



PII: S0959-8049(99)00070-2

European Journal of Cancer
**Millennium
Review
2000**

Screening for Cancer: Future Potential

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Much progress has been made in cancer screening over the past decade, but a great deal more needs to be done if screening is to make a major impact on worldwide cancer mortality. Where fully implemented, cytological screening for cervical precursor lesions has had a major impact on mortality. However, the cost and required infrastructure levels are high, and new approaches are needed if screening is to be effective in the developing world. Testing for the human papillomavirus and automated liquid based cytology offer great promise to improve quality, reduce overall cost and make screening more viable generally. Breast screening has been less successful, although useful mortality benefits have been achieved in women aged over 50 years. Full implementation in countries that can afford it will save lives, but radical new approaches will be needed to conquer breast cancer. Colorectal cancer screening offers the best hope of a major reduction in cancer mortality over the next decade. Less certainty exists about screening for other major cancers such as lung, prostate and ovary, but a range of potential approaches merit investigation. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: cancer screening, cervical cancer, cytology, human papillomavirus, breast cancer, mammography, colorectal cancer, sigmoidoscopy, prostate cancer, ovarian cancer

Eur J Cancer, Vol. 35, No. 5, pp. 685–692, 1999

INTRODUCTION

SCREENING HAS been a very active area of research and implementation over the last decade with some notable successes. A range of exciting new approaches suggest that much

more will be achieved as we move into the next millennium. Owing to the low annual incidence of cancer, screening studies take a long time to accrue enough events to provide clear directions for implementation, and progress is slow. Milestones like the millennium are an appropriate point to review the field, although it might be hoped that substantial gains would be made at shorter intervals such as the decade!

The three areas where the greatest advancements have been made are cervical, breast, and colorectal cancer screening. For each of these the type of progress has been of a very different character. For cervical cancer, population coverage has been substantially increased in some parts of the developed world, with clear and gratifying reductions in disease mortality. However, an enormous unmet need exists in most of the developing world, where the disease burden is greatest and the required infrastructure and resources to mount such programmes do not exist. For breast cancer, clinical trials have pointed to clear mortality benefits, at least for women aged above 50 years, and these results have been translated into well-organised national screening programmes in some countries. Here a major challenge is to develop quality control and management networks that can convert the benefits seen in trials to population mortality reductions. For colon cancer, trials of faecal occult blood testing have shown a modest mortality reduction, and non-randomised studies of flexible sigmoidoscopy have suggested that this is an effective method for achieving much larger reductions for the distal colon. The challenge here is to validate these endoscopic results in trials and large prospective studies, to develop methods which are as effective for the proximal bowel and learn how to best integrate all the available methods. Much more work needs to be done to convert these promising approaches into cost-effective screening programmes.

Since screening can only identify individuals in need of treatment, it alone cannot affect the course of cancer without appropriate treatment. In most cases, this is surgical, but when an increased risk of developing cancer is found and/or potentially recurrent pre-cancerous lesions are detected, there is increasing interest in the use of agents to arrest the development of cancer. This is known as chemoprevention.

Screening tests can be divided according to the type of abnormality they aim to detect. Many tests are aimed at early detection of the cancer itself. Such tests can never reduce the incidence of disease, but do hope to reduce the mortality and morbidity associated with advanced disease. For example, a reduction in breast cancer mortality has been clearly demonstrated in women over the age of 50 years who have been screened by mammography, and this is due to the fact that, at least in some women, early detection permits the surgical removal of the lump *before* it has metastasised, so that the chances of cure are high. However, this example also illustrates the limitations of screening tests aimed at early detection, since some breast cancers metastasise at a very early stage, before they are detectable by mammography. For these women earlier detection of their cancers by mammography is of little benefit.

Other screening modalities aim to detect pre-cancerous lesions. The classic example of this is cervical cytology, but sigmoidoscopy also has this goal. Here the goal is to detect precursor lesions before they become invasive, so that removal carries an almost 100% cure rate. In this case a major problem is knowing which lesions are likely to become cancerous if left untreated, so as to avoid over-treatment of benign lesions with no malignant potential.

A third form of screening, which is becoming increasingly common, is genetic testing. This field will develop enormously in the future as more cancer associated genes are found, and tests for mutations become simpler. Genetic screening will lead to very different sorts of programmes, which will involve whole families, require intensive follow-up of individuals testing positive, and the use of chemopreventive agents or prophylactic surgical removal of the organs at risk.

Little similarity exists between the specific screening modalities for the different cancer sites, and a meaningful discussion requires that we examine the approaches for each type of cancer separately.

CERVICAL CANCER

The universally accepted screening method for preventing cervical cancer is cytological examination of cervical scrapes which have been smeared onto slides and stained by Papanicolaou's method. This procedure has a long history. In 1928 Papanicolaou published a report indicating that cervical cancer could be diagnosed from exfoliated cells. Working with Traut, he developed this into a screening test in the 1930s and they published their definitive work in 1943. The war delayed initial attempts at implementation but the subsequent slow acceptance of the approach meant that large-scale field trials did not begin until the 1960s. These were turned into organised screening programmes in the Nordic countries (except Norway) during the 1960s and already by the mid-1970s large reductions in incidence and mortality were seen in these countries (except Norway) [1, 2]. In Britain the programme was not well organised until the late 1980s and mortality reductions have only been apparent in the last few years [3]. However, these are now substantial and are continuing at a rate of 7% mortality reduction per year. Screening programmes have been less well organised in most other countries (British Columbia being a notable exception) and the benefits in terms of national mortality trends have been less clear. Improved coverage, quality control and national or regional audit has to be the first priority in areas where screening services are available.

Successful as it has been, screening by cytology is not without its problems. It is very tedious and labour intensive, and requires high skilled subjective judgements. On a world-wide basis, cervical cancer is still the second commonest cancer in women (after breast cancer) with an estimated 450 000 cases in 1980. This has not changed appreciably in 50 years, and unless drastic measures are taken, it looks to remain one of the three most common cancers among women for many years to come. The costs and infrastructure required for cytology screening are still beyond the reach of the most needy countries, and even in the developed world this is a very expensive business.

New technologies are being developed which, although initially expensive, may ultimately make it possible to undertake screening at a much lower cost and with less technical expertise. These approaches are likely to give new life to cervical screening in the next millennium. Work on automating the reading of smears has been ongoing for over 30 years [4] and a range of computer-assisted systems are now beginning to become available. These systems offer the possibility of avoiding human reading of the majority of normal smears, and also assisting in assessing abnormal smears by displaying suspicious areas on a video screen.

Use of liquid based cytology is also likely to lead to improvements in results. With liquid cytology the cells are put directly into a liquid transport medium by the smear taker and are later plated out as a thin-layer of cells on glass in the laboratory. This provides a uniform thin-layer (almost monolayer) of approximately 80 000 cells in a convenient 1 cm disk on the slide, which is ideally suited to automated reading, as many of the problems which have plagued automated reading, such as drying artefacts, clumps of cells and obscuring blood and mucus, are removed. The cells remaining in the liquid medium are also suitable for additional testing for the human papillomavirus or other sexually transmitted diseases, as needed.

Stains for new targets may also revolutionise cytology. The recent understanding of the regulatory proteins of the cell cycle offer a potential target for screening. Abnormal cells are still proliferating, while normal squamous cells are end cells and no longer express many of the proteins found in cycling cells. Initial results using Cdc6 or Mcm5 [5], are encouraging.

Another, far more fully developed approach, is to screen for high risk types of human papillomavirus (HPV_{hr}). This virus is found in over 95% of all cervix cancers and has been clearly established as the primary causal agent. HPV_{hr} can only be reliably detected by DNA-based tests, and morphological changes on cytology or histology more often detect HPV 6 and other low risk types which produce benign lesions. Early tests for HPV DNA had both sensitivity and specificity problems, but reproducible results are now being achieved with the newer tests.

Definitive studies have yet to be completed but a number of studies have shown very promising results [6–9] using consensus primer PCR or the Hybrid Capture microtitre assay. Sensitivities for CIN 2/3 are almost always higher than for cytology (Table 1) and specificities are similar to that for borderline smears. Overall these studies suggest that adding HPV_{hr} testing to primary screening could increase the yield of high grade CIN by 30–100%, with a positive predictive value similar to that for mild/moderate dyskaryosis. This may both reduce the incidence of cancer, and allow the screening interval to be increased to 5 years or longer, especially in women over the age of 50 years who have never had an abnormal smear.

Persistence is the key attribute of HPV_{hr} infections related to high grade disease. This can only be directly verified by repeated testing using current assays, but transient infections lead to a large number of 'false-positive' results, especially in younger women. Fortunately there are correlates available

which make it possible to improve the predictive value of a single test. The most important of these is age. Transient infections are much more common in younger women, and restricting HPV testing to women over the age of 30 or 35 years (at least for primary screening) substantially reduces the false-positive rate. Viral load is also important. PCR based tests are able to detect very low levels of virus, which are often transient and not of clinical significance, and quantitative assays with thresholds for positivity of approximately 10⁴ HPV copies in a smear give much better specificity and little loss of sensitivity for high grade CIN [10]. Restricting positivity to high risk HPV types is also important but even within this group, there may be important differences. New tests are also being developed to detect HPV DNA integration in the human genome and to look for levels of expression of the E6/E7 proteins which are associated with transformation. These may become useful second level tests which will improve specificity and more accurately identify women with high grade CIN missed by cytology.

Additionally, HPV_{hr} testing offers scope for better detection of incomplete excision and residual disease in women who have been treated for CIN. Currently these women receive annual smears for at least 5 years and often for the rest of their life. Several reports suggest that the persistence of HPV positivity after treatment is an accurate method of assessing treatment failures and this could be used to safely return negative women to positive screening after a single follow-up [11, 12]. This could be yet another way in which HPV testing improves the management of women with cervical abnormalities.

In summary, the new technology promises to revolutionise the practice of cervical screening. Liquid based sample collection provides better material for a range of tests and will facilitate automation. New markers, especially the use of HPV testing, offer great potential within the cervical screening programme. They offer the possibility of greater sensitivity, reduced follow-up of low grade cytological abnormalities and treated lesions, increased screening intervals, and overall cost reductions. Large-scale evaluation projects are needed to explore this potential and to compare the range of new technologies now available.

BREAST CANCER

The most fully investigated modality for early detection of breast cancer is mammography. This method is aimed at early detection of invasive cancer and so is limited by the fact that this may still be too late to affect survival. As a result,

Table 1. Direct comparisons of HPV with cytology

Author [Ref.]	HPV method	Sensitivity for HSIL		Specificity for HSIL		Comments
		Cytology ≥ LSIL	HPV	Cytology < LSIL	HPV	
Reid [6]	Southern blot	52	55	92.3	95.8	Only HPV 16, 18, 31, 33
Cuzick [7]	TS-PCR	46	75	96.4	95.5	
Schneider [8]	HC	29	50	96	96	
Ratnam [9]	HC	37.9	86.2	76.5	57.1	Zimbabwe—high HIV rate
Womack [46]	HCII (HR)	44	81	NA	62	
Gurley [47]	HCII (HR)	50	95	NA	37	
Clavel [48]	HC	75	97.4	97.3	86.4	Age ≥ 35 y
Cuzick [49]	HCII (HR)	79	95.2	98.7	95.1	

LSIL, low grade squamous intra-epithelial lesion; HSIL, high grade squamous intra-epithelial lesion; NA, not applicable; TS-PCR, type specific-polymerase chain reaction; HC, hybrid capture; HCII, hybrid capture generation II; HR, high risk.

only moderate benefits of the order of 20–30% mortality reduction can be expected from this approach. However, because breast cancer is so common (occurs in approximately 1 in 12 women in the Western world) even modest benefits can be worth having and would amount to a larger reduction in the death toll from cancer in the Western world than the complete eradication of cervical cancer.

There is a consensus that mammography is effective in women aged over 50 years and the studies overall suggest that 2–3 yearly screening can reduce breast cancer mortality by approximately 30% in this age group [13]. However, there is considerable controversy about the value of mammography at ages 40–49 and, to date, studies indicate a much smaller benefit in the order of 10–15% [14], although one recent study has reported better results [15]. There are at least three mutually non-exclusive possible reasons for this: (1) Breast cancer is rare in this age group and the confidence intervals (CIs) based on the available data do not rule out the possibility of a 20–30% mortality reduction, although the much lower incidence of breast cancer at this age would make this an even smaller absolute effect than for older women; (2) the lead time gained by screening is shorter in younger women so that screening must be done annually to have an effect; and (3) the breast is more dense in premenopausal women, making imaging more difficult and limiting its application.

There appears to be limited scope for further improvements in mammography although digital mammographic and computer aided techniques will aid somewhat in detecting smaller tumours. The more widespread use of hormone replacement therapy, which increases the radiographical density of the breast, may even erode some of the benefits previously seen. Nevertheless, wider implementation of high quality mammography in women aged above 50 years will ensure that the available mortality reduction will be more fully realised, and this should be a goal for countries able to afford it.

There are a number of new approaches to breast cancer diagnosis and screening based on membrane depolarisation [16]; impedance changes [17]; temperature changes [18], dielectric properties [19] and light scattering [19], but all of these are at a very early stage of development and it will be sometime before it becomes clear whether they will have a role to play.

COLORECTAL CANCER

The screening method that has received the most attention for colorectal cancer is the faecal occult blood test, which uses a guaiac impregnated slide to test for small amounts of blood in a stool sample. The goal of the test is to detect cancers at an early stage when they are still treatable, and the very good survival of Dukes' stage A cancers (better than 90% at 5 years) compared with colorectal cancer overall (approximately 30% at 5 years) suggests this could be successful.

In one study [20] a mortality reduction of 33% for colorectal cancer was found for annual faecal occult blood testing. In that trial, rehydrated tests were used which increased the positivity rate to almost 10%, leading to many unnecessary colonoscopies. Rehydration improves sensitivity but at the expense of a large number of false-positive tests. It is unclear how much of the benefits can be attributed to any selective value of screening, or merely due to the fact that 38% of this

group received a colonoscopy and polypectomy as needed at some stage as a result of a positive test. Three other large trials have now been undertaken using un-rehydrated tests and two have reported a more modest but highly significant 15–20% population mortality reduction [21, 22]. A recent French case-control study is also consistent with these results [23].

The guaiac test aims to detect haem but will react positively to any peroxidase and is not very specific. It detects blood from any lesion in the bowel and also reacts to a number of foods (red meat, fresh fruits and vegetables with peroxidase activity, e.g. tomatoes) and aspirin-induced gastrointestinal bleeding. Dietary restriction before testing or retesting has been used to try to minimise false-positives. The sensitivity of the test is also an area for concern [24]. New occult blood tests are being developed to attempt to improve on the test (Haemoccult II) currently in use. These include an immunological test specific for human haemoglobin (Heme-select) and a more sensitive guaiac based test (Haemoccult-SENSA) which detects heme-derived porphyrins, so that it can detect degraded de-ironed hemes as well as the intact heme detected by Haemoccult II [25]. These have yet to be evaluated in prospective randomised trials.

Another approach to colorectal cancer screening is based on the work of Morson [26] who proposed that most cancers arise from pre-existing adenomas. Adenomas are pre-cancerous growths which occur throughout the bowel and have the same sub-site distribution as cancers, but occur at a younger age. Thus, a better strategy to control colon cancer might be to detect and remove adenomas, since the transition time from a small adenoma to a carcinoma is thought to be very long (of the order of 10–25 years), implying that screening need only be carried out very infrequently. Also, since one is now preventing cancer rather than detecting it early, the potential for mortality reduction is much greater.

An approach based specifically on this idea is to use flexible 60 cm sigmoidoscopy as a screening tool. This is far less expensive or traumatic than complete colonoscopy and approximately 60% of colorectal cancers occur in the region accessible by this instrument. Evidence is mounting of its efficacy. Selby and colleagues [27] have shown, in a case-control study, that mortality due to cancers within the reach of the rigid sigmoidoscope (approximately within 20 cm of the anus) was reduced by 60% for at least 10 years and similar results have been reported in another smaller study [28]. A very large study looking at the effect of any endoscopic procedure on colorectal cancer has also shown a large benefit that does not diminish over a 10-year period [29]. Several other studies have suggested that endoscopic surveillance of the bowel greatly reduces colon cancer rates (Table 2), but a direct demonstration that infrequent screening by sigmoidoscopy will reduce mortality requires a large randomised trial. Such a trial, proposed by Atkin and colleagues [30] has now completed screening of over 40 000 individuals and has 100 000 controls. This trial is based on the promise that most of the benefit of sigmoidoscopy will accrue from a single screening test and only a small group of individuals (approximately 5%) would need colonoscopy and further surveillance. A key issue is at what age this single screen should take place. Ideally, this should be after most adenomas have appeared, but few of the cancers have developed. This window of opportunity is probably between the ages of 55 and 65 years. (Figure 1).

Table 2. Efficacy of sigmoidoscopy

First author [Ref.]	Year	Cases/no. of subjects	Reduction in colorectal cancer incidence in region examined (95% CI)	Type of study
Gilbertson [50]	1978	13/21150	60–85%	Prospective uncontrolled
Friedman [51]	1986	110/10713	60%	Prospective randomised
Selby [27]	1992	261/1129	70% (52–81)	Case-control
Newcomb [28]	1992	66/290	79% (48–92)	Case-control
Atkin [52]	1992	3†/1618	85%	Retrospective cohort
Winawer [53]	1993	5/1418	90% (76–97)	Prospective cohort (colonoscopy)
Muller [29]	1995	4358/16531	59%* (50–67)	Case-control

*Any colorectal procedure. †Excluding cancers arising in incompletely excised adenomas. CI, confidence interval.

PROSTATE CANCER

Screening for prostate cancer provides a dilemma unique among cancer sites. The disease is exceedingly common, but many cancers are indolent and remain asymptomatic at the time of death from another cause. Indeed, autopsy studies have shown that approximately 10% of men aged 50 years who died from other causes have a focus of invasive disease and this increases to 40% in 80 year old men [31]. Thus, while death from prostate cancer is common, being only second to lung cancer in men in many Western countries, the true incidence is much higher. As yet the problem of how to discriminate aggressive disease with lethal potential from indolent cancers which are likely to remain asymptomatic for the remainder of the patient's lifetime remains unsolved, and this is a key issue for the new millennium.

Nevertheless, prostate cancer is a significant public health problem and an obvious target for screening. Digital rectal examinations have been used for many years and still have a role in screening, but are subjective and lack sensitivity [32]. Prostate specific antigen (PSA) testing has good sensitivity, especially when used at a 4 µg/ml cut-off. However, specificity is less good, and the test measures tumour volume but not aggressiveness, and so does not distinguish benign prostatic hypertrophy from invasive cancer. Age-specific cut-offs have been suggested to improve specificity, but there is still substantial overlap between normals and those with cancer. Transrectal ultrasound is probably too invasive and expensive to use as a primary screening test, but may have a role as a secondary test in individuals with slightly elevated PSA level. Further markers of tumour aggressiveness, either measured in serum or needle biopsy specimens, are needed to determine which patients are in need of curative treatment. A number of

approaches exist including looking at changes in serum PSA levels, proliferation markers in biopsies such as Ki67, expression levels of m-RNA and/or proteins for bcl-2, p53, p27, etc. and molecular changes in tumour suppresser genes such as pten or mutations in genes such as the androgen receptor. This is urgently needed since radical surgery carries a high morbidity, often leading to impotence and/or incontinence.

OVARIAN CANCER

Screening for ovarian cancer is still at a research stage. Two methods—transabdominal/transvaginal ultrasonography and a blood test for the tumour marker CA-125—have been most actively studied.

Ultrasound screening involves looking for enlarged ovaries. Its main problem is a lack of specificity since most enlarged ovaries are due to benign cysts. Campbell and colleagues [33] conducted a screening study on 5479 volunteers aged above 40 years. They performed annual transabdominal ultrasound for up to 3 years and 326 (5.9%) women were found to be positive and referred to a surgeon for laparotomy/laparoscopy. Only 5 of these women were found to have primary ovarian cancer (all stage I) and an additional 4 had metastatic cancer in the ovary from a primary in the breast or colon. The positive predictive value per test was 1.4%, which is too low when the next stage involves abdominal surgery. To improve the specificity, transvaginal colour Doppler ultrasound has been used to image blood flow. Blood vessel formation is thought to be a good discriminant between cancer and benign cysts and early reports indicate that the test can substantially reduce the false-positive rate [34], although it is still unclear whether this will be enough to make population screening viable.

Another approach is to measure serum CA-125. This has an established place in monitoring tumour burden, response to treatment and recurrence in women with established ovarian cancer, but its role in screening is less clear. Using a cut-off of 30 U/ml for serum CA-125, Jacobs and colleagues [35] reported a false-positive rate of approximately 1.4% in a study of 22 000 asymptomatic postmenopausal women aged over 45 years and a sensitivity of 60%. Better specificity can be obtained by requiring both ultrasound and CA-125 to be positive and in this study the false-positive rate was reduced to 1.4 per 1000 when ultrasound was used as a second stage screen. Concern has been raised about the low sensitivity of this approach (60%) and Bourne and colleagues [36] suggested that a lower threshold for CA-125 should be used. However, gains in sensitivity by this approach will be at the expense of specificity. Other serum markers may help to refine the diagnosis, and more work is needed here. One way

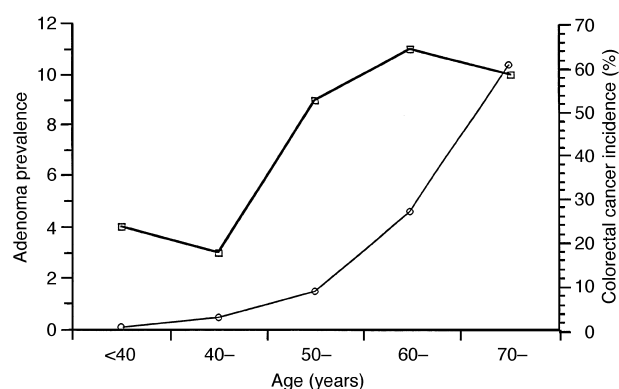


Figure 1. Distal adenomas detected at screening by sigmoidoscopy versus colorectal cancer incidences.

of easing the burden is to focus screening on high risk women (currently only those whose mother or sister has developed the disease), but even here randomised trials are necessary to obtain reliable assessments. Questions regarding the appropriate age and interval at which to screen are even less well understood.

LUNG CANCER

Several relatively small studies have examined the use of chest X-rays and sputum cytology as a method of early diagnosis of lung cancer. Whilst the studies have shown evidence of earlier detection, this has not had any effect on mortality [37] and detection still may be too late to affect the natural history of the disease. However, as lung cancer is the most common cancer worldwide, even a small benefit would be useful, and a trial of chest X-rays large enough to detect a 10% reduction in mortality (which would have been missed on previous studies), is now ongoing in the US [37]. In view of the enormity of the lung cancer problem, new imaging procedures using spiral computed tomography (CT) scanning which can detect much smaller nodals in the lung would seem a useful area for future research. Additionally the rapid development of our understanding of the biology of cancer, suggests that new cancer-associated markers in sputum may be developed to aid screening and early detection.

STOMACH CANCER

With its high incidence and mortality, screening for gastric cancer by barium X-ray is already a national programme in Japan. The aim is to screen everyone over the age of 40 years every year in order to detect cancer at an earlier stage. In Miyagi Prefecture almost 3 million tests were performed between 1960 and 1988 and the test was positive in approximately 10% of cases leading to a recommendation for gastroscopy. The positive predictive value is reported to be 1.7% [38]. No randomised trials have been reported, but indications of effectiveness have been seen in time trends of mortality, cohort studies and case-control studies [38]. The results from a case-control study in Miyagi Prefecture suggest a substantial benefit in the year following screening, but little benefit subsequently. Potential biases exist in all these analyses since the incidence of stomach cancer is falling in Japan and compliers may have a different risk than non-compliers.

Another approach to stomach cancer prevention is screening for *Helicobacter pylori* infection and eradication by antibiotic therapy. *H. pylori* causes chronic active gastritis which can progress to chronic atrophic gastritis which is thought to be one of the early steps in gastric carcinogenesis. Several epidemiological studies have linked *H. pylori* to stomach cancer [39] and studies are ongoing in Venezuela to examine the effect of intensive treatment of *H. pylori* infection on stomach cancer incidence, although work in this area is still at an early stage. Population screening is not viable in Western countries, but stomach cancer is still very common in South America, Eastern Europe and parts of Asia and the possibility that screening can reduce mortality should be more fully investigated there.

OTHER CANCERS

The only available screening modality for melanoma is early recognition, and the 10-year survival rate for early thin lesions (less than 0.76 mm) is very good (approximately 90%) whereas thicker lesions (greater than 4 mm) have a much

poorer prognosis (approximately 30%). As it has the highest rate of melanoma in the world, Australia has taken the lead in promoting screening. Methods used include public education, free skin examinations at the beach or in city centres, and teaching people with high risk skin types or many naevi how to recognise a melanoma. Regular examination of people with the atypical mole syndrome by a dermatologist is also carried out, but one of the most important aspects of this may be to teach these people how to recognise malignant changes or new malignant lesions. None of these approaches have been subjected to serious scientific evaluation and at present it is difficult to confidently ascribe benefit to any of them.

Work on liver cancer prevention has focused primarily on preventing infection with hepatitis B by vaccination. Chronic carriers of hepatitis B virus surface antigen are at a greatly increased risk of liver cancer. Both of these are common in South-eastern China and tropical Africa. A possible approach to screening for liver cancer is first to look for chronic carriers, who are then screened for an increased level of α -feto-protein which is a tumour marker for liver cancer. Further investigation by ultrasound could be useful in detecting small cancers which are surgically resectable. Such an approach has been suggested by Sun and colleagues [40].

Screening for oesophageal and nasopharyngeal cancer has been studied in parts of China [41, 42] but these are too rare to be considered in the Western world.

In Japan neonates are screened by looking for elevated levels of the catecholamine metabolites vanillylmandolic acid (VMA) and homovallic acid (HVA) in urine at ages 3 and 6 months. Sensitivity is approximately 80% and approximately 1 in 8500 infants tested turn out to have neuroblastoma. Prognosis appears to be much improved by early detection [43, 44] but there is no evidence of reduced incidence rates at older ages or a decrease in mortality. It is possible that the cases picked up by screening are of a different variety which would regress spontaneously and are not related to the more aggressive tumours which arise in children aged over 1 year [45]. A randomised trial is needed to see if overall mortality is actually reduced.

Bladder cancer screening by cytology is routinely offered to occupationally exposed workers in the rubber and dyestuff industries. Some pilot work has been done in north Africa in high risk areas where schistosomiasis is endemic. Haematuria has also been suggested as a screening test. Neither of these tests are very specific and a greater positive predictive value needs to be achieved before screening and the attendant invasive follow-up investigations can be contemplated in the general population.

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