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USE OF BIOMARKERS IN SCREENING FOR CANCER

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Abstract

Background: Screening for premalignant lesions or early invasive disease has the potential to reduce mortality from cancer. Potential screening tests for malignancy include measurement of (bio)markers.

Content: The literature relevant to the use of biomarkers as screening tests for cancer was reviewed with particular attention given to systematic reviews, prospective randomised trials and guidelines published by Expert Panels.

Because of their ease of measurement, several biomarkers have been evaluated or are currently undergoing evaluation as screening tests for early malignancy. These include the use of vanillymandelic acid and homovanillic acid in screening for neuroblastoma in newborn infants, AFP in screening for hepatocellular cancer in high-risk subjects, CA 125 in combination with transvaginal ultrasound (TVU) in screening for ovarian cancer, PSA in screening for prostate cancer and fecal occult blood testing (FOBT) in screening for CRC. Of these markers, only the use of FOBT in screening for CRC has been shown to reduce mortality from cancer. Large randomized prospective trials are currently in progress aimed at evaluating the potential value of PSA screening in reducing mortality from prostate cancer and CA 125 in combination with TVU in reducing mortality form ovarian cancer.

Conclusion: Although biomarkers have many attractions as screening tests, inadequate sensitivity and specificity, when combined with the low prevalence of cancer in asymptomatic subjects, limit their value for the early detection of malignancy.

Screening has been defined as the systematic application of a test to identify subjects at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder (1). To be of value, screening must detect disease earlier and result in an efficacious treatment and the earlier use of efficacious treatment must lead to better outcome compared to treatment available at the onset of symptoms (2). Screening differs from diagnosis in that the aim is to detect disease or a predisease state when subjects are asymptomatic.

Currently, only a small number of screening tests have been shown to reduce mortality from cancer. These include mammography in screening for breast cancer (especially in women >50 years of age), the Papanicalaou (PAP) test in screening for cervical cancer and fecal occult blood testing (FOBT) in screening for colorectal cancer (CRC) (for review, see refs. 2,3).

Compared to procedures such as radiology, cytology and endoscopy, the use of biomarkers as cancer screening tests have several advantages (4). These advantages include:

- Biomarkers can be measured in biological fluids such as blood and urine that can be obtained with minimal inconvenience to subjects undergoing screening. This in turn should lead to high compliance rates.
- For many biomarkers, automated assays are available, thus allowing the processing of large numbers of samples in a relatively short period of time.
- Tests for biomarkers provide quantitative results with objective endpoints.
- Assays for biomarkers are relatively cheap.

In practice however, lack of sensitivity for early invasive disease or premalignant lesions and lack of specificity for malignancy limit the use of existing biomarkers in screening asymptomatic subjects for early malignancy (4,5). This lack of sensitivity and specificity when combined with the low prevalence of cancers in the general population means that most biomarkers, if used alone, have a low positive predictive value in screening asymptomatic populations. Indeed, it is the low prevalence of cancer in the general population that prohibits most biomarkers from being used alone, in screening for cancer (4,5).

Despite these limitations, a number of biomarkers have either undergone or are currently undergoing evaluation as potential cancer screening tests. These markers include the use of vanillymandelic acid (VMA) and homovanillic acid (HVA) in screening for neuroblastoma in newborns, AFP in screening for hepatocellular cancer in high-risk subjects, CA 125 in combination with transvaginal ultrasound (TVU) in screening for ovarian cancer, PSA in screening for prostate cancer and fecal occult blood testing (FOBT) in screening for CRC. The aim of this article is to critically review the role of these biomarkers in screening normal-risk asymptomatic subjects for early cancer. Screening subjects with a genetic predisposition to cancer will not be discussed.

USE OF AFP IN SCREENING FOR HEPATOCELLULAR CANCER IN HEPATITIS B AND HEPATITIS C INFECTED SUBJECTS

Worldwide, hepatocellular cancer (HCC) is the 5th most common cancer and the 3rd most frequent cause of cancer-related death (6). HCC is particularly prevalent in South-east Asia and sub-Saharan Africa. In contrast to these regions, rates are relatively low in most of the Western world. These wide variations in incidence of HCC are mostly due to variations in risk factors, especially exposure to hepatitis B virus (HBV) or hepatitis C virus (HCV). HBV is responsible for most cases of HCC in China and Africa whereas HCV accounts for most of the cases in the Western world (7). As well as infection with HBV or HCV, other diseases that increase the risk of HCC include alcoholic cirrhosis, primary biliary cirrhosis and genetic haemochromatosis.

Since a group of subjects at high risk of developing HCC can be identified, screening is potentially of value for the detection of early HCC in these subjects. The main screening tests for HCC are serum AFP and liver ultrasound (6,7).

Two relatively large randomised trials using AFP and/or liver ultrasound to screen for HCC in subjects infected with HBV, have been carried out in China. In the first of these trials which was based in Shanghai, 18,816 subjects aged 35-55 years of age with hepatitis B infection or chronic hepatitis were recruited and randomised into 2 groups (8). The screened group comprised 9373 subjects and were offered bi-annual AFP measurement plus ultrasound. The control group (n = 9443) were not offered any screening, at least for a period of 5 years. Using a cut-off point of 20 µg/L, the sensitivity of AFP for HCC was 69% (95% confidence interval (CI), 54%-80%), the specificity was 95% (95% CI, 94.7%-95.3%), while the PPV was 3.3% (95% CI, 2.2-4.4). The combination of ultrasound with AFP increased sensitivity to 92% (95% CI, 80-97%) but decreased specificity to 92.5% (95% CI, 92.1-92.9). Mortality from HCC was reported to be significantly lower in the screened compared to the control group, being 83.2 per 100,000 in the screened group versus 131.5 per 100,000 in the control group. The rate ratio for mortality from HCC was 0.63 (95% CI, 0.41-0.98) (9).

In the second randomised trial carried out in China (Qidong), 5581 HbsAg carriers were randomly assigned to screening (n = 3112) or a control group (n =1869) (10). Although AFP measurements were planned for 6-monthly intervals, this did not always occur. Using a cut-off value of 20 µg/L for AFP, overall sensitivity and specificity was 55.3% and 86.5%, respectively. However, for those who completed all the scheduled tests, sensitivity and specificity were 80.0% and 80.9%, respectively. In this study, screening with AFP resulted in the earlier diagnosis of hepatocellular cancer but this did not lead to an overall reduction in mortality.

Less work has been carried out on the role of AFP in screening for HCC in HCV-infected compared with HBV-infected subjects. Following a systematic literature review, Gebo et al (11) identified 19 studies that investigated the use of AFP in screening for HCC in patients with chronic B or chronic C hepatitis or both. Three of these were in patients with HCV only, while 16 were in patients with HBV or HBC or both. No prospective randomized trial was identified. Using cut-off points between 10 and 19 μg/L, the sensitivity of AFP for HCC varied from 45% to 100%, while specificity varied from 70% to 95%.

Despite the limited high level evidence that screening for HCC in high risk subjects reduce mortality, a number of expert panels such as the National Academy of Clinical Biochemistry (NACB) (12) and the National Cancer Center Network (NCCN) (13) recommend the use of both AFP and ultrasound in screening certain high risk subjects for HCC. According to the NACB, AFP should be measured and abdominal ultrasound performed at six-monthly intervals in patients at high risk of HCC, especially in those with hepatitis B and hepatitis C-related liver cirrhosis. AFP concentrations that are >20 μg/L and increasing should prompt further investigation, even if ultrasound is negative (12). Similarly, the NCCN recommends the use of both periodic AFP and ultrasound in screening high risk subjects for HCC. This organization also recommend additional imaging if serum AFP is rising or following identification of a liver mass nodule on ultrasound (13). The American Association for the Study of Liver Disease (AASLD) however, state that AFP should not be used in the surveillance of high-risk groups for HCC unless ultrasound is not available (14).

USE OF URINARY HOMOVANILLIC (HVA) AND VANILLYLMANDELIC ACID (VMA) IN SCREENING FOR NEUROBLASTOMA IN NEWBORN INFANTS

Neuroblastoma is the most common extracranial tumor in children. Neuroblastomas synthesise catecholamines such as adrenaline, noradrenaline and dopamine. These molecules are metabolised in the liver and the breakdown products, homovanillic (HVA) and vanillylmandelic acid (VMA) are excreted in the urine. Approximately 90% of patients with neuroblastoma produce elevated levels of urinary HVA and VMA. A number of large population-based studies have investigated the potential use of these catecholamines as screening tests for neuroblastoma in children l year old or less.

One of the most extensive of these studies has been carried out in Japan. Nationwide screening of 6-month old newborns for neuroblastoma began in Japan in 1984. Initially, this involved a qualitative urine test for VMA. In 1990, the qualitative test was replaced with a quantitative high performance liquid chromatography (HPLC) analysis of urine VMA and HVA. Although some reports suggested that screening resulted in a reduction in the rate of death from neuroblastoma (15), the practice was terminated in 2003 (16).

In 2008 however, Hiyama et al (17) carried out a retrospective analysis on the effect of this screening on mortality from neuroblastoma. Over 22 million children were divided into 3 groups: children born prior to screening (n=6,130,423), those born during qualitative screening (n=5,290,412) and those born during quantitative screening (n=10,868,860). Analysis showed that that the incidence of infantile neuroblastomas was higher in children who were screened compared to those who did not undergo screening. In addition, mortality from neuroblastoma in children who were screened was lower than that in the prescreened group, particularly in children screened using quantitative analysis (17).

Although this analysis suggested that screening for neuroblastoma at 6 months of age reduced mortality, the study had a number of flaws (18). The most serious of these were the retrospective nature of the study and the lack of a population-based control group. Since a historical group was used as a control, the decrease in mortality in the screened group could have resulted from advances in treatment rather than from a direct effect of screening. Ideally, a large prospective randomized trial is necessary to investigate the potential impact of a screening test in reducing mortality from a disease.

As well as the Japanese trial, 2 other large population-based studies have investigated the impact of screening for neuroblastoma on mortality. In one of these carried out in Quebec, Canada, almost 500,000 children were screened at 3 weeks and 6 months of age (19). All were followed-up for a minimum of 6 years. Forty three cases of neuroblastoma

were detected by screening, 20 were detected clinically prior to screening and 55 were detected after 3 weeks of age having a negative screen or never having undergone screening. Twenty two children died, i.e., 19 that screened negative and 3 with disease detected clinically prior to screening at 3 weeks of age. The standardized mortality ratio for the screened group compared with a concurrent group in the rest of Canada was 1.39 (95% CI, 0.85-2.3) and the standardized incidence ratio was 2.17 (95% CI, 1.79-2.57). The trial investigators concluded that although screening for neuroblastoma in the first year of life increased its incidence, it did not appear to decrease mortality. Indeed, one child in the screened group that suffered severely from the surgery carried out to excise the neuroblastoma.

Another major study in which over 2.5 million German children were screened at 1 year of age, reached a similar conclusion (20). Although neither the Canadian or German studies involved randomised controlled trials, they both concluded that screening for neuroblastoma within the first year of life failed to reduce mortality (19). Consequently, screening for neuroblastoma within the first year of life is not currently recommended (21).

The reason why screening for neuroblastoma early in life failed to reduce mortality may be due to the detection of tumors that have favourable prognostic characteristics or that spontaneously regress, whereas subjects with aggressive disease that are destined to present clinically at an older age may be missed by screening (19). Screening in the first year of life may therefore lead to overdiagnosis and overtreatment and thus has the potential to do more harm than good. Whether screening later in life (e.g., after 1 year) would lead to a higher detection rate of aggressive tumors is unknown.

USE OF PSA IN SCREENING FOR PROSTATE CANCER

By far the most widely measured cancer screening biomarker is PSA which is used to screen for prostate cancer (22). Screening for prostate cancer however is controversial. It is controversial because:

- It may lead to overdiagnosis and consequently overtreatment.
- The optimum treatment for early prostate cancer is unclear.
- Consistent data from randomised prospective trials showing that screening decreases mortality from prostate cancer is lacking.

In an attempt to address the effectiveness of PSA screening in decreasing mortality from prostate cancer, 4 prospective randomized controlled trials have been carried out or are still ongoing. In one of the earliest of these trials performed in Quebec, Canada, 46,193 men aged 45 to 80 years of age were randomly allocated either to the group invited by letter for annual screening or to the control group not invited for screening, at a ratio of 2:1 in favour of screening (23,24). Men in the control group were monitored according to the then current medical practice. The first round of screening involved both PSA testing and digital rectal examination (DRE). These 2 tests were performed independently. If the PSA concentration was > 3 µg/L or DRE was abnormal, a prostate biopsy was carried out. Mortality from prostate cancer was the primary end point. After 11 years of follow-up, screening was claimed to be associated with a 61.5% reduction in prostate cancer mortality or a relative risk of death from prostate cancer of 0.39 (95% CI, 0.27-0.72).

This study however, had a number of flaws (25-28):

- Of the 31,133 men invited for screening, only 7,348 (23.6%) underwent screening. This low response meant that the trial had limited power to either detect or exclude a possible benefit of screening.
- Of the 15,353 in the control group, 1,122 (7.3%) were actually screened for prostate cancer.
- Mortality was not based on the intention-to-screen principle. Analysis of the original data according to the intention-to-treat approach showed no significant difference in mortality between the screened and control groups, i.e., a relative risk of 1.08 (p = 0.56).
- The time from randomisation to screening was 3 years in the screened arm. Thus, the time to assess mortality was 3 years less compared to the control arm, as men diagnosed with prostate cancer prior to the screening date were excluded.

The second randomised controlled trial for prostate cancer screening was performed in Norrkoping, Sweden (29). This trial contained 9,026 men, aged 50 to 69 years with every 6th man randomised to screening. The first round of screening involved only DRE while the second round had both DRE and PSA. A prostate biopsy was carried out if the PSA concentration was > 4 µg/L or if the DRE was abnormal. After 15 years of follow-up, 292 (3.7%) cancers were detected in the control group and 85 (5.7%) in the screened group. Twenty (1.3%) prostate cancer-specific deaths occurred in the screened group and 97 (1.3%) in the control group. Log-rank analysis failed to show a significant difference in either overall or cancer-specific survival between the group undergoing screening and the control group, although a trend towards a better cancer-specific survival was seen in the screened group.

Like the Quebec study described above, this trial also had methodological problems. Firstly, as the authors pointed out, this study was insufficiently powered to detect a possible statistically significant difference in mortality between the screened and control groups (29). Secondly, prostate cancer diagnosis was based on aspiration cytology which would be expected to have a lower sensitivity than the more widely used approach of ultrasound-guided core biopsy. Thirdly, a comparison of the socio-demographic data between the screened and the control group was not reported.

Meta-analysis of the data from the above 2 randomized studies also concluded that there was no significant difference in mortality between the screened and control groups (30).

As well as the above relatively small trials, 2 large prospective randomised trials comparing survival in screened and control groups have been carried out, i.e., the European Randomized Study of Prostate Cancer (ERSPC) (31) and the Prostate, Lung, Colon and Ovary trial (PLCO) (32). The ERSPC trial took place at 7 different European countries while the PLCO trial was based at 10 different sites in the US. Both these trials started in the middle 1990s and by 2002, over 200,000 men had been randomised (31).

Preliminary findings from both the ERSPC and PLCO studies were recently published. In the PLCO trial, 76,693 men were randomized to either annual screening or standard care (33). After 7-10 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screened group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% CI, 1.16- 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75-1.70). Thus, after 7-10 years of follow-up, similar rates of death were found in the 2 groups. A limitation of this study was that approximately 50% of men in the control group underwent screening during the study. This trial might thus be regarded as a comparison between annual and ad hoc screening.

In the ERSPC study, 162,243 men, 55-69 years of age, were randomly assigned to PSA screening at an average of once every 4 years or to a control group not subjected to screening (34). During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI, 0.65-0.98; adjusted P=0.04). The absolute risk difference was 0.71 deaths per 1000 men. Although PSA-based screening reduced the rate of death from prostate cancer by 20%, the authors calculated that 1410 men would have to be screened and 48 cases of prostate cancer would have to undergo treatment to prevent one death from prostate cancer. A limitation of this study was that the different screening protocols were used in the different countries.

The premature publications of the above 2 studies has done little to resolve the PSA screening controversy (35). A reasonable conclusion is that at best, screening has only a modest impact on death from prostate cancer over the first 10 years of follow-up. Furthermore, any possible benefit comes at the cost of overdiagnosis and overtreatment.

Until the final results from these trials are known, confusion will exist as to whether PSA screening does more good than harm. In the absence of clear data from randomised controlled trial and conflicting data from different Expert Panels (Table 1), a practical way forward is to encourage a shared approach to decision making between doctor and patient (30). This approach can be facilitated with appropriate patient education literature describing the benefits and risks of undergoing screening.

USE OF CA 125 IN SCREENING FOR OVARIAN CANCER

Epithelial ovarian cancer is the 4th most common cause of tumor-related death in women and the most lethal gynecological malignancy (42). The main screening tests for ovarian cancer are CA 125 and TVU (43,44). According to Jacobs and Bast (45), a screening test for ovarian cancer should have a PPV of at least 10% to be clinically useful. With a PPV of 10%, 10 women would need to undergo surgery for each case of ovarian cancer detected.

Although widely used in monitoring patients with diagnosed ovarian cancer, lack of sensitivity for stage 1 disease and lack of specificity preclude the use of CA 125, alone, in screening healthy women for ovarian cancer (43,44). In order to enhance the clinical utility of CA 125 as a screening test for ovarian cancer, a variety of strategies have been attempted. These include assay of other biomarkers in addition to CA 125, sequential assays of CA 125 and a combination of CA 125 with ultrasound (i.e., multi-modal screening) (43,44).

It is the latter approach that has been used most frequently in the ovarian cancer screening studies reported to date (for review, see refs. 43-46). In multi-modal screening, CA 125 is usually assayed first and ultrasound only carried out if elevated marker concentrations are found. The advantage of this strategy is that only a minority of women need to have ultrasound which reduces costs and the need for a clinical examination.

In a systematic review of the literature, Bell et al (47) identified 4 prospective but non-randomised studies that used multi-modal screening for ovarian cancer in the general population. In total, over 27,000 women were screened and 14 ovarian cancers were detected, of which 7 were stage 1 disease. In the largest study (N = 22,000), the PPV of CA 125 followed by ultrasound for the detection of ovarian cancer was 27%, while the specificity was 99.9% and the sensitivity was 79% (at 1 year) (48).

Having shown that the combination of CA 125 and ultrasound provided adequate specificity and PPV, a pilot randomised trial was initiated (49). In this trial, postmenopausal women aged 45 years or older were randomised to either a control group (N = 10,977) or a screened group (N = 10,958). Women in the screened group were offered 3 annual screens, i.e., CA 125, pelvic ultrasound if CA 125 value was greater than 30 kU/L and referral for gynaecological investigation if ovarian volume was 8.8 ml or greater. Of the women allocated to screening, 29 underwent surgical investigation and 6 ovarian cancers were detected, i.e., the PPV was 20.7%.

During 7 years of follow-up, 10 further cases of ovarian cancer were detected in the screened group and 20 in the control group. In the women who developed cancer, survival was longer in those who underwent screening than in the control group (73 versus 42 months, p = 0.011). Nine deaths occurred in the screened group, compared to 18 in the control group but this difference was not statistically significant. The study however, had insufficient numbers of subjects to show a possible difference in mortality. It nevertheless demonstrated that a multimodal approach to ovarian cancer screening was feasible in a randomised trial.

Rather than using absolute CA 125 concentrations and TVS, Menon et al (50) investigated a risk of ovarian cancer or ROC algorithm as a potential ovarian cancer screening strategy. The algorithm incorporated subject's age, rate of change in CA 125 level and absolute level of CA 125 (50-52). The inclusion of the rate of change in CA 125 concentration in the algorithm was based on the observation that while women with ovarian malignancy generally have rising marker concentrations, women with other diseases tend to have constant or declining values (52). The algorithm calculates the slope (change in levels over time) and intercept (initial value) of the best-fit line drawn between sequential CA 125 values. The greater the slope or intercept, the higher was the risk of ovarian cancer. The ROC algorithm was found to be superior to that of fixed cut-off points for the preclinical detection of ovarian cancer in postmenopausal women (53).

This ROC algorithm is currently undergoing evaluation in a large randomized prospective trial, i.e., the UKCTOCS trial (54). In this trial, approximately 200,000 postmenopausal women, aged 50 to 74 years were randomized in a ratio of 1:1:2 to annual ultrasound screening, annual CA 125 assay (interpreted using ROC algorithm) and a control group. All CA 125 assays were measured in the same center, using the same method. Preliminary results from this trial were recently published (54).

During the first 4 years, surgery was carried out on 845 (1.8%) of women undergoing ultrasound-sound-only screening. Twenty four of these were found to have invasive ovarian malignancy. In the group undergoing multimodal screening, surgery was performed in 97 (0.2%) of 50,078 women, of whom 34 had invasive ovarian cancer. Of the 58 cancer detected through screening, 28 (48%) were found to be either stage I or II. Overall sensitivity, specificity and PPV for all primary and tubal malignancies were 89.4%, 99.8% and 35.1%, when CA 125 and ultrasound were used in screening. Specificity and PPV but not sensitivity was significantly greater with the combined versus the ultrasound-only approach was used. Approximately 3 surgeries had to be done to detect one invasive cancer when multimodal screening was used (54). Due to inadequate follow-up, results on mortality were not presented.

The PLCO study in the US is also addressing whether screening with CA 125 and ultrasound can reduce mortality from ovarian cancer in postmenopausal women (55). Here, women in the screening arm have annual CA 125 screening for 6 years and annual ultrasound performed concurrently for 4 years. Women in the control group are receiving "usual" treatment. Follow-up will be for at least 13 years from the time of entry. Although is trial is based at 10 separate locations, CA 125 is being measured centrally.

Preliminary finding from this trial have also been published (56). During the initial 4 years, 34,261 women underwent screening, of which 3,388 had an abnormal finding. Of these, 1,170 (34.5%) underwent surgery and 60 (5.1%) were diagnosed with ovarian or peritoneal malignancy. Most of the cancers (72%) were advanced, i.e., stages III and IV. The PPV using the combination of tests ranged from 1.0 to

1.3 over the 4 years of screening. As with the UKCTOCS trial, the impact of screening on survival has not yet been reported.

Based on our current state of knowledge, it is not surprising that Expert Groups in Europe and the US recommend against using CA 125, either alone or in combination with TVU, in population screening for ovarian cancer (40,57,58).

USE OF FAECAL OCCULT BLOOD TESTS IN SCREENING FOR COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer, worldwide with an estimated 1 million new cases and a half million deaths each year (59). The life-time risk of developing CRC is about 6% and of developing colorectal adenomas is about 50% (59,60). Although several types of screening tests are available for CRC (61,62), this article will focus exclusively on faecal-based markers. It should be stated that compared to endoscopic techniques (e.g., colonoscopy or sigmoidoscopy), measurement of faecal markers is relatively simple, low cost and non-invasive. These tests are thus suitable for large population-based screening.

Although several faecal-based markers have been described, the most frequently used involves the measured of fecal occult blood, i.e., FOBT, either by the guaiac test which detects the pseudo peroxidase activity of haem/haemoglobin or an immunochemical test which detects the globin antigen in haemoglobin (61-63). Of these 2 methods, the older guaiac test has been the more widely evaluated, especially in large randomized controlled trials.

A systematic review of the literature published in 2007 identified 11 articles containing results from 4 prospective randomized controlled trials that evaluated the guaiac test in population-based screening studies for CRC (64). Overall, the trials involved >320,000 subjects, with follow-up ranging from 8 to 18 years. Cumulative results of the 4 randomized controlled studies showed that the subjects allocated to screening had a 16% reduction in the relative risk of CRC mortality (RR, 0.84: 95% CI, 0.78-0.90). Following adjustment of the relative risk for attendance at screening, the overall predicted relative mortality reduction was 25% (RR, 0.75; 95% CI, 0.66-0.84), for the screened group. The authors concluded that FOBT screening had the potential to reduce approximately 1 in 6 deaths from CRC.

Although screening with the guaiac test has clearly been shown to reduce mortality from CRC, this test is being replaced with faecal immunochemical tests (FITs). Some of the advantages of the FIT tests compared to guaiac tests include (40,65-67):

- FITs have better analytical sensitivity and specificity for human haemoglobin than guaiac-based test.

- Some FITs can be automated, thus increasing throughput and reproducibility.
- Some FITs can be quantitated, enabling adjustment of sensitivity, specificity and positivity rates to meet local needs.
- Unlike the guaiac tests which may be affected by certain dietary components (e.g., red meat, vitamin C) and some medications (e.g., aspirin), FITs are free from interference by these factors.

FITs however, are more expensive than guaiac-based tests. Furthermore, FITs have not to-date been shown to reduce mortality from CRC in randomized clinical trials. However, since their accuracy in detecting CRC and advanced adenomas is at least as good if not better than guaiac-based tests (65-67), such validation should not be necessary. It is likely that FITs will replace guaiac-based tests in screening for CRC, in the future.

Because of the general lack of specificity of FOBT, interest has shifted in recent years to the measurement of fecal DNA-based markers for CRC screening. These DNA markers usually involved the detection of genes that are mutated or altered in CRC and its precursor lesions. One of the most widely investigated panels involves measurement of mutations in the K-RAS, APC and P53 genes as well as the detection of BAT-26 (a marker of microsatellite instability) and L-DNA (a marker of DNA integrity) (68-70). Like the FITs, the effectiveness of fecal DNA markers in reducing mortality from CRC has not yet been validated in a large prospective randomized trial. However, as with FITs, such validation should not be required. A potential problem in the use of DNA panels in screening for CRC is their relative high cost compared with occult blood-based tests. Despite this, guidelines jointly published by the American Cancer Society, the US Multi-Society Task Force and the American College of Radiology concluded that DNA panels were an acceptable option for CRC screening (61).

Currently, several expert panels recommend that all subjects 50 years or older should undergo screening for CRC (61, 71-74). Since the optimum screening test/strategy is still unclear, most organizations are not prescriptive as to the specific screening procedure to be used. A joint statement from the American Cancer Society, the US Multi-Society Task Force and the American College of Radiology (61) however, stated that “clinicians should make patients aware of the full range of screening options but at a minimum, they should be prepared to offer patients a choice between a screening test that is effective at both early cancer detection and cancer prevention (e.g., colonoscopy) and a screening test that primarily is effective at early cancer detection (e.g., FOBT). It was the strong opinion of these 3 organizations that colon cancer prevention should be the main goal of cancer screening.

CONCLUSION

Although intuitively appealing, the success of biomarkers in screening for early cancer has been disappointing. Indeed, the discovery and validation of biomarkers for this purpose presents a major challenge. Despite efforts by the Early Detection Research Network (EDRN) (75), few new promising cancer screening markers have emerged in recent years. Furthermore, new technologies such as gene expression microarray and proteomics have so far been slow in providing useful leads. The “holy grail” of a simple blood test for the early detection of cancer therefore remains.

Indeed, the question needs to be addressed whether the measurement of a single biomarker in serum can provide a reliable test for the early detection of cancer. Small or surgically resectable cancers are likely to release relatively low concentrations of biomarkers into blood. This, coupled with the large dilution in blood following release, presents a major challenge in devising assays to detect biomarker levels above background. Rather than using blood, an alternative might be to use proximal fluids, i.e., fluids that are adjacent to tumors. In this context, it should be pointed out that preliminary results suggest that the measurement of methylated genes in sputum can provide a promising new test for the early detection of lung cancer (76,77).

Table 1. Recommendations from various expert panels regarding the use of PSA in screening for prostate cancer.

The American Cancer Society

Recommended discussion regarding benefits and limitations of early detection and state that both PSA and digital rectal examination (DRE) be offered annually from age 50 to men with a life expectancy >10 years (36).

The US Preventative Services Task Force

Stated that the available evidence was insufficient to recommend for or against routine screening for prostate cancer in men < 75 years of age. For men 75 years of age or older, it was concluded that the harms of screening for prostate cancer outweighed the benefits (37).

The American Urological Association

Recommended PSA screening for well-informed men with a life expectancy of at least 10 years who wish to pursue early diagnosis. Baseline PSA concentrations should be determined at 40 years of age (38).

The European Group on Tumor Markers (EGTM)

Stated that "assay of PSA can be recommended in symptomatic men, if the diagnosis of prostate cancer alters the treatment decision. However, in the absence of data showing that the early detection of prostate cancer does more good than harm, it may be reasonable to restrict PSA testing to asymptomatic men who are prepared to undergo prostate biopsy in the event of an elevated PSA level and have a life expectancy of more than 10 years" (39).

The National Academy of Clinical Biochemistry

Stated that screening for prostate cancer is not recommended at present (40).

The European Society of Clinical Oncology (ESMO)

Stated that the effect of screening on mortality was controversial and cannot be currently recommended (41).

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