INVITED ARTICLE

GYNAECOLOGICAL SCREENING -- THE BENEFITS AND PITFALLS

Y M Salmon

ABSTRACT

Gynaecological screening, as with all screening, must have clear indications, objectives and modus operandi. The types of screening addressed are osteoporotic screening, gynaecological oncological screening involving the various hormonal target organs and breast cancer screening. Apropos osteoporotic screening, a suggestion is made that assessment of bone mineral content be used as a research tool in following the progress of therapy in osteoporosis rather than a screening modality.

Cervical cytological screening remains the mainstay of screening for pre-invasive cancer of the cervix, and has contributed significantly to reduction of the incidence and mortality in cervical cancer over the past decade in many countries worldwide. Data should be standardised. Causes of false negative smears are outlined. Colposcopy, with colposcopically directed biopsies where necessary, is advocated in selected cases, namely all CIN, atypical and persistenly inflammatory cytological smears. In the near future, DNA hybridisation tests could become desirable for the detection of HPV in targetted cases. Oncology screening for vagina and vulva follow a similar pattern for the cervix. Ultrasound screening of the uterine body and endometrium as well as the ovaries has had favourable reports.

Mammographic screening is recommended in patients at higher risk for breast cancer.

The benefits and pitfalls of screening are outlined both for individual screening modalities and generally.

Key Words: - Gynaecological screening, pre-invasion, benefits, pitfalls.

SING MED J. 1989; No 30: 297 - 301

INTRODUCTION

In conducting a screening service, the objectives must be clearly outlined and the modus operandi determined. By connotation, screening is a method of investigating and detecting a potentially serious lesion in an otherwise asymptomatic and healthy person. The sky is the limit, if screening is performed with abandon, and teleologically, every individual should be scanned from head to toe to achieve the ideal; this of course is a proposition ad absurdum, as it is not only unattainable economically, but it is based on a negative premise of general ill-health.

Is there a need for Gynaecological screening and what then are the critical criteria for such a screening programme? Is the specific disease or lesion prevalent and serious enough to warrant screening? Does screening have a beneficial effect on mortality and morbidity of the disease or lesion? What are the benefits and pitfalls of screening? These issues will be addressed in the following specific fields of screening.

Screening, apropos gynaecology, can take a few forms eg screening for puberty problems, oncology screening and screening for postmenopausal osteoporosis. Each has its own scale of values, benefits and pitfalls. Suffice it to say that puberty problems are often not life-threatening.

OSTEOPOROTIC SCREENING

Osteoporotic Screening is a controversial subject. The problem of osteoporosis and osteoporotic fractures is a difficult one, but fortunately, such induced fractures are not as common in Singapore as in Western countries(1). The various non-invasive techniques of measuring bone mass have spurred enthusiasts to advance the necessity for widespread screening, using such techniques to attempt to detect a "fracture threshold." However, pitfalls lie in the fact that current state-of-the-art techniques are poorly reproducible, a decrease of bone density in one site is not predictive of fractures at other sites and the tests are of uncertain value for predicting future rates of bone loss(2). They may not prove to be cost-effective. It would be wise to focus on the typical risk factors in osteoporosis(3), such as thin, small built females with a poor dietary intake especially of calcium, who are inactive, smoke and drink alcohol or who have an early menopause, and to give priority to their detection and preventive management. Besides, the beneficial effect of oestrogen therapy on coronary artery disease in the postmenopausal patient may make osteoporotic screening of hardly any import. Instead, a suggestion is made that assessment of bone mineral content is useful as a research tool in following the progress of therapy in individual patients(4). Recently, using a single measurement of height and weight with serum alkaline phosphatase and urine calcium and hydroxyproline estimations, Danish workers correctly identified which postmenopausal women were at high risk of developing osteoporosis; these tests were simple, non-invasive, cost-effective and preceded any substantial bone mineral content loss(5).

GYNAECOLOGICAL ONCOLOGY SCREENING

The next screening modality relates to gynaecological oncology. These tests scan the target organs of hormonal effect for evidence of pre or early malignant change, namely cervix, vagina, vulva, endometrium, ovaries and breasts. Each will be considered in turn.

Department of Obstetrics & Gynaecology
Kandang Kerbau Hospital
Ministry of Health
Singapore 0821

YM Salmon, MBBS, FRCOG, AM, Senior Consultant/Adviser

CERVIX

Cancer still remains the major cause of death in 1987 in Singapore at 24.1% of the population, with cancer of the cervix as the fourth commonest cancer in women. The 5 year matched mortality rate from 1977-81 for Cancer of the Cervix was 6.4/100,000 female population and 6.7/ 100,000 from 1982-86(6). However the incidence of cervical cancer has fallen - the age stratified incidence rate of 18.2 per 100,000 female population during 1968-72 has fallen to 16.5 per 100,000 women during 1978-82(7). This is largely due to the implementation of the cervical cytological screening programme. A similar fall from 12.53 to 9.10 deaths per 100,000 women between 1968-84 was noted in England and Wales(8). Decrease in mortality rates in Nordic countries(9) has shown correlation with well-organised cytological screening programmes. The fall was highest in Iceland, 80%, with women aged 25 to 59 years screened (the upper age limit has now been raised to 70 years), and decreasing to 10% in Norway with 5% of the female population screened. Composite gynaecological oncology screening was first introduced in Singapore by the B Unit, KKH, in October 1986, and among the well-women reviewed, cases of unsuspecting CIN and even a couple of invasive cancer of the cervix were detected(10).

The success of cervical cytological screening accrues from the fact that the cervix lends itself to ready examination, precancerous cells exfoliate easily and there is a gradation from pre-invasive to invasive cervical cancer. Apart from invasive carcinoma, cytology can detect mild, moderate or severe dyskariotic cells, suggestive of cervical intra-epithelial neoplasia (CIN 1,2 & 3 inclusive of in-situ cancer) as well as inflammatory and atypical cells. There must however be standardisation of terminology for data to be compared. The British Society for Clinical Cytology in their report on Terminology in Gynaecological Cytopathology, 1986(11), made specific recommendations. Although not recommended, the terms "inflammatory" and "atypia" are often used in Singapore to alert the need for further investigation. By detecting the pre-invasive stage of cervical cancer and treating it, a 100% cure rate can be achieved. But not all screening programmes can achieve a 100% successful detection rate. The validity of a cytological screening programme is adequately described by the sensitivity and specificity of the test. In turn sensitivity depends on a low false negative rate, while specificity is measured against a low false positive rate. Both these rates should not exceed 5% for detection of squamous cell lesions, but the results vary from laboratory to laboratory(12). False negative smears have ranged from 2.4 to 69% of patients with CIN(13-17) Reasons for false negativity include errors of the 'takers' and 'readers', more aggressive cervical cancer growth, failure of the smaller lesions to exfoliate sufficient abnormal cells and infection or much bleeding which may affect the accuracy of the report. All forms of CIN require detection and treatment, because although CIN 1 has been known to regress, progression to invasive cancer can take as long as 10 years to occur. Progression rates of dysplasia to CIS vary from 0 to 70%. The corresponding figures for CIS to invasive cancer vary from all or most through 20 to 10% down to almost nil(18). Furthermore, there is the pitfall that 62% of atypical smears(19) and 20% of inflammatory smears can show CIN(20). Reversion to normal may occur, but even a repeat normal smear does not preclude the subsequent development of CIN 2 or 3(18). It is also imperative to use a swab or cytobrush to sample the endocervical epithelium in order not to miss an endocervical lesion.

What role does the Human Papilloma Virus (HPV) play in the etiology of cancer of the cervix? From the majority of reports, HPV especially Types 16 and 18, has been found to have a high association with Cancer of the Cervix; 90% of cervical cancers and 70% of preinvasive cancers contain DNA sequences of HPV 16(21).Another report concurs, with the association of specific HPV in cervical carcinoma being 80 - 90% with HPV 16, 18, 33 or HPV as yet untyped. The HPV DNA is found integrated into the cellular genome in the cervical cancer tissue, while it is extrachromosomal in benign or premalignant lesions(22).Conversely, the risk of CIN developing in women with vulval warts is 30%. The male sexual partner is thought to be the vector in the transmission of the oncologic agent, suggestedly HPV, and the risk of a woman developing HPV infection from an affected male sexual partner is 76%, while 32% of sexual partners of men with penile HPV infection have pre-malignant cervical lesions(23,24). There is also a four-fold increased risk of cervical neoplasia in women, whose husbands had at some time been married to a woman with cervical neoplasia(25).

A pitfall to be aware of is that HPV DNA can still be found in cervical samples after laser ablation for CIN grades 2 & 3, (26,27) suggesting that, once detected, patients with HPV should have prolonged follow-up; the infection may be a recurrent one from the surrounding epithelium or reinfection from a sexual partner.

On the other hand, other studies indicate a high prevalence of clinically inapparent HPV infections of the cervix in a normal population of women, 10% – 11.5% – 35%(28,29,30). The suggestion is that the association of HPV and neoplasia is age-related, irrespective of whether a patient has cervical cancer or not. This argument was refuted by others, who found CIN in ages 18 - 39 yrs(31) The weight of evidence, although tilted towards a close association of HPV with cervical pre and invasive cancer, is still not clear cut. HPV infection is suggested by the presence of visible condylomata, koilocytosis in cytology smears and viral vesicles on colposcopy, and every attempt should be made to identify and treat them, especially if they are associated with CIN changes.

More disturbing are recent reports about the changing face of cervical cancer. In the United Kingdom, the age-specific death rate for cancer of the cervix over the last 10 years has shown a doubling in women aged 25-29 and 30-34 years; the incidence has also doubled in the 20-24 years group. The prevalence of pre-invasive cancer showed a 117% increase between 1973 and 79(32,21). Histology of the lesions has changed, most showing a poorly differentiated type with a high proportion metastasising to pelvic lymph nodes at an early age, as well as a rise in adenocarcinomatous types.

All these data emphasize the need for greater vigilance and the benefits of early detection by whatever appropriate means. So far we have been considering cytological cervical screening. This however is not a science, and in view of the high false negative rate, colposcopy with colposcopically directed biopsies, was introduced. Colposcopy gives a dynamic, three dimensional view of the cervix, vagina and vulva, and biopsies can be accurately targetted. In most cases, it can abolish the need for cervical cone biopsies, with the attendant risks of general anaesthesia, haemorrhage and infection; even those cones which need to be done, can be performed with colposcopically directed laser under local analgesia as outpatients. Although the false negative rate varies from 4.6 to 13%(33), yet colposcopy complements cytology, and the two together can achieve a high pick-up rate of over 90%.

Nevertheless there are also failures with colposcopy especially when the transformation zone is within the cervical canal. These cases must be screened with the cytobrush and spatula scrape. Endocervical curettage is rather traumatic for screening purposes.

Should colposcopy then be a modality of screening for all women? The enthusiasts feel that it should be, but cost-benefit wise, it is not feasible and with long queues, the more urgent cases will be in danger of being relegated down the line. The best course of action will be to have more colposcopy facilities, to be used in selected target groups.

The next modality to be considered is Viral DNA studies, using HPV DNA probes and hybridisation techniques. In view of the high association of HPV with CIN and Invasive Cancer and the fact that HPV can be detected in asymptomatic women, it is even suggested that HPV DNA detection be incorporated in a screening programme. This may be of questionable benefit, but it certainly is not cost effective; such investigations should be reserved for specific cases such as those showing evidence of wart virus infection on cytology and colposcopy and those with CIN. Cervicography is a further development of colposcopy, but its use is limited.

In the final analysis, the basic screening modality must still be cytological, with facilities for colposcopy and HPV hybridisation in selected and high risk groups. This will be cost effective and cost-beneficial. High risk groups are those women with early age of intercourse, many sexual partners especially those with warts affecting their or their male partner's genitalia, and who smoke or drink excessive alcohol. In some reports, a question mark has been placed over the oral contraceptive pill, as an associated factor with the increased cervical adenocarcinoma incidence in younger women and in various cancers(34,35). However, the pitfall of non-attendance of these high risk groups from screening is one of the main causes of failure of any screening programme.

Vagina

Screening for pre-invasive lesions of the vagina follows a pattern similar to that of the cervix.

Vulva

There is no effective method of screening for pre-malignant vulval lesions, which fortunately are rare. Colposcopy may however detect the presence of warts.

Endometrium

Screening tests for the detection of endometrial carcinoma have been reported as successful in 90% and above cases using such techniques as endometrical brush, jet wash, aspiration, biopsy and aspiration curettage. However, the pitfall is a low detection rate with premalignant lesions and D&C is advocated if there are suggestive symptoms with a negative screen test. As an adjunct, hysteroscopy is mentioned, but is not widely used. Recently, ultrasonographic assessment of uterine size and endometrial thickness was found beneficial as a non-invasive screening technique.

Ovaries

At present there is no fool-proof screening technique for ovarian cancer detection. To compound the problem, there is no known pre-clinical stage and by the time symptoms appear, the cancer is in the more advanced stage. Vaginal cytology may pick up malignant cells in advanced disease but not in the early stage. Tumor markers are not specific and sensitive enough in detecting ovarian malignancy, but encouraging data have emerged from ultrasound scanning(36). Prediction of ovarian malignancy by ultrasound was 73% accurate in one series(37). Basically, a meticulous physical examination to detect ovarian enlargement, coupled with ultrasonography, forms the cornerstone of current ovarian screening.

Breasts

Scanning of the breasts is of two types, ultrasonographic and radiological. Whole breast ultrasound mammog raphy(38) permits evaluation of the parenchymal pattern and its benefit is that it can be repeated many times with no known adverse effect. Its major pitfall, however, is poor spatial resolution. X-ray mammograms can detect microcalcifications that may be the only sign of early carcinoma. Thus one view is that ultrasound should not be performed as the initial imaging breast examination. On the other hand, the combination of ultrasound and X-ray mammography may lead to increased accuracy of the disease. Due to cost-benefit considerations, however, most centres perform radiologic mammography alone, and this has shown reduction in mortality of between 30 and 40% in randomised trials in New York and Sweden. A report from the American Breast Cancer Detection project with 280,000 women, in whom 3,550 cancers were detected, also support the concept of benefit derived from screening. In Singapore, the 5 year age-stratified mortality from Breast Cancer(6), which is the top cancer among women, has risen slightly from 10.2 during 1977-81 to 10.6 per 100,000 female population during 1982-86; thus benefit could arguably be derived from more aggressive screening. The Forrest report in UK(40) recommends routine mammography for all women between the ages of 50 and 64 years every 3 years. Singapore women, however, tend to have small breasts, so that regular self-examination, reinforced by the physician's clinical examination may be all that is necessary. Where silicone implants are used, mammography may prove ineffective too. In our local context, therefore, routine mammography may not be cost beneficial, but it should be targetted for high risk groups such as women over 30 years old with any breast symptoms, with large or lumpy breasts, after unilateral mastectomy, or with a family history of breast carcinoma. If there are dubious scans, these can be repeated on a yearly basis.

General considerations

The benefits and pitfalls of each screening procedure have been outlined with the individual target organ. Certain generalised considerations, however, are applicable to all screening programmes. The benefits of a screening programme may be easy or difficult to quantify, depending on the angle of approach. To the individual, her life saved is worth all the money in the world, but what cost effectiveness does an expensively expansive screening schedule hold for the country's economy? Apart from reducing mortality, screening can also reduce morbidity by detecting lesions at the pre-invasive stage so that treatment can be simpler, often on an outpatient basis, is more conservative and the expense of treatment is drastically contained. Thus, for example, CIN can be treated with laser vaporisation or laser therapeutic conisation on an outpatient basis without general anaesthesia; early breast cancer can be treated by lumpectomy or simple mastectomy. There is no necessity for recourse to radiotherapy or chemotherapy in early gynaecological cancer, thus reducing the morbidity associated with such treatment. Also, by detecting the lesion at the early stage, there is less chance of lymph node involvement and hence a better prognosis. There is a 100% cure rate in eradicating CIN and a good outlook for a small breast lump. The economic aspect of screening versus cost - saving in treatment merits consideration, and if the former is kept within bounds, benefits will accrue. The modalities of major surgery, chemotherapy and radiotherapy are very expense-generating.

Psychologically, the benefit of a clean bill of health after a negative screen is best seen than described. The patient steps warily into the Doctor's consultation room, and strides out beaming when the report is negative. A spin-off benefit of screening is the opportunity of counselling the patient on self-examination, healthy lifestyles and the need for repeat screening.

On the other hand, if certain criteria and conditions are not fulfilled, then the screening programme will meet with pitfalls. The screening tests should have a high sensitivity and specificity rating. If this is not so, and there is an unacceptable level of false negative and positive results, the screening tests become meaningless, and worse

still, dangerous, lulling the patient into a false sense of security. The risk of infection must be guarded against by paying attention to scrupulous asepsis in the use of specula and other instruments. In our enthusiasm, the danger of over investigation must be guarded against, so that the patient does not run the risk of developing cancerophobia, fearing that she already has cancer, when in fact she has CIN or mammary dysplasia; the hazard of psychosexual problems may also be the result, sowing the seed for divorce in extreme cases. A pitfall may be occasioned by repeated requests for screening from low-risk groups of women to the exclusion of those who really need them. Moreover, screening should not be the monopoly of those who can pay for services to the neglect of the poor and needy, who constitute the high risk group. Cancer of the cervix is mainly a disease of the lower social classes, who are generally indifferent to their health and screening advantages. Death stalks the non-screened. There should be a well-organised and publicised national programme with call and recall facilities and a computerised data recording system, connected to cancer registration as well as population and mortality statistics to prevent pitfalls such as when to start, frequency of recall and when to stop screening. Various formatted schemes have been advocated in the Western world, but the ideal for Singapore would be a clinical examination for all women and cervical cytological screen for all sexually experienced women once a year until 60 years of age. Other tests, including mammography would be indicated on a selective and targetted high risk group. To guard against the pitfall of poor quality care, there should always be quality control of the screening programme with checks on every test at periodic intervals. Another pitfall to be prevented is the possible abuse of screening programmes for financial gain, either by individual doctors or corporate health-care delivery bodies. Finally comes the ever-present pitfall of the financial burden of such a comprehensive screening service. Who should bear the cost? Perhaps a tripartite arrangement of patient's contribution, insurance coverage and Government subsidy would be ideal.

Conclusion

The conclusion of the matter is this. In Gynaecological screening, as in all forms of screening, the foremost consideration must be the achievement of maximal benefit for the majority of women with cost-effective resources - in the case of osteoporotic screening, it is the prevention of osteoporotic fracture, while in oncology screening it is the detection of the pre-invasive or early stage of female genital cancer. Although cervical cancer incidence in Singapore has fallen, it has not reached the irreducible minimum, and more preventive measures must be undertaken. Such steps are even more imperative with cancer of the breast in the face of increasing incidence. I believe our aims can be achieved.

An adaptation from Churchill, "Never in the field of Gynaecology was so much owed by so many to so few", may one day prove true.

References

1. Tan S K , Head of Orthopaedic 'O' Unit, SGH (personal communication)
2. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? Ann Intern Med 1986; 104: 81723.
3. Bleicher M, Martin JL. Osteoporosis & the hormonal regulation of bone metabolism - Sandoz publication : 70
4. Saxon RR, Bassett LW. Osteoporosis: Current concepts. Hospimedica 1987; V: 53-9
5. Christiansen C et al. Prediction of rapid bone loss in postmenopausal women. Lancet 1987;i: 1005-8.
6. Report on Registration of Births & Deaths 1977-1986. Registry of Births and Deaths.
7. Lee HP, Day NE, Shanmugaratnam K. Trends in Cancer incidence in Singapore 1968-1982, IARC Scientific Publications, International Agency for Research on Cancer, Lyon 1988;91:13-27.
8. Hiscock E, Riece G. Cytological screening for Cervical Cancer & human papillomavirus in general practice. Br Med J 1988; 297: 724-6.
9. Laara E et al. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programme Lancet 1987;i: 1247-9
10. Salmon Y M. Results of Screening to be published.
11. Evans DMD, Hudson EA, Brown CL et al. Terminology in Gynaecological cytopathology: report of the Working Party of the British Society for Clinical Cytology. J Clin Pathol 1986;39: 933-44.
12. Ng ABP. Diagnostic cytopathology. In Coppleson M ed. Gynecologic oncology. Churchill Livingstone, New York 1981; 1: 187-204.
13. Beilby JOW, Bourne R, Guillebaud J et al. Paired cervical smears: a method of reducing the false negative rate in population screening. Obstet Gynecol 1982;60: 46-8.
14. Coppleson LW, Brown B. Estimation of the screening error rate from the observed detection rates in repeated cervical cytology. Am J Obstet Gynecol 1974;119: 953-8.
15. Evans AS, Walls M. False negative cervical cytology obtained at colposcopy. J Obstet Gynaecol 1982; 3: 114-6.
16. Husain OAN, Butler EB, Evans DMD et al. Quality control in cervical cytology. J Clin Path 1974; 27: 935-44.
17. Richard RM. Evaluation of the true false negative rate in cytology. Am J Obstet Gynecol 1964;89: 723-7.
18. Coppleson M. Cervical Intraepithelial neoplasia: Clinical features & management. In Coppleson M ed. Gynecologic oncology. Churchill Livingstone, New York 1981; 1: 408-33.
19. Walker EM, Dodgson J, Duncan ID. Does mild atypia on a cervical smear warrant further investigation? Lancet 1986;ii: 672-3.
20. Singer A. The abnormal cervical smear. Br Med J 1986;293: 1551-6.
21. Singer A. Cervical neoplasia and young women. IPPF Medical Bulletin 1986; 20: 1-3.
22. Gissman L, Schwartz E. Persistence & expression of human papillomavirus DNA in genital cancer. In Evered D, Clark C, eds. Papillomaviruses. Ciba Foundation Symposium 120. Wiley, Chichester 1986: 190-207.
23. Skegg DCG, Corwin PA et al. Importance of the male factor in cancer of the cervix. Lancet 1982;ii: 581-3.
24. Campion MJ, Singer A et al. Increased risk of cervical neoplasia in consorts of men with penile condylomata accuminata.

Lancet 1985;i: 943-6.
25. Kessler II. Human cervix cancer as a veneral disease. Cancer Res 1976;36: 783-91.
26. Wickenden C, Malcom ADB, Byrne MA et at. Prevalence of HPV DNA & viral copy numbers in cervical scrapes from women with normal & abnormal cervices. J Pathol 1987; 153: 127-35.
27. Byrne MA et al. Prevalence of human papillomavirus types in the cervices of women before and after laser ablation. Br J Obstet Gynaecol 1977;95: 201-2.
28. De Villier EM, zur Hausen H et al. Human papillomavirus infections in women with and without abnormal cervical cytology. Lancet 1987;i: 703-6.
29. Toon PG, Arrand JR et al. Human papillomavirus infection of uterine cervix of women without cytological signs of neoplasia. Br Med J 1986;293: 1261-4.
30. Meanwell CA. Cox MF, Blackledge G. HPV 16 DNA in normal & malignant cervical epithelium: Implications for the aetiology & behaviour of cervical neoplasia. Lancet 1987;i: 703-7.
31. Ms Cance DJ, Campion MJ, Clarkson PK et al. Prevalence of human papillomavirus type 16 DNA sequences in cervical intraepithelial neoplasia and invasive carcinoma of the cervix. Br J Obstet Gynaecol 1985; 92: 1101-5.
32. Draper GJ, Cooke GA. Br Med J 1983;287: 510.
33. Byrne P, Woodman C. False negative colposcopic cervical biopsy. Br Med J 1988;296: 932-3.
34. Chilvers C, Mant D. Cervical adenocarcinoma & oral contraceptives. Br Med J 1987;295: 1446-7.
35. WHO. Invasive cervical cancer & combined oral contraceptives. Collaborative study of Neoplasia & Steroid contraceptives. Br Med J 1985;290: 961-5.
36. Campbell S, Goessens L, Goswamy R. Real time ultrasonography for determination of ovarian morphology & volume: possible early screening test for ovarian cancer? Lancet 1982;i: 425.
37. Herrmann UJ, Locher GW, Goldhirsch A. Sonographic patterns of Ovarian tumours: Prediction of Malignancy. Obstet Gynecol 1987; 69: 777-81.
38. Cole-Beuglet C. The use of ultrasound in breast evaluation. In Sanders RC and James AE eds. The principles & practice of ultrasonography in Obstetrics & Gynecology. Appleton-Century -Crofts, Connecticut 1985; 603-15.
39. Baker LH. Breast Cancer demonstration project. Five year summary report. CA 1982;32: 194-225.
40. Breast Cancer Screening: report to the Health Ministers of England, Wales, Scotland & Northern Ireland by a working group chaired by Sir Patrick Forrest. H.M.Stationery Office, 1987.