of the aetiology of their disease. Also compensation, if paid, is often inadequate and does not compensate for the loss of income.
2.15 Confirmation of the diagnosis of malignant mesothelioma among those without histology proof

Professor Paul Baas, Netherlands Cancer Institute

In the Netherlands, the use of crocidolite was prohibited in 1977 and the use of all asbestos was banned in 1993. Only in 2000, reimbursement for occupationally-induced malignant mesothelioma was agreed by regulation providing that the diagnosis was pathologically confirmed. However, for 177 out of 1747 patients for whom there was no diagnosis because of the absence of histology, all available evidence was reviewed by three pneumonologists not involved in the management of the patient. The diagnosis was confirmed in 73% of cases, with uniformity of all three reviewers in 70% of cases.

2.16 Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid

Professor Paul Baas, Netherlands Cancer Institute

Access to mesotheliomas in the pleura is often difficult because adhesions and biopsies may not represent the pathology of the tumour. Photodynamic techniques using 5-aminolaevulinic acid (ALA) are safe and enable the physician to identify the relevant tissues. Thickening of the pleura can be induced by epithelial thickening but fluorescence diagnosis in rats using ALA has shown 11 times greater accumulation in tumours than in normal tissue. The technique can be used in thoracoscopy. So far, only small numbers of patients have been studied. One investigator found a sensitivity of 100% and a specificity of 85%. In Professor Baas’ studies, ALA was given 3–5 hours before examination, inspection was with white and blue light and biopsies were taken of suspicious areas. Among 26 patients, 111 biopsies were taken at a rate of up to 7 per patient. Abnormal appearance on white light and diffuse or sharply delineated red fluorescence was regarded as abnormal; in 37 biopsies, both were abnormal, 21 were among patients with mesothelioma. There were several negative to both, some with mesothelioma, and some positive to one and negative to the other. The sensitivity ranged from between 65% and 70%, specificity was only a little better, positive among some patients with inflammation. The study has identified problems with both the technique and the pathology diagnosis and further development and research on new markers that become available is needed.

2.17 Diagnosis of pleural malignant mesothelioma by thoracoscopy

Professor Abdel Rahman Mohamed Abdel Rahman, National Cancer Institute

Thoracoscopy is being used to try and diagnose patients at an earlier stage and improve their survival rate and quality of life as clinical examination is usually non-specific at an early stage. Nearly 85% of patients present with pleural effusion but cytology is positive in only 30%. Thoracoscopy with biopsy increases this proportion with a diagnosis of 90%. High resolution video-endoscopy systems have revolutionized thoracoscopy. The procedure is simple, safe and without complications. There is no need for a chest tube and the patient can usually be discharged on the same day. In patients with an early stage of the disease, thoracoscopy also facilitates distinction between stage Ia and stage Ib.
Discussion

It was emphasized that thoracoscopy can not be regarded as a screening test but constitutes a diagnostic test. There are complications associated with its use, thus subjects, even high-risk subjects without symptoms or signs detected in chest X-ray should not be exposed to thoracoscopy.

3. CONCLUSIONS

Considerable consideration was given to the question of whether people occupationally exposed to asbestos should be screened. Even though the lifetime risk of mesothelioma in the West is 1%, it is anticipated that this rate could be higher in Egypt. However, there is no established screening test which can provide a benefit and although continued research should be advocated, at present, it is clear that no programme of screening can be recommended for any at-risk population.

In the discussion it was also emphasized that governments sometime consider that there are economic benefits from tobacco use although the World Bank has determined that there is, in practice, an overall economic loss from the use of tobacco.

In terms of asbestos there are still activities occurring in the Region and false claims that asbestos products are less dangerous than the alternatives, such as fibreglass or PVC products. Such claims need to be counteracted. For example, there is no evidence for the claim that chlorine in water interacts with plastic used for pipes to produce a carcinogen.

These issues need to be carefully evaluated; one mechanism to counteract false claims is to form a national committee, carefully structured, with appropriate representation from politicians, doctors and scientists, trade unions and the community, appointed with mechanisms established to promulgate recommendations to the appropriate government authorities. Such a committee should be established by government in collaboration with WHO and nongovernmental organizations.

4. RECOMMENDATIONS

1. All countries in the Region should strive to fully implement the WHO Framework Convention on Tobacco Control (FCTC).

2. Countries that are already party to the FCTC should review their national situation, align national legislation with the treaty and ensure that the requirements are implemented.

3. Legislation to introduce regulations to forbid exposure to tobacco smoking in public places, the banning of tobacco advertising and the mandatory use of warning labels should be applied in all countries of the Region.
4. All countries in the Region should consider increasing taxes on all tobacco products in line with the cost of living. The resulting revenue should be used to strengthen tobacco-control measures.

5. Sales of tobacco products to children and adolescents (up to the age of 18) should be banned and the regulation strictly enforced.

6. Public education should be promulgated in countries of the Region on the dangers of waterpipes (shisha), directed particularly to the youth, pointing to the unhygienic nature of the social sharing of pipes, the high levels of tobacco exposure, the potential danger of charcoal products and the risk of nicotine addiction.

7. Specific research efforts should be conducted on ways to change the attitude of the public, particularly youth, designed to counter the use of shisha.

8. Shisha should be subject to regulations in the same way as other forms of tobacco, including cigarettes as per article 10 and 11 of the FCTC. Any regulations introduced with regard to the smoking of cigarettes, including warning labels and prohibition of exposure in public places and taxation, should also be applied to the use of shisha.

9. An important target audience for tobacco control efforts are young people aged between 15 and 35. WHO Regional Office should encourage and support initiatives by governments and nongovernmental organizations to promote cessation of tobacco use among youth.

10. On general health grounds, consumption of fruit and vegetables should be recommended for the prevention of noncommunicable diseases and may contribute to lung cancer prevention. However, tobacco control is the priority as the positive effects of eating fruit and vegetables are far less than the benefits that follow the cessation of smoking at any age.

11. At present, there is no evidence that early detection or screening for lung cancer is effective, and accordingly, screening should not be recommended for lung cancer control.

12. For all types of asbestos there is no safe threshold, therefore, elimination of use by banning the importation and processing of asbestos should be recommended for all countries of the Region. Left-over stocks of asbestos fibre and asbestos-cement products should be disposed of safely. The resale of second-hand asbestos cement products should be prohibited.

13. Care should be taken over the disposal of asbestos-containing products and the demolition of buildings containing asbestos. There is no rationale for the wholesale replacement of asbestos-containing insulation. However, if there is evidence of fragmentation and dissemination of fibres in the air the insulation should be replaced
with appropriate safety precautions. Installed asbestos-containing materials should be identified and managed according to national guidelines.

14. Research is ongoing on tests that could be used for the early diagnosis of mesothelioma. Chest X-rays should not be recommended, the data suggest lower specificity for low-dose CT than in non-asbestos exposed individuals. New biomarkers are potentially available but further validation of these markers is required before they can be recommended for routine use for early diagnosis.

15. Research into screening for malignant mesothelioma should continue.

16. Specialist centres in the Region with adequate facilities for diagnosis and staff willing to spend time on research should contribute to advancing knowledge on these issues by joining groups from Europe and North America to perform research on cohorts of asbestos-exposed individuals and heavy smokers.

17. To address the complex public health problems created by asbestos, national asbestos working parties should be convened by governments in collaboration with nongovernmental organizations in all countries of the Region, comprised of politicians, doctors and scientists, trade unions and community representatives.

18. For patients with asbestos-associated cancers, compensation, adequate to compensate for the costs of medical care and reduction in life expectancy, should be paid to all patients confirmed to have mesothelioma without a requirement for proof of exposure (as in Ontario, Canada). For those with lung cancer with established prior exposure to asbestos, compensation should be provided. Statutory bodies should be established to ensure that compensation is provided, such as exist in Canada and the Netherlands. It should not be necessary to have recourse to the courts.
Annex 1

PROGRAMME

Sunday, 25 June 2006: Lung cancer

08:00–08:30  Registration
08:30–09:00  Opening session
09:00–09:30  Regional overview of lung cancer, Dr Ossama Khatib, RA/NCD, WHO/EMRO
09:30–10:00  Magnitude of the lung cancer problem in Egypt, Professor Hussein Khaled, WHO Temporary Adviser
10:00–11:00  Risk factors for lung cancer, Dr Marilys Corbex, TO/NCD, WHO/EMRO
11:00–11:30  Tobacco prevention in the Region, Dr Fatimah El-Awa, RA/TFI, WHO/EMRO
11:30–12:00  Social and economic issues: The role of the community in tobacco prevention, Dr Hisham El Rouby, WHO Temporary Adviser
12:00–12:30  The role of the community in lung cancer prevention: Experience of a rural centre (Fakkous), Professor Sherif Omar, WHO Temporary Adviser
12:30–14:00  Discussion
14:00–14:30  Chemo-prevention of lung cancer, Professor Paul Baas, WHO Temporary Adviser
14:30–15:00  The role of early detection and screening of lung cancer in cancer control, Professor Anthony Miller, WHO Temporary Adviser
15:00–16:00  Discussion

Monday, 26 June 2006: Malignant mesothelioma

09:00–09:30  Early detection of lung cancer, Professor Jan VanMeerbeeck, WHO Temporary Adviser
09:30–10:00  The emerging epidemic of mesothelioma in Egypt, Professor Nelly Ali El Din, NCD, WHO/EMRO
10:00–11:00  Risk factors for mesothelioma, Professor Rabab Gaafar, WHO Temporary Adviser
11:00–11:30  Malignant mesothelioma: Clinical-pathological approach at NCI CAIRO, Professor Rabab Gaafar, WHO Temporary Adviser
11:30–12:00  Biomarkers of mesothelioma, Professor Jan VanMeerbeeck, WHO Temporary Adviser
12:00–12:30  Asbestos: Truth and consequences, Mrs Laurie Kazan, WHO Temporary Adviser
12:30–14:00  Discussion
14:00–14:30  Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid, Professor Paul Baas, WHO Temporary Adviser
14:30–15:00  Early detection of mesothelioma by thoracoscopy, Professor Abdel Rahman Mohamed Abdel Rahman, WHO Temporary Adviser
15:00–16:00  Discussion

Tuesday, 27 June 2006: Conclusion and recommendations

09:30–11:00  Open discussion
11:00–12:30  Conclusions and recommendations
12:30–13:00  Closing session
Annex 2

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