REVIEW

Cancer Screening: A Review with Particular Attention to Areas for Future International Research Efforts

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Abstract

For almost all of the sites of most common cancers, particularly the lung, colo-rectum and cervix, relatively inexpensive and reliable tests have been available for some time. Advances in imaging techniques now allow identification of early tumours in many other organs, including those that are normally associated with a very poor prognosis. In addition, increasing knowledge of the risk factors for cancer development in different organs imply more effective screening for early malignancies in high risk populations and the associated increase in the predictive value should mean that early intervention will result in a marked decrease in the mortality and morbidity due to a wide range of major cancers. However, there are many difficulties which remain to be overcome, especially in the psychosocial area. Problems with overdiagnosis and distinction of lesions most likely to actually give rise to cancers also require especial attention for the full promise of screening to be realised. In addition, choice of the most appropriate approach will require an in depth understanding of cultural factors impacting on screening behaviour and it is of paramount importance that both physicians and the public at large be fully aware of pitfalls and potential benefits. Thus research needs to be concentrated on effective education approaches as well as how to increase practical sensitivity and specificity of individual tests and determine the best follow-up for individuals testing positive.

Key Words: Screening for early detection - methodology - psychosocial factors - education

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Screening: General Principles

A great deal has already been elucidated about risk factors underlying cancer development, whether environmental chemical, viral, bacterial, inflammatory, hormonal or dietary. Development of effective strategies for primary prevention will now dpend on generate an awareness of what environmental, including cultural, determinants may underlie high incidences of neoplasia and how lifestyle and diet can be optimised to reduce the likelihood of malignant tumours arising during the normal lifespan. This can hopefully be supplemented by use of chemopreventive agents, especially for those individuals with a high probability of neoplastic development. However, no matter how efficacious the measures taken to delay the appearance of cancers they will still occur, even if only in older populations, and to avoid or at least reduce mortality from this cause early detection by screening and appropriate surgical or other intervention will clearly continue to be necessary.

Given the restraints of limited financial resources, the main questions are which are the most suitable target lesions, methodologies and human populations for screening efforts. Despite a general concensus that more attention should be devoted to this area, the number of comprehensive studies of relative cost and benefit have been few. As general advisers to the population at large, the physicians obviously must play a major role, but the lack of stress given to general prevention and screening in medical education at the undergraduate and postgraduate level may be a major hindrance in this regard (Chamberlain et al., 1995). The relative lack of publications focusing on this area (Tsuda and Moore, 2002) is an obvious reflection of this situation. Especially in the third world, attitudes of doctors may be a barrier to effective screening (Soliman et al., 1997). Furthermore, the lack of general appreciation among the public, in many cases, of the real benefits which can accrue from early detection is also a major challenge (Breslow et al., 1997).

Principles of screening and surveillance have been

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Table 1. Factors for Efficacious Screening

1) Directed at diseases of relatively high incidence
2) Condition to be screened for must have relatively high death or disability rate
3) The screening tool must be acceptable to patients with good predictive value
4) Follow-up measures and subsequent treatment must be acceptable to patients
5) Early treatment must reduce death or disability
6) If it is to be widely used the screening test must be economic

discussed in detail by Parsonnet and Axon (1996), Smith (1999) and Grimes and Schulz (2002), and as applied to gastric premalignancy in Japan by Yoshida and Saito (1996). The basic essentials for efficacy are listed in Table 1. Giving advice on screening presents a dilemma to consulting physicians in themselves weighing up relative benefit and risk. The patient is usually not demanding to be screened, although this depends on the general level of cancer education in the community. He or she is by definition asymptomatic for cancer in the normally accepted sense. However, it could be argued that any individual presenting with a condition predisposing to cancer, whether it be obesity, chronic inflammatory change or a smoking habit, is indeed showing signs of increased risk. Viewed in this light the doctor might be considered to have a responsibility to recommend screening. This will of course depend on many factors like the relative levels of cost and inconvenience associated with the screening measures and the likelihood of a beneficial outcome. Whereas a negative screening test can be reassuring, a positive result is usually very traumatic and even the fact of introduction of screening protocols into a community may generate concern. This underlines the necessity for a knowledge-based approach accommodating all of the relevant factors. However, even the so-called experts may differ in conclusions drawn from the same data base and thus Sackett (6) has pleaded for a concensus with appropriate emphasis on education, whereby each individual should be in a position to take on a certain amount of responsibility for his or her own decision-making. Naturally, the efficiency of specific tests must be maximized and the adverse effects,whether psychological or physical, reduced to a minimum.

Medical, social and financial aspects of importance include disease prevalence and the achievable reduction in suffering or death, attitudes to cancer in the general society and overall level of economic development. In assessing the results of a screening program, it must be borne in mind that selection bias plays a role, those individuals accepting the proffered advice for screening perhaps belonging to social categories having a different risk of cancer because of a particular lifestyle. Furthermore, there is a lead time bias. If the extension fo the life-span due to screening is only of the order of the time before clinical symptoms would have arisen in the first place, then there is no benefit since the patients simply live longer with the presence of the lesion.

In addition, the existence of lesions which only have a low likelihood of progression to malignancy means that a pseudo-disease bias must be expected (Parsonnet and Axon, 1996). Slow growing lesions, because they are around for a long time, are more likely to be detected and this introduces another complicating factor in consideration of survival, leading to possible overestimation of the validity of a particular screening measure.

It is clearly essential that the early treatment allowed by successful screening is freely available and acceptable to patients.The sensitivity and specificity, respectively the probabilities that a diseased person will be detected and that a non-diseased individual will give a negative result are very important and a high sensitivity is obviously necessary to reduce false negatives and increase the reassurance factor.

Table 2. Relative Importance of Sensitivity and Specificity in Determining the Predictive Value

Prevalence (/100.000)	--- Sensitivity --- Value	True Positive	False Negative	Total	-------- Specificity ------- Value	True Negative	False Positive	Positive Predictive Value
100	80%	80	20	99,900	80%	79,920	19,980	0.4%
1000	80%	800	200	99,000	80%	79,200	19,800	4.0%
100	80%	80	20	99,900	98%	97,902	1,198	6.7%
1000	80%	800	200	99,000	98%	97,020	1,980	40.4%
100	98%	98	2	99,900	80%	79,920	19,980	0.5%
1000	98%	980	20	99,000	80%	79,200	19,800	4.9%
100	98%	98	2	99,900	98%	97,902	1,198	8.2%
1000	98%	980	20	99,000	98%	97,020	1,980	49.5%

Comparison of results with two levels of both sensitivity and specificity, 80% and 98%.

Specificity may, however, have very much more impact. Even with a small percentage of false positives, each of the affected individuals undergoes stress and the need for further testing, often at great expense. The costs of time and transportation to the screening venue can be considerable and medical risks of intervention also need to be taken into account. These points underline the importance of identification of high risk groups (see Table 2).With tests using cut-off points, like the PSA serum value, the sensitivity and specificity are inversely related so that setting the value is of overriding significance.

The existence of restrictions on the finances available for health care within societies is a fact of life. There is theoretically no limit on what could be undertaken to improve the lifespan and therefore decisions must be made as to which areas should receive what priority in division of finite resources. Attention spent on prevention and screening means that there is less for therapy of established disease, but the aim is naturally that a reduced necessity for therapeutic health care will ensue. It is therefore imperative that the cost-effectiveness of different programs be compared in terms of their requirement for finance and human resources as well as outcome (Wagner, 1997). The fact that some screening techniques can be readily performed by paramedical staff while others are dependent on relatively sophisticated facilities and practising physicians deserves stress, particularly in the context of Asian countries. Whatever the status of the screening staff, the importance of training and professional experience is paramount, as exemplified by a comparison of consultants, junior hospital dentists and auxiliaries screening for oral cancer and other lesions, the former demonstrating 5.5 and 2.7 times more correct decisions than the last of these (Jullien et al., 1996). Costs are naturally dependent to a large extent on the number of people taking part, the larger the population the lower the single charge (Hristova and Hakama, 1997). Furthermore, the expense can be considerably reduced if a number of tests are conducted simultaneously (Mandelblatt et al., 1997), this perhaps allowing the best results to be obtained (Sasamori et al., 1999). In considering costs it is also important to be aware of the considerable temporal discounting which must be overcome to implement preventive health measures (Chapman and Elstein, 1995). Another facet of affordability concerns the possibility that introduction of a superior but more expensive test might have the paradoxic effect of making screening unattainable for those at greatest risk (Myers et al., 2000).

With regard to individual cancer sites, the level of information available and research output varies greatly (Tsuda and Moore, 2002). Partly this reflects geographical variation but there is also a socioeconomic aspect, those cancers most prevalent in the western world in some senses continuing to receive the most attention, as well as a technical dimension in terms of the necessary equipment and facilities. Here we have concentrated on giving a brief coverage of individual organs or tissues with the emphasis on future research directions.

Screening: Organ-Based Approaches

Skin

The incidence of skin cancers is increasing at an alarming rate in many countries and there is currently no consensus by major health policy organizations regarding skin cancer screening. Since the skin is so accessible to view it is a natural candidate for self-screening, with early lesions being simply removed by surgery. In Australia, with its sun and a Caucasian population, the developed country with the highest incidence, one study of clinical melanoma screening revealed a cost effectiveness of $6,853 per life year in men over 50 examined for a 5 year period (Girgis et al., 1996a). A cost-effectiveness analysis in the US (Freedberg et al., 1999) demonstrated results similar to those with other cancer screening strategies, with increase in discounted life expectancy for high-risk cases. In Canada, Engelberg and colleagues (1999) found yield and predictive values to be virtually identical to those previously reported in larger US studies, stressing the need for good communication between screening physicians and screening participants for effective follow-up. A randomised trial for population screening has been established in Queensland and a 2.5-fold increase in participation in screening in the intervention communities was noted in the first phase after 12 months (Aitken et al., 2002). Subsequent results should provide the evidence required for public health recommendations for population screening for melanoma. In a review of full-text published studies of skin screening, Helfand et al (2001) concluded that whereas basal cell carcinoma and squamous cell carcinoma are very common,detection and treatment in the absence of formal screening are almost always curative.The same is clearly not true for melanomas, for which they commented on the lack of randomized or case-control studies that had successfully demonstrated that routine screening had reduced morbidity or mortality. However, a media campaign conducted in Belgium with relevant information combined with screening opportunities lead to early detection of melanomas in a considerable number of patients, continuing to alert people at risk for an extended period of time (Vandaele et al., 2000). The 166 melanomas found in one month represented 15-20% of the total number of this cancer per year in the country. In Sweden, it was found that participants in a screening program were more often in action/maintenance stages of change to sun-protective behaviour than a control beach interviewed group (Krisjansson et al., 2001). Screening itself apparently leads to an increase in self-screening (Geller et al., 1999). An integrated intervention programtargeting outdoor workers in Israel led to significantly improved sun protection and skin cancer awareness (Azizi et al., 2000). Repeated intervention, combined with the supply of sun-protective gear, contributed to the impact. In Britain the professional social class appear to require particular attention in terms of comliance with recommendations (Jackson et al., 1999).

A survey of beliefs and practices pointed to the need for formal training for family physicians in skin cancer prevention (Girgis et al. 1996b). The proportion of primary

care visits in which skin cancer screening and prevention occurs may be generally low (Oliveria et al., 2001a), although those in practice for more than 30 years ranked skin cancer screening as extremely important. (Altman et al., 2000). Clearly this depends on the prevalence of the disease, Australian family physicians in the north of the country being much more likely to advocate screening (Sladden et al, 1999). Particularly significant is the role that dermatologists might play. In the US a recent study revealed that whereas they report a high rate of screening for skin cancer, their knowledge of screening recommendations is limited (Federman et al., 2002). Inadequate time to perform full-body skin examinations and lack of emphasis during training were identified as possible

Table 3. Summary of Details for Skin Cancer Screening

Target Lesions: Early Melanomas, Basal Cell Carcinomas, SCCs
Modality: Naked Eye, Brush Biopsy
High Risk Population: Caucasian Sunbathers, Outdoor workers
Utility: General populace in high risk countries
Research Areas: Effective awareness education

barriers to effective practice. Oliveria et al (2002) have shown that primary care physicians are currently utilizing nonphysician health care providers to perform cancer screening examinations, the majority of those surveyed being amenable to this approach to skin cancer screening. The results were in line with an earlier study of trained nurse practitioners (Oliveria et al., 2001b), showing that they are capable of accurately identifying and triaging suspicious lesions. McCormick and co-workers (1999) positively evaluated a skin cancer prevention module for nurses but stressed the necessity for those who were knowledgeable to educate their colleagues, their supervisors, and the public about the priority of skin cancer screening and develop strategies for creating organizational change.

Thyroid

High risk groups for thyroid cancer include individuals suffering from congenital goiter (Cooper et al., 1981) and those receiving head and neck radiation therapy as children (Crom et al., 1997), although doubt has been cast on whether they warrant introduction of regular screening programs (From et al., 2000). A special case is the very high incidences seen after the Chernobyl disaster (Pacini et al., 1999). Ultrasonography has been found to be a sensitive non-invasive means for detection of subtle parenchymal abnormalities in the latter but comprehensive data on cost effectiveness have yet to be published.No improvement in prognosis from enforced mass screening for thyroid cancer was detected in a study conducted in Japan (Miki et al., 1998), although it was economic in this instance because it was performed together with screening for other cancers, such as breast cancer, and the intervention seemed to find thyroid cancers in a relatively early stage.

Table 4. Summary for Thyroid Cancer Screening

Target Lesions: Early follicular/papillary/medullary lesions
Modality: Ultrasound
High Risk Factors: Goiter, radiation exposure
Utility: High risk groups, Surgery necessary
Research Areas: Likelihood of progression

Ultrasonographic mass screening for thyroid carcinoma was also found to be effective for the detection of subclinical thyroid carcinomas in women requiring breast examinations (Chung et al., 2001). Bucci et al (2001), however, again stressed the necessity for a sufficiently high prevalence of thyroid cancer to offset the adverse effects of unnecessary treatment due to false positive results. While testing initially with ultrasound detects several times more cases of thyroid cancer than palpation, many more patients also have surgery for nonmalignant nodules (Eden et al., 2001). For patients with nodular goiter, routine basal serum calcitonin measurement may be recommended for early diagnosis of medullary thyroid carcinoma (Ozgen et al., 1999).

Oral Cavity

In some regions of the world, oral cancers are particularly prevalent due to their link with betel chewing and tobacco (Hashibe et al., 2002). As stated in the review by Warnakulasuriya and Johnson (1996), the lack of randomized controlled trials performed to assess the impact of screening on morbidity and mortality means that recommendations for mass screening are premature. However, in a community-based, cluster-randomized, controlled oral cancer screening trial in India, the sensitivity for detection was 76.6% and the specificity 76.2%, with a positive predictive value of 1.0% (Sankaranarayanan et al., 2000). How beneficial screening can be is evidenced by results with 60 year old residents in a city in Japan, with very good predictive values reported (Ikeda et al., 1995).Reasonable results have also been described elsewhere (Burzynski et al., 1997) and since preneoplastic lesions are accessible to visual detection and palpation, dentists can play a major role (Lodi et al., 1997). Many demonstrate a positive attitude (Warnakulasuriya and Johnson, 1999), although it has been emphasized that effective training is a basic requirement (Smith et al., 1995). One aid which appears to be acceptable is toluidine blue staining for identification of oral cancerous and precancerous lesions (Feaver et al., 1999). Regarding treatment, cold knife surgical excision gives good results (Pandey et al., 2001). Only from 10 to 20% of gross mucosal lesions have a risk of progressing to malignancy so that more definitive diagnostic tests are clearly required (Calabrese et al., 1998). The minimally invasive brush biopsy lets general dentists evaluate macroscopic lesions (Christian 2002). The potential role of oral exfoliative cytology clearly warrants further attention (McClusky and Ogden, 2000), especially in conjunction with molecular genetic analysis (Suhr et al., 2000). For the hypopharynx and larynx, endoscopy has been

recommended for detection of subclinical disorders (Watanabe et al., 1996).

In one study, routine examination of the general population revealed only just over 1 cancer per 1000 individuals, but this was found to increase to 5 in a population of smokers and heavy drinkers aged more than 40 (Mashberg and Borsa, 1984). A major problem, however, is non-participation of at-risk subjects (Warnakulasuriya and Johnson, 1996) and there is clearly a need for health education materials that incorporate the oral cancer risk perception of high-risk individuals (Hay et al., 2002). The lack of awareness of the disease burden and risk factors, as well as the tendency for occurrence in lower socioeconomic and poorly compliant populations can be cited in this context (Freije and Kumar, 2001). In Indian workers on plantations in Malaysia, more than half did not consider oral cancer as a preventable disease (Tan et al., 2001). In the US, an educational program to promote screening through primary health care for the squamous cell cancers of the buccal cavity, pharynx, and larynx developed by Prout et al. (1992), greatly increased the documented screening for these cancers.

Table 5. Summary for Oral Cancer Screening

Target Lesion: Leukoplakia, eryhroplakia
Modality: Naked eye, Brush biopsy
High Risk Factors: Betel chewing, tobacco
Utility: General populace with dentists, excision possible
Research Areas: Effective awareness education Likelihood of progression

A case-control study conducted to evaluate the efficacy of an on-going oral cancer screening programme using visual inspection in Cuba also provided evidence of prevention of advanced lesions (Sankaranarayanan et al., 2002). Attendance may be best if offered as part of a general health screen (Nagao et al., 2000) and Dombi and co-workers (2001) in Hungary also considered a so-called multiphasic screening system, in conjunction with other examinations, to be the optimal approach.

Esophageal

Early detection of both squamous cell and adenomatous lesions of the esophagus is possible using assays for occult blood in the stomach (Qin et al., 1993) and cytology with an abrasive balloon (Liu et al., 1994), as well as endoscopy (Lambert, 2002; el Khoury and Sahai, 2002). Endoscopic iodine or lugol dyestaining in high risk patients may be useful in screening for very early stage esophageal carcinomas (Shimizu et al., 2001; Tincani et al., 2000).Unfortunately, it is necessary to take multiple biopsy samples given the frequently multifocal nature of underlying disease states. With regard to the benefits, it has been shown that clinically presenting squamous cell carcinomas and adenocarcinomas have a poor prognosis, with a 5-year survival between 5-25%, whereas removal of early lesions limited to the mucosa or submucosas is associated with a figure of 90% or more (Riddle, 1996).

For adenocarcinomas, individuals with Barrett's esophagus because of gastroesophageal reflux disease are at high risk, with a 30- to 125-fold excess (McArdle et al., 1992; Haggitt, 1994). endoscopic biopsy will remain the cornerstone of Barrett's esophagus surveillance strategies unless newer alternatives are clearly advantageous in terms of accuracy, cost, availability,and ease of application. In the future, however, advances in techniques for minimally invasive ablation of Barrett's epithelium may make endoscopic surveillance obsolete (el Khoury and Sahai, 2002).

For squamous cell carcinomas, esophagitis is the most common risk factor, along with high alcohol consumption and smoking, and virus infection (Riddle, 1996). In one high risk alcoholic population 25% of patients demonstrated iodine unstained lesions, 3% being SCCs (Yokoyama et al., 1995). As far as treatment is concerned, surgery results depend on the morphological findings (Lerut et al., 1994). Endoscopic removal may be possible, especially for those lesions found to be without invasion by ultrasonography (Toh et al., 1993). Mortality associated with major esophageal surgery can be in the order of 5% but approaches zero in clinics with much experience. With regard to the efficacy of screening, an increase in life expectancy has been reported with endoscopy performed every 2-3 years after detection of Barrett's esophagus develops (Provenzale et al., 1994). With affected children this may be very early and it has been proposed that screening should start at the end of the first decade in this population (Hassall et al., 1993). Some time ago the cost was estimated at US$60,000 per carcinoma detected (Achkar and Carey, 1989).

Table 6. Summary for Oesophageal Cancer Screening

Target Lesion: Dysplasia
Modality: Balloon cytology, Endoscopy
High Risk Factors: , Tobacco+Alcohol, Hot foods, Barretts metaplasia
Utility: High risk groups
Research Areas: Effective awareness education Treatment modalities

Gastric

The efficacy of gastric cancer screening has been reviewed by Yoshida and Saito (1996). Doubts has been expressed, however, as to its application for individuals under 50 (Babazono et al., 1995) and the cost-benefit ratio in a study in Venezuela proved disappointing (Miller, 1995). However, clear benefit was more recently found in Korea (Kim et al., 2000). In Japan, serum persinogen levels have been shown to be as useful as fluorography (Yoshihara et al., 1997; Kitahara et al., 2001), best results being obtained when the two approaches to detection were combined. This is very encouraging since while mass screening in Japan has been

Table 7. Summary for Gastric Cancer Screening

Target Lesion: Adenoma
Modality: Serum pepsinogen, fluorography, endoscopy
High Risk Factors: High salt diet, H pylori, Atrophic gastritis
Utility: General populace in high risk countries
Research Areas: Association with H pylori- determination of high risk individuals

shown to reduce mortality, a simpler and less expensive test is urgently required (Yoshida and Saito, 1996). The Helsinki Gastritis Study Group also concluded that serum pepsinogen I followed by endoscopic diagnosis is the best approach (Varis et al., 2000).While endoscopy remains the gold standard (Kubota et al., 2000) it is itself not suitable for general application. For example, there was no impact of repeated endoscopic screens on gastric cancer mortality in a prospectively followed Chinese population at high risk (Riecken et al., 2002).With regard to risk mention should perhaps be made of individuals with atrophic gastritis, usually due toheavy Helicobacter pylori infections and those living in areas of high salt consumption (Tsugane et al., 1993; Tsubono et al., 1997). Risk of gastric cancer has also found to be elevated in hereditary nonpolyposis colorectal cancer cases in Korea (Park et al., 2000).

Colorectal

Colorectal screening has been reviewed by Vernon (1997) and more recently in the Asian asetting by Saito (2000). High risk groups do exist, like those with a family history (Thrasher et al., 2001; Turkiewicz et al., 2001) including patients with primary sclerosing cholangitis and ulcerative colitis (Brentnall et al., 1996) and prevention of 18 % of colorectal cancers was described with early detection in one large series (Hristova and Hakama, 1997). Another revealed a 15% reduction in cumulative mortality (Hardcastle et al., 1996), and risk of tumor induction within three years may be halved (Saito et al., 1995). A survival rate for five years of 87% as opposed to 57% for symptomatic cases has been reported (Shida et al., 1996) (see Table 6).Long-lasting reduction of risk of colorectal cancer has been described following screening endoscopy (Brenner et al., 2001).

Regarding target population use of testing, significantly increased compliance may be achieved by provision of leaflets explaining the incidence of cancer and the rationale for screening (Hart et al., 1997). Compliance is significantly greater among subjects with family histories of colorectal cancer (Schoenet al 2002) and it has been suggested that physicians should incorporate patient values in regard to certain test features when discussing colorectal cancer screening (Ling et al., 2001). It has been found that geographic location is less important than knowledge and attitudes in predicting practitioners screening practices, so that more specific education is required (Hawley et al., 2001). Regarding compliance, the existence of psychiatric morbidity appears not to be a factor affecting a person's decision to accept or refuse a screening test for colorectal cancer (Parker et al., 2002). In a study in Israel, refusers were more likely to be male, of Asian-African descent, and more likely to smoke, consume more coffee, and less tea or dairy foods (Niv et al., 2002). Individuals who refuse FOBT have a significantly higher colon cancer incidence and mortality rates than those who accept testing (Niv et al., 2002).

Table 9. Summary for Colorectal Cancer Screening

Target Lesion: Adenoma
Modality: IFOBT, FOBT, sigmoidoscopy, endoscopy
High Risk Factors: Cholitis
Utility: General populace in high risk countries
Research Areas: Awareness

The faecal occult blood test (FOBT), while itself leading to mortality reduction of 33% when conducted annually (Mandel, 1997), gives best results when followed by sigmoidoscopy (Manus et al., 1996), a comparison revealing costs of $1,436 for each polyp in the combined case, as opposed to $271 with endoscopy alone, but the number of

Table 8. Reports on Evaluation of Colorectal Screening in Terms of Mortality Reduction (after Saito, 2000)

Country	Methods	Mortality Reduction	Study Design	Reference
USA	Sigmoidoscopy	70%	Case-control	Selby et al., 1992
USA	FOBT	31	Case-control	Selby et al., 1993
USA	FOBT	33	RCT	Mandel et al., 1993/1996
Japan	FOBT+IFOBT	76	Case-control	Hiwatashi et al., 1993
Japan	IFOBT	60	Case-control	Saito et al., 1995
Great Britain	FOBT	15	RCT	Hardcastle et al., 1996
Denmark	FOBT	18	RCT	Kronborg et al., 1996
Italy	FOBT+IFOBT	40	Case-control	Zappa et al., 1997
Finland	FOBT	18	Time trend	Hristova and Hakama, 1997
	Sigmoidoscopy	~50		Geul et al., 1997

FOBT, guaiac-based fecal occult blood test; IFOBT, immunochemical FOBT; RCT, randomized controlled trial.

cancers found was much greater. With FOBT alone, sensitivities of 90% for 1 year, 83% for 2 and 71% for 3, have been reported, with a specificity of 95.6% (Nakama et al., 1996). Findings indicate that the stool obtained by routine screening has a better positive predictive value than stool collected during the digital rectal examination (Nakama et al., 2001).The assumption that FOBT screening has to be based on a guaiac test should be reconsidered, and reversed passive hemagglutination should be recommended as the standard FOBT for screening purposes (Zappa et al., 2001). In Japan, the immune FOBT is generally applied (Saito, 2000).

Care must be taken with recommendations of sigmoidoscopy for mass-screening of average-risk asymptomatic populations (Mandel, 1997; Verne et al., 1998) but it may prevent 50% of cancers occurring after the age of 60 (Geul et al., 1997) with costs per year of life saved calculated as between $12,000 and $67,000 (Salkeld et al., 1996). Colorectal cancer screening using annual FOBT, flexible sigmoidoscopy at 3 or 5 years, the combination of FOBT and flexible sigmoidoscopy, barium enema, colonoscopy, and even virtual colonoscopy had incremental cost-effectiveness ratios ranging from $6300 to $92,900 per LY saved with most of the cost-effectiveness ratio ranging from $10,000 to $40,000 per LY saved (Provenzale, 2002). Compared with no screening, the incremental cost-effectiveness ratio of a single or repeated colonoscopy amounts to $2981 or to $10 983 per life year saved, respectively. A single colonoscopy saves most life years if conducted at the age of 60, but becomes most cost-effective after the age of 70 (Sonnenberg and Delco, 2002).The frequency of right-sided colon cancer increases with patient age. Hence, colonoscopy may be especially indicated in the elderly for colorectal cancer screening. Over half of colon carcinomas may be missed if sigmoidoscopy alone is used for screening (Okamoto et al., 2002).. Flexible sigmoidoscopy detects a higher proportion of colorectal cancers in Asians and Latinos than in whites or blacks, because of variation in location (Theur et al., 2001).One-time screening with both a fecal occult-blood test with rehydration and sigmoidoscopy failed to detect advanced colonic neoplasia in 24 percent of subjects in the US (Lieberman et al., 2001).

Which test should be employed? Screening recommendations should be tailored to the compliance levels achievable in different practice settings (Vijan et al., 2001). Dietary restrictions create a barrier to FOBT-based screening for colorectal cancer. The use of immunochemical rather than guaiac FOBT removes this barrier (Cole and Young, 2001).

Recently an alternative has been proposed, using the marker galactose-N acetylgalactosamine, purported to have greater accuracy than FOBT, which may also find application for other cancers, like those arising in the breast, lungs, prostate and pancreas (Shamsuddin, 1996).The ICG-sulfo-OSu-labeled anti-MUC1 antibody has possible usefulness for the screening of colon cancer via infrared fluorescence endoscopy (Bando et al., 2002) Faecal calprotectin is a simple and sensitive non-invasive marker of colorectal cancer and adenomatous polyps. It is more sensitive than faecal occult blood tests for detection of colorectal neoplasia at the cost of a somewhat lower specificity (Tibble et al., 2001).PCR/RFLP analysis could also be employed in mass screening for colorectal cancer, since K-ras pont mutations are highly specific, with a low detection limit, and it is simpler than conventional methods for detecting genetic abnormalities (Nishikawa et al., 2002). The K-ras biochip is well suited for fast mutation detection in stool samples for colorectal cancer screening (Prix et al., 2002).Interest has also grown in CT colonography as a developing technique to challenge existing methods such as the barium enema and conventional colonoscopy (Bruzzi et al., 2001). Magnetic resonance colonography may also be applied for colorectal cancer screening (Lauenstein and Debatin, 2001).

Liver

With regard to liver cancer it is well established that serum evidence of HBV or HCV-related hepatitis or alcoholic cirrhosis points to an increased risk (Colombo, 2001) and this has lead to suggestions that screening should be performed every 3 months for the affected individuals (Curley et al., 1995). It has been stressed that HBsAg carriers older than 35 years or with family histories of HCC should be screened for HCC by determinations of serum AFP levels and aminotransferase levels once a year (Colombo, 2001).In U.S. patients with established cirrhosis, CT scans exhibited higher sensitivity for detecting HCC than ultrasound or AFP (Chalasani et al., 1999).Zhang and yang (1999), in China, found that combined alpha fetoprotein testing and ultrasonography increased detection but not in proportion with costs so tha US alone is more appropriate where cost is the most important factor.

Using ultrasound, liver cancers were detected in 1.1% of high risk individuals tested in one study conducted in Hokkaido, in conjunction with serum a-fetoprotein to minimize false negatives (Mima et al., 1994). The costs were approximately $25,000 for each cancer identified but this was superior to figures of up to $55,000 per year of life gained in a Swiss study (Sarasin et al., 1996). In the latter case, benefits in life expectancy were negligible other than in individuals with a good prognosis for cirrhosis. However, in another study recently reported in China, with subclinical stage lesions detected by ultrasound and a-fetoprotein, resection was possible in 70% of cases, and 2 year survival

Table 10. Summary for Liver Cancer Screening

Target Lesion: Adenoma, HCC
Modality: Ultrasound, a-fetoprotein, CT
High Risk Factors: Hepatitis, cirrhosis
Utility: High risk individuals
Research Areas: Timing of screening

was 77%, as compared to all patients dying within 1 year in the clinical symptom group, with an estimated cost per cancer of US$1,500 (Yang et al., 1997). In the United States one study estimated charges at approximately $35,000 to $40,000/quality-adjusted life-year (Everson,m 2000).With multinodular hepatocellular carcinomas intrervals between screening may have to be shortended, however, increasing costs (Fasani et al., 1999).

Gallbladder

Gallstones and a history of gallbladder disease, along with anomalous junctions of the pancreaticobiliary duct are major risk factors for cancer development so that an appropriate target population is available (Yamauchi et al., 1987; Zatonski et al., 1997). Preliminary screening data have been published for CEA and CA 19-9 as serum markers (Strom et al., 1990) but this area basically remains to be explored. Cotton swab anal smears instead of stool occult blood test scan not only be used as a mass screening method for colorectal cancer, but may be an auxiliary way to screen for hepatobiliary or pancreatic carcinomas (Qin et al., 2000). Ultrasound may provide an additional tool (Bartlett, 2000)

Pancreas

High sensitivity and specificity values for pancreatic cancer may be achievable with sonographic screening for upper abdominal disorders (Tanaka et al., 1996). Intraductal ultrasound probes are capable of image cystic lesions of less than 30 mm in diameter and solid lesions of less than 20 mm in diameter.(Furukawa et al., 1997). The relatively low

Table 11. Summary for Pancreas Cancer Screening

Target Lesion: Adenoma, Adenocarcinoma
Modality: US, CA 19-9
High Risk Factors: Pancreatitis
Utility: High risk individuals
Research Areas: Progression of lesions

incidence means that predictive values, however, are very poor and therefore there is a need to determine high risk groups, for example individuals with a familial link (Lynch et al., 1995; Tersmette et al., 2001), or those suffering from chronic pancreatitis (Lowenfels et al., 1997). Recent advances in understanding of molecular alterations raise the possibility that within well defined risk groups it will be possible to use a combined set of molecular markers to screen clinical samples and detect early pancreatic cancer or even pre-malignant lesions (Caldas, 1999). One of the biggest problems at the present is determining whether any one particular lesion warrants potentially dangerous surgery or presents little risk of progression (Yamao et al., 1999; 2001). Whether molecular markers can be applied for distinction purposes is another area requiring clarification (Caldas, 1999).

Kidney

Risk groups are those with analgesic nephropathy (Thon et al., 1995) and acquired cystic kidney disease (Marple et al., 1994) and ultrasound has been recommended for screening on the basis of the finding that detected carcinomas are smaller, have a lower T-stage and grading, and average 5 year survival rates of up to 90% can be achieved (Reuss, 1994). A large series of abdominal ultrasonographic (US) screens of 219,640 persons performed in Japan over 13 y, detected 723 (0.33%) cases of malignant neoplasms (Mihara et al., 1999). Van Poppel et al (2000), however, concluded from their review of the literature that mass screening with the purpose of detecting renal cell carcinmoma (RCC) at its earliest stages is not recommended at the present time,but screening focused on certain risk groups can be advocated.

Table 12. Summary for Kidney Cancer Screening

Target Lesion: Adenoma, RCC
Modality: Ultrasound
High Risk Factors: Nephropathy, acquired cystic kidney disease
Utility: High risk individuals
Research Areas: Progression of lesions

Urinary Bladder

Although major risk factors other than parasites in some parts of the world have not been described, even for the general population over 50, regular hematuria testing appears to significantly decrease cancer morbidity and mortality in a cost-effective fashion (Kryger and Messing, 1996). Occult blood approaches for urological cancers, mostly in the bladder, have been found to have a positive predictive value of 0.41 in those aged over 40 (Bintinx and Wauters, 1997), although single dipstick urinalysis for microhematuria, was found in one study to demonstrate a sensitivity within 3 years of only 3%, a specificity of 96.7% and a positive predictive value as low as 0.5% (Hiatt and Ordonnez, 1994). Reliability is supported by the finding of a better predictive power than cystoscopy (Friedman et al., 1996), the latter not being recommended for patients with only a single microscopic haematuria and those younger than 40 years (Suzuki et al., 2000).Virtual cystoscopy with color mapping of bladder wall thickness was also recently found to be inappropriate for screening (Fielding et al , 2002).

Regarding other methods, analysis of urinary red blood cell volume distribution may be helpful (Wakui andShiigai, 2000) and microsatellite analysis of free tumor DNA in urine is a minimally invasive method for the detection of bladder cancer (Utting et al., 2002). Planz and co-workers (2001) consider that DNA image cytometry is superior to standard cytology as a primary method. In addition, fetal fibronectin (Wunderlich et al., 2001), nuclear matrix protein-22 (Fukui et al., 2001), NMP22 (Ponsky et al., 2001) and BLCA-4 (Konety et al., 2000) have all been proposed as markers and occupationally exposed workers at risk for bladder cancer could be individually stratified, screened, monitored, and

Table 13. Summary for U.Bladder Cancer Screening

Target Lesion: Transitional cell papilloma, TCC
Modality: Occult blood, DNA markers
High Risk Factors: Cystitis, Schistosomiasis
Utility: High risk individuals
Research Areas: Molecular markers

diagnosed based on predefined molecular biomarker profiles in one study (Hemstreet et al., 2001).

Prostate

It is estimated that the lifetime risk of being diagnosed with prostate cancer is 1 in 5 in the US. Age, African-American ancestry, family history, and possibly diet are risk factors (Greumet and Bruner, 2000). While prostate cancer is a major cause of death, the presently available screening practice is controversial and for a number of reasons many consider that it is without advantage (Albertsen, 1996). Firstly, the existing tests, especially those focusing on prostate-specific antigen (PSA), suffer from high false positive rates (Gann et al., 1995). Digital rectal examinations have only limited effectiveness (Friedman et al., 1991) and indeed, in a series of blood donors, serum PSA proved the better option (Reissigl et al., 1997). Secondly there is doubt about whether early detection and treatment changes the natural history of the disease. Allied to this is the difficulty in distinguishing between lesions that will progress to malignancy and those that will lie dormant. However, in a prospective setting with long-term followup free PSA strategies can be identified that decrease unnecessary biopsies, while preserving or even improving cancer detection. Thus, total and free PSA can be combined without the need to weigh subjectively the trade-offs and relative costs of false-negative and false-positive results (Gann et al., 2002).

PSA screening was found not to be associated with, and therefore cannot explain, the decline in prostate cancer mortality in Canada (Perron et al., 2002). In Japan, early detection and longer survival of patients with prostate cancer detected by mass screening suggested efficicy, however (Kubota et al., 2002). In this context, the results of the European Randomised Screening for Prostate Cancer (ERSPC) trial (de Koning et al., 2002) are being awaited with interest. The results indicate a significant positive correlation between total PSA levels and macrophages and a significant negative correlation between percent free PSA levels and T and B lymphocytes. Additional studies are needed to compare the amount and types of inflammatory cells with the stage and grade of prostate cancer in positive biopsies and radical prostatectomy specimens (Moser et al., 2002). Assessment of PSA-value change after antibacterial treatment can improve prostate screening accuracy in cases of PSA 4-10 ng/ml, nonsuspicious DRE and inflammation (Karazanashvili and Managadze, 2001).

Table 14. Summary for Prostate Cancer Screening

Target Lesion: Prostate Intraepithelial Neoplasia
Modality: PSA, Digital Rectal Examination
High Risk Factors: Nephropathy, acquired cystic kidney disease
Utility: General populace in high risk countries
Research Areas: Progression of lesions, molecular markers

Routine prostate biopsy should not be undertaken except for highly suspicious DRE findings in subjects with PSA levels less than 2.0 ng/mL. The additional use of TRUS in subjects with PSA levels of 2.0 to 4.0 ng/mL would improve the sensitivity of prostate cancer detection (Yamamoto et al., 2001). Depending on the threshold value applied as an indication for biopsy, when using the total PSA alone or combined with the free/total PSA, care is needed in interpreting patient groups because of the discordance among PSA assays (Blijenberg et al., 2001). Contrast enhanced color Doppler targeted biopsy has been shown to detect as many cancers as systematic biopsy with fewer than half the number of biopsy cores (Frauscher et al 2002).

The findings of Bartsch et al (2001) are consistent with the hypothesis that the policy of making PSA testing freely available, and wide acceptance by men in the population, is associated with a reduction in prostate cancer mortality in an area in which urology services and radiotherapy are available freely to all patients. Early detection using both PSA and DRE-based screening may benefit men who present with biopsy Gleason scores of 5 or 6 prostate cancer and a PSA level greater than 4 to 7 ng/mL compared with greater than 8 up to 10 ng/mL (D'Amico et al., 2001). In Finland use of percentage free PSA increased the detection rate of aggressive disease compared with digital rectal examination and provided higher specificity than PSA alone (Makinen et al., 2001).

Regarding new methodology, ttelomerase activity and GSTP1 promoter methylation in ejaculate have been suggested as potential screening markers for prostate cancer (Suh et al., 2000). Human glandular kallikrein 2 may also have clinical value (Becker et al., 2000). While Wolk et al (2000) argued in favour of IGF-1 as a useful aid, this has been contested by Finne et al (2000a), who proposed use of the complex between prostate specific antigen and alpha 1-protease inhibitor in its place (Finne et al., 2000b).

Finally there is the problem of subjecting asymptomatic individuals to potential psychological stress, discomfort from the biopsy procedure and incontinence and impotence associated with agressive treatment. The report from a conference held on this theme was thus less than optimistic (McNaughton-Collins and Fletcher, 1997). However, it is perhaps illuminating to mention that the majority of general practitioners are positive about screening, especially for those older than 50 (Morris and McNoe, 1997).

Breast

The advantageous effect of breast screening on mammary

cancer mortality persists after long-term follow-up (Nystrom et al., 2002), although early detection outside organized screening was only partially efficient in reducing advanced breast cancer incidence in one study in Italy (Buiatti et al., 2002). Family history is a very important factor in dertermining behaviour (Isaacs et al., 2002) and family physicians can increase the utilization of mammography among women under their care (Eilat-Tsanani et al., 2001). Race/ethnicity appear to interact with age, education, health insurance, and family history of breast cancer to influence the probability of adherence to screening guidelines (Strzelczyk and Dignan, 2002). Furthermore, a church-based breast cancer screening education program demonstrated a pronounced effect on mammography rates among African-American women (Husaini et al., 2002). Inviting women with lower educational levels to participate in a breast cancer screening program through direct contact by trained personnel may also increase participation rates compared with mailed-letter methods (Segura et al., 2001).

Both self-examination and mammography can be recommended for early detection, depending on the population (Ng et al., 2000). Demonstrating that population-based screening mammography reduces breast cancer mortality requires collection of high-quality data on key aspects of the multi-step screening process. Thus, assuring the quality of data collection systems for screening mammography programs is an important and evolving area for International Breast Cancer Screening Network countries (Klabunde et al., 2001). The specificity of mammography has been reported to be very high at over 99%, but attendance rates tend to drop in those over 70 (Otten et al., 1996). Predictive values of 39%, 59% and 68% for those aged under 50, 50-69 and over 70, respectively, have been obtained, so that it is very important that older individuals continue to participate. Most debate regarding breast screening measures has hinged on whether the 40-49 age group should be included (Baines, 1995). A special concensus meeting, however, decided that it is in fact worthwhile, so that medical costs are reimbursed for those that wish the test (National Institutes of Health Concensus Development Panel, 1997). In fact, sensitivities of 72-83% and predictive values of 39-89% have been reported for this age group (Duffy et al., 1996). Furthermore, one study provided evidence that African-American women in the 30-39 age category represent a high-risk group that may benefit from efforts at earlier detection (Johnson, 2002). Certainly, mammography appears better than physical examination for those aged 50 and over, especially in the sixth and seventh decades of life (Morimoto et al., 1994; Torgerson and Gosden, 1997). A predictive value of 47% as compared to 28% for the general population, with smaller lesions detected, was obtained for a group of individuals 65-74 years of age (Gabriel et al., 1997).

Recently, ultrasound has been proposed as an effective alternative. As opposed to palpation alone, significantly smaller nodules were found with this approach, half of the non-palpable lesions being observed in individuals younger than 50years old (Okamoto et al., 1996). The quality of mammographic screening in terms of the sensitivity and specificity is clearly very important, as evidenced by the findings of a study conducted in Germany, with a cost per life year gained of 15,000DM for the high quality scenario and 22,000DM for low quality testing (Warmerdam et al., 1997). Although somewhat more expensive costs upward of 21,000$ for each year of life saved have been reported in the USA (Mandelblatt et al., 1997), cost-effectiveness can be maximized by intensive recruitment and follow-up strategies.

Table 15. Summary for Breast Cancer Screening

Target Lesion: Intraductal cancer
Modality: Self-examination, mammography, MR, Ultrasound
High Risk Factors: Family history
Utility: General population, >40
Research Areas: Progression of lesions Awareness and compliance

Mammographic parenchymal patterns are important in terms of breast cancer natural history (Sala et al., 2001) and breadth of experience in interpretation is a major factor in determining success of screening (Esserman et al., 2002). Keith and co-workers (2002) have argued that a third screening modality based on thermal detection monitoring is required. This is a noninvasive and nonradiogenic tool which might enable clinicians to provide patients with a better chance of early diagnosis for high risk cases. With younger groups having a family history of breast cancer it has been stressed that the dose of radiation applied must be restricted, which requires particular expertise for effective screening (Law, 1997). Breast MRI may be superior to mammography and ultrasound for the screening of women with hereditary factors (Boetes and Stoutjesdijk, 2001; Warner et al. 2001). Analysis of proteins in nipple aspirate fluid may also predict the presence of breast cancer (Sauter et al., 2002). Regarding differentiation of lesions, for example CIS from invasive cancer, fine needle aspiration cytologygives accurate results (Sauer et al., 2002).

Ovary

Risk groups for ovarian cancer include those with a family history (Dorum et al., 1996), BRCA1 mutation carriers (van Roosmalen et al., 2002), individuals with low serum gonadotropins and high androgen levels (Helzlsouer et al., 1995) and patients with dermatomyositis (Whitmore et al., 1997). In a series of the latter, sensitivity of CA-125 for detection of cancer 5-19 months prior to clinical symptoms was 50%, with a specificity of 100% (Whitmore et al., 1997). However, prospective studies have so far been lacking and while pelvic examination combined with serum CA-125 has been recommended as having a relatively good predictive value (Adonakis et al., 1996), other authors disagree, suggesting that transvaginal ultrasound is a better diagnostic method (van Nagell et al., 1995). Again however, opinions

Table 16. Summary for Ovarian Cancer Screening

Target Lesion: Serous etc. adenomas
Modality: Transvaginal ultrasound, CA-125, serum proteins
High Risk Factors: Family history
Utility: High risk groups
Research Areas: Methodology Awareness and compliance

vary, one disadvantage being a low sensitivity and specificity (Karlan and Platt, 1995). Laframboise and co-workers (2002) and Menon et al (2000) have argued in favour of use of CA-125 and ultrasound in high-risk women, in contrast to the earlier publication by Grover and co-workers (1995) . Cohen and Fishman (2002), in their review, concluded that transvaginal ultrasound in expert hands is sensitive but not specific for discriminating benign from malignant disease, recommending color Doppler evaluation as an aid for this purpose. Use of proteomic patterns in serum to identify ovarian cancer has recently been recommended (Petricoin et al., 2002) and multiple markers may be applied, although they may vary consideerably even in healthy women (Crump et al., 2000).

Prophylactic oophorectomy in one study was concluded to be superior to screening for BRCA1 mutation carriers (van Roosmalen et al., 2002). However, women who have undergone prophylactic oophorectomy may have more physical and emotional symptoms than their counterparts who remain on an ovarian cancer screening programme, and may report equivalent levels of cancer worry. Awareness is a major problem, with some average-risk women undergoing screening, although it is not recommended outside of randomized trials, and a significant percentage of women at high risk failing to get recommended screening (Andersen et al., 2002; Isaacs et al., 2002).

Endometrium

Abnormal endometrial thickness as assessed by transvaginal ultrasonography has been reported to be a reliable indicator of asymptomatic carcinoma, with a cost per detected cancer similar to those for other major malignancies (Ciatto et al., 1995). However, the question of the potential lethality of lesions, and the doubtful necessity of intervention in some cases, was stressed. A study in Sweden showed prevalence of 0.2% for cancer and 3.2% for polyps in a randomly selected population of postmenopausal women aged 45-80, the authors concluding no support for generalized screening (Gull et al., 1996). However, high risk groups such as those suffering from type II diabetes mellitus might warrant attention (Gronroos et al., 1993).

A comparison of endometrial cytology and transvaginal ultrasonography for identification of endometrial malignancies showed the latter to be useful for confirmation (Tsuda et al., 1997). Endocyte smears found to be effective for mass screening in Japan (Nakagawa-Okamura et al., 2002). Ultrasound screening may not be suitable for women taking tamoxifen and those with recurrent or late-onset abnormal uterine bleeding (Symonds, 2001). Furthermore, ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients was reported to offer no prognostic advantage over symptomatic disease discovered by uterine bleeding (Gerber et al., 2001). Doppler sonography does not improve the detection of premalignant and malignant endometrial lesions compared with normal ultrasound (Vuento et al., 1999).Comparative genomic hybridization for serum tumor markers is conceivable (Numa et al., 2001)

Cervix

It has been estimated that 91 % of cervical cancers can be prevented by screening (Hristova and Hakama, 1997). With appropriate management an incidence of invasive squamous cell carcinomas of 0.8 rather than 38.2 per 100,000 population was noted for one study (Stenkvist and Soderstrom, 1996). However, in another, the estimate was that the number of cancers would only have been 57% greater without screening (Sasieni et al., 1996). A further problem is that protection is only conferred for one or two years, although this is better than for adenocarcinomas, necessitating regular testing (Makino et al., 1995). Nevertheless, the concensus is generally very positive, the major problem being the decrease in interest in the Papanicalou (PAP) test in older indivuals who are paradoxically more at risk of cancer.

Recently, a great deal of attention has been paid to alternative methods for screening. Improvements to the PAP test may be possible andthe so-called ThinPrep Pap Test may be more accurate than the conventional approach with potential to optimize the effectiveness of primary cervical cancer screening (Monsonego et al., 2001). Microsatellite analysis of cervical cytologic samples may provide a complementary method to further analyze suspicious but not diagnostic cytologic samples (Rha et al., 2001). A second approach is to concentrate on the viral risk factors and test for HPV strains, especially in high risk populations (Oh et al., 2001).

It has also been argued that for the developing world the most effective means for early detection may be direct visual inspection with acetic acid (Wesley et al,. 1997; Sankaranarayanan et al 1998; Chirenje et al., 1999; Singh et al., 2001). However, the results of one recent comparison of PAP, HPV and direct visual methods (Costa et al. ,2000) prompted the authors to conclude that no single test can be adopted to replace the PAP smear in routine clinical studies. Choice of test may be complicated by cultural variables and in some cases self-sampling may be of assistance in improving compliance (Dzuba et al., 2002). One device for this purpose has already been tested and shown to give reliable results (Pengsaa et al., 1997). Gravitt et al (2001) also demonstrated that a self-collected Dacron swab sample of cervicovaginal cells is a technically feasible alternative to clinician-administered cervical cell collection for studies

of the natural history studies of HPV and cervical cancer.

Education is clearly an important area and Mays and co-workers reported very interesting results (2001) Among both adults and adolescents they found a good deal of misunderstanding about symptoms associated with genital warts, about the purpose of Pap smears, and about the association of genital HPV with abnormal Pap smears and cervical cancer. The gaps in women's understanding about this potentially deadly infection suggest the need for more comprehensive education about preventing genital HPV, possible sequelae, and the significance of Pap or other screening for cancer detection and prevention.

Table 17. Summary for Cervical Cancer Screening

Target Lesion: Cervical Intraepithelial Noeplasia
Modality: Pap smear, HPV test, Direct Visual Acetic Acid
High Risk Factors: Sexual ctivity, HPV
Utility: General population, >30
Research Areas: Awareness and compliance

Lung

Lung cancer screening with chest radiographs was once routine but is no longer considered useful or widely practiced by physicians (McNaughton-Collins and Barry, 1996). Nevertheless, in one mass screened group identifying 116 patients, 50% of the detected lung cancers were stage 1 as opposed to 8.2% in patients with clinical symptoms (Satoh et al., 1997). Surgical treatment was therefore possible in a greater proportion of cases and the outcome was significantly better. For example, five year survival rates may be as high as 50-70% with early stage lesions, as opposed to about 12% in general (Flehinger et al., 1992; Nesbitt et al., 1995). Clinically meaningful improvements in stage distribution, resectability, and survival were found in review of studies with periodic annual chest radiographs, although mortality was unchanged (Strauss et al., 1997). Randomised trials have failed to show significant reduction in mortality rate although this might be partly due to methodological problems and the less than optimal chest radioagraphy as a screening technique. While mortality reductions have not been observed, significant stage and long term survival advantages have consistently been demonstrated in populations randomized to screening Strauss and Dominioni, 2000).

Tests for sputum occult blood have been applied in attempts to detect early lesions but the predictive value was found to be somewhat low (Qin et al., 1991). Rather better results have been obtained with sputum cytology (Saito et al., 1996), especially in patients with airflow obstruction or significant smoking histories (Kennedy et al., 1996). One alternative is PCR detection of aberrant methylation of the p16 and/or O6-methyl-guanine-DNA methyltransferase promoters, detected in DNA from sputum in 100% of patients with squamous cell lung carcinoma up to 3 years before clinical diagnosis (Palmisano et al., 2000). Detection of p53 mutations in sputum smears precedes diagnosis of non-small cell lung carcinoma (Chen et al., 2000). Cost effective (Rabb et al., 1997) it can be followed by fluorescence bronchoscopy/autofluorescence for identification of lesions and their localization (Sato et al., 2001; Sutedja et al., 2001). Laser-induced fluorescence endoscopy may be more sensitive than conventional white-light bronchoscopy in detecting preneoplastic bronchial changes in high-risk subjects (Hirsch et al., 2001). It has been reported that sensitivity can be improved by homogenization with dithiothreitol (Tang et al., 1995). It has also been proposed that inhalation of 5-aminolevulinic acid is a useful technique for fluorescence detection of early stage lung cancer (Baumgartner et al., 1996).

Table 18. Summary for Lung Cancer Screening

Target Lesion: SCC, adenoma
Modality: Sputum cytology, Spiral CT, X-rays
High Risk Factors: Smoking
Utility: General population, >40
Research Areas: Progression of lesions

Chest x-rays and cytology were recently found to have increased survival in the Mayo Lung Project (Strauss, 2002). In Japan, annual lung cancer screening has been estimated to reduce mortality from lung cancer by approximately 40-60% (Nishii et al., 2001; Sagawa et al., 2001; Tsukada et al., 2001). However, in Australia, current evidence does not support screening for lung cancer with chest radiography or sputum cytology. It has in fact been argued that frequent chest x-ray screening might even be harmful (Manser et al., 2001).

Another recent main theme of contention is use of low-dose spiral CT for very early lesions in the lung parenchyma, tumours being generally resectable peripheral adenomas (Henschke et al., Sone et al., 1998; Kaneko et al., 1996; Sobue et al., 2002). There are stong proponents (Miettinen and Henshker, 2001) but others argue it is too early to draw conclusions (Patz et al., 2001) and appropriate hypothesis-driven studies still must be performed and the results carefully analyzed before CT screening for lung cancer can be accepted as standard. It has been argued that since autopsies do not identify all small pulmonary nodules found at CT, the true incidence of clinically insignificant lung cancer is uncertain, and overdiagnosis bias in lung cancer screening may be more important than previously recognized (Dammas et al., 2001). Annual mass screening CT for 3 successive years resulted in the identification of a large number of slowly growing adenocarcinomas that were not visible on chest radiographs (Hasegawa et al., 2000). Lung nodules can be detected with similar detection rates when viewing conventional film or videotaped helical CT images. Videotaped images incur a lower cost, an important consideration in mass screening for lung cancer (Iwano et al., 2000).

Another factor is that analyses suggest that low-dose helical CT scanning may serve as a strong catalyst for

smoking cessation and provide a good opportunity for delivery of effective smoking cessation interventions. This type of benefit is clearly important regarding overall cancer prevention (Ostroff et al., 2001). For high risk cases CT screening may be advisable (Tiitola et al., 2002) although there may be problems with patient compliance with suggested measures. Regarding financial costs, one study in Canada demonstrated annual lung cancer screening over a period of 5 years to be relatively cost effective at approximately $19000 per life year saved (Marshall et al., 2001).

Computer aided diagnosis has recently been advocated (Wormanns et al., 2002) and part solid or non-solid nodules found but more likely to become malignatn than their solid counterparts (Henschke et al., 2002). Small peripheral lung adenocarcinomas shown on CT exhibit four high-resolution CT patterns that corresponded to the histopathologic findings of different tumor growth patterns (Yang et al., 2001). Pure Ground Glass Opacity clearly defined on high resolution CT, some will never progress to clinical disease and would be included in the category of overdiagnosis bias (Kodama et al., 2002).

Table 20. Screening Levels of Sophistication

Method		Organ
Level 1		
Naked Eye		Skin, Buccal Cavity
Direct Visual Acetic		Cervix
Palpation		Breast
Occult Blood	Urine	Kidney and Urinary Bladder
	Faeces	Colon and Rectum
	Sputum	Lung
Level 2		
Body Fluid (Pap. HPV)		Cervix
Serum Testing		Prostate, Pancreas, Gallbladder, Stomach, Ovary
Occult Blood		Oesophagus and Stomach
Level 3		
Ultrasound		Thyroid, Liver, Pancreas, Ovary Prostate, Endometrium
X-Rays		Lung, Stomach
Endoscopy		Oesophagus, Stomach, Colon
Spiral CT		Lung

General Conclusions

As can be seen from the above a large number of screening approaches have now been established, allowing detection of the vast majority of major cancers in man Table 19). Whether they are feasible depends to a very large extent on identification of high risk groups and the resources which are available. Parameters like convenience and treatment acceptability vary with the individual but there is clearly a need for heightened awareness of the benefit. To obtain maximum compliance and efficiency of effort a coordinated screening regimen with increasing levels of sophistication might be developed along the lines shown in Table 20. Thus

Table 19. Assessment Parameters for Screening Potential

Organ	Level	Endpoint/ Methodology	Sensitivity	Treatment Ease	Screening Approach			Feasibility	
					Convenience	Specificity	Cost	General	High Risk
Skin	1	Naked Eye	+++*	+++	+++	++	+/-	+++	+++
Thyroid	3	Ultrasound	++	++	++	++	--	-	++
Oral Cavity	1	Naked Eye	+++	++	+/++	++	--	++	+++
Oesophagus	2	Occult Blood	++	+	+++	+	-	+	+++
	3	Endoscopy	++	+	+	+++	--	-	++
Stomach	2	Barium Meal	++	+	++	+	--	+	+++
Colon	1	Occult Blood	++	+	+++	+	-	++	+++
	2	Sigmoidoscopy	++	+	-	+++	-	++	+++
	3	Colonoscopy	+++	+	--	+++	--	+	+++
	2	DNA	++	++	++	++	--	-	++
Liver	3	Ultrasound	++	+	++	++	-	--	++
Pancreas	3	Ultrasound	++	+	++	++	-	--	++
Prostate	2	PSA Test	+	++	++	+	-	+	++
Breast	1	Self-examination	+	++	+++	+	-	++	++
	3	Mammography	++	++	++	++	-	+	++
Ovary	2	CA 19-9	+	++	++	+	--	-	++
	3	Ultrasound	++	++	+	++	--	-	+
Endometrium	3	Ultrasound	++	++	+	++	--	-	++
Cervix	1	Direct Visual	++	++	+++	+	+/-	++	+++
	2	PAP Smear	++	++	++	++	-	++	+++
	2	HPV Testing	+	++	++	+	-	++	+++
Lung	1	Sputum Cytology	++	+	++	++	-	++	+++
	3	X-Ray Imaging	++	+	+	++	--	+	+++
	3	Spiral CT	+++	+	-	+	--	-	++

* Positive and negative aspects for the screening equation: +, ++, +++/- --, increasing degrees of advantage/disadvantage (subjective)

occult blood tests for colorectal and urogenital cancers could be married to superficial observation for skin and palpation for the breast, perhaps self administered to a large extent, to achieve a great deal in the general populace (Qin et al., 1996). By accessing nursing expertise this could be expanded to include serum tests, occult blood for the esophagus and stomach, and assays for human papilloma viruses in swabs for sites including the buccal cavity, cervix and rectum/anus (Pisani et al., 1997). In the context of the latter, possible use of parameters such as α-tocopherol as a serum marker might be explored (Kwasniewski et al., 1997). At the more technically advanced level, in addition to X-rays for lung, ultrasonography could be expected to reap rewards for assessment of the pancreas, liver, gastric, urinary tract, and endometrium, for example in general high-risk populations such as atomic bomb-exposed subjects (Russell et al., 1994). For cost-effectiveness it can be expected that many abdominal cancers, such as hepatocellular carcinoma, gallbladder cancer, pancreatic cancer, and so on, could be found in the early stage by broad implementation of ultrasonography for screening. (Mihara et al., 1999).

With regard to compliance, education is obviously a major aspect although the presence of other factors is evidenced by the lack of a direct relation between perception of personal risk of cancer and screening attendance found in an Oncology center (Helzlsouer et al., 1994). However, the general level of knowledge may be low, only half of Americans surveyed in one study thinking they had a good chance of survival following early detection of colon and cervical cancers, both of which have 5 year rates exceeding 90% (Breslow et al., 1997). This serves as a potent negative motivation. To overcome this it is necessary to employ sophisticated information strategies, for example using videotapes which have been shown to impact well on the public (Wilson and Stein, 1997). Reaching people in their work environment has clear benefits for screening but the importance of an awareness of sociodemographic factors has been emphasized in this context (Haynes et al., 1990). Behavioural research with respect to cancer prevention clearly is a high priority (Lerman et al., 1997). In general there is a need for open discourse, founded on an efficient public education system and shared decision-making. This may be especially the case for disadvantaged minorities, for example like Mexican-American women who often demonstrate significant misconceptions and fatalism, but in whom major improvement can be obtained with increased awareness (Carpenter and Colwell, 1995). Simple, written messages provided art screening clinics, tailored to the knowledge levels of the individual, are effective at least in the short termfor modifying cancer-protective dietary behaviors (Baker et al., 2002). The public need to be made aware of what the screening programmesreally offer, balanced against the expectations they may have.

There needs to have a clearer understanding of the nature of the contractual and other legal rights of patients/consumers as against providers. A positive screening test may carry adverse consequences as well as benefits. It could alert an insurance company to a risk and lead to additional weighting or even outright rejection for life insurance policies. While cancer screening is generally increasing in the United States, usage is relatively low for colorectal cancer screening and among groups that lack health insurance or a usual source of care (Breen et al., 2001). Job prospects may also be affected for employees. The method of informing patients in relation to screening and screening failure has already been considered by the courts and the risk of law suits has received attention (Collins et al., 1997). Realistic information about both screening and treatment efficiency needs to be offered to patients so that they can have a real understanding of what can and cannot be achieved by current science. The development of understanding of the human genome makes the need for clearer legislation in this regard more urgent.(Eaden et al., 2001).

Thus, as recently argued by Sackett (1997), the physician and other health care specialists have a responsibility to the patients and populations in their care to only recommend screening maneuvers for which there is evidence that the benefit will clearly outweigh the adverse effects. How the latter are conceived, however, depends to large extent on the individual and the level of knowledge. Where benefit can be attained, a concensus approach may offer the best chance of success in ensuring participation and increased well-being. Achieving that concensus through education and debate (Grol, 1997) is a very worthy challenge.

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