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Review Article

Screening the High Risk Patient for Gynaecological Cancer

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It is often difficult to conclude that improvements in survival with time are due to a screening programme alone. Although a reduction in the death rate from a given cancer may reflect the benefits of early detection or improved treatment, the benefits may also result from lead time bias and over-diagnosis, the former resulting in longer survival of screen-identified cancers because the time before the cancer would have been clinically diagnosed is included in calculations. Furthermore, recent reviews on randomised clinical trials of cancer screening have provided strong evidence that misclassifications in causes of death have been a major problem, leading to an over-estimation of the effectiveness (or alternatively an under-estimation of potential harm) of screening.

Key Words: Screening, gynaecologic cancer

CANCER INCIDENCE AND MORTALITY

In 2002 an estimated 1,284,900 people in the United States will be diagnosed with cancer, and 555,500 will ultimately die of the disease.[1] It has been variably estimated that between 3-35% of deaths could have been avoided through screening and furthermore, of course, screening may reduce cancer morbidity since treatment for the early stage disease is often less aggressive than that of a more advanced malignancy.

In comparison, however, because screening may identify early cancers that would never have clinically manifested, more screened people than unscreened populations will undergo diagnostic and therapeutic procedures, which they otherwise might not have required, and in such circumstances, any treatment related side effects are of course unacceptable. Furthermore, screening can cause both physical and psychological trauma in individuals who experience a false positive result, equally those who have a false negative result may be falsely reassured, and may ignore symptoms and ultimately die of an otherwise treatable cancer had it been diagnosed at an earlier stage. Table 1. outlines the requirements for a successful screening programme.

It is often difficult to conclude that improvements in survival with time are due to a screening programme alone. Although a reduction in the death rate from a given cancer may reflect the benefits of early detection or improved treatment, the benefits may also result from a lead time bias and over-diagnosis, the former resulting in longer survival of screen-identified cancers because the time before the cancer would have been clinically diagnosed is included in calculations. For instance, a high percentage of occult early prostate cancers in elderly men have been identified in autopsy series in men who have died of causes unrelated to malignancy.[2] Indeed, an analysis of data reported by the SEER Programme for 1950-1966 suggested that changes in five year survival or stage shifts are not appropriate measures of the success of screening for an early disease, but that reductions in incidence rates for late stage tumors represents a better measure for the success of any given screening programme.[3] Furthermore, recent reviews on randomised clinical trials of cancer screening have provided strong evidence that misclassifications in causes of death have been a major problem, leading to an over-estimation of the effectiveness (or alternatively an under-estimation of potential harm) of screening.[4,5]

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Table 1. Requirements for a Successful Screening Programme

1	The disease must be common.
2	There must be a test or procedure that will detect cancer earlier than if the cancer were detected as a result of symptomatology.
3	There must be evidence that treatment initiated earlier as a result of the screening results in an improved outcome.
4	The screening test or procedure needs to be acceptable to the population being screened.
5	The sensitivity and specificity of the test need to be acceptable to the population being screened.
6	The screening programme must be cost effective.
7	The screening programme must be associated with a fall in the mortality from the disease.

Table 2. Three Large Ongoing Randomised Trials into Screening for Ovarian Cancer

	BART'S	ERTOC	NIC
Protocol	Ca125 → TVS if positive	TVS for either 18 or 36 months	TVS and Ca125 and vaginal exam
How Long	Annual for 6 years	-	Annual for 4 years
Age	> 50 years	50-64 years	60 - 74 years
Target Number	60,000 each arm	30,000 × 2 60,000 controls	37,000 each arm
Costing?	Possible	Yes	No
Completion Date- Follow-up	7 years	10 years	10 years

BART'S, St. Bartholomew's hospital; ERTOC, the European randomised trial of ovarian cancer; TVS, transvaginal ultrasonography.

OVARIAN CANCER SCREENING

In ovarian cancer, a reduction in mortality from the disease can only be achieved if either, pre-neoplastic change can be identified, or the disease can be detected frequently enough when confined to the ovary. The former situation has been addressed recently[6] in a cohort study of over 5,000 self-referred women for removal of benign epithelial tumors, where no association with a reduction in the death rate from this malignancy was found. The latter situation assumes that all ovarian malignancies are monoclonal, commence within the ovary, and then spread transperitoneally, whereas, most evidence would suggest that ovarian cancer may represent a multifocal polyclonal disease. Furthermore, CA125 is only positive in approximately 50% of Stage I cases, which makes its unaccompanied use as a screening test unattractive.[7,8] Our own studies have shown, that in up to 10% of cases, the ovarian size at the time of primary surgery is less than 3cm (Rome R and Quinn MA - unpublished observations). There are currently three large ongoing randomised trials into screening for ovarian cancer (Table 2). The emanation of useful data from these trials is unlikely before 2005, and given the advances in genomics and proteomics, it is likely that new markers will become available. Nonetheless, the enormous data bank resource resulting from these studies will allow quick assessment for the efficacy and predictive value of new tumor markers.

Approximately 5% of all ovarian malignancies will have an hereditary basis, with the most common being due to a mutation in the BRCA1 (lifetime risk 27 - 50%) or the BRCA2 (lifetime risk 25 - 30%). Patients who carry mismatch repair gene mutations have an approximate 10% risk of subsequently developing the disease; such carriers have a mean age at diagnosis of ovarian cancer of 42 years, the tumors are more likely to be well-

differentiated, and are more likely to have a synchronous endometrial cancer.[9] The best way to screen BRCA mutation carriers has not been evaluated, but most family cancer clinics currently recommend six-monthly CA125 levels together with annual transvaginal scanning. It should be noted that the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers does not rise until the ages of 40 and 50, respectively. This obviously needs to be taken into account when counseling patients as to the timing of the initiation of any screening programme.

It is essential that when women are being interviewed by their family practitioners that a detailed family history is elicited, and when two first degree relatives have a history of either breast or ovarian cancer, particularly if one of these occurred pre-menopausally, then mutation analysis should be undertaken. In this respect it should be noted that such high-risk families may be over-represented in the development of multifocal peritoneal serous papillary carcinomas where screening with ultrasound and CA125 may not be helpful.[10] Furthermore, preliminary studies from clinics screening high-risk women with possible BRCA mutations have suggested that the use of CA125 and ultrasound have picked up fewer cancers than expected. This is supported by a report on 252 women with a family history of ovarian cancer in at least one first degree relative, where 23 patients underwent surgery with 2 advanced ovarian cancers, 1 colon cancer and 1 renal cell cancer were detected, but with no early ovarian cancers being uncovered.[11]

In contrast to the above, recent publications have supported the concept of prophylactic surgery in mutation carriers, where not only have there been reductions in the incidences of ovarian malignancies (and detection of some incidental ovarian cancers), but also a 50 percent reduction in the incidence of breast cancers in woman having undergone a prophylactic bilateral salpingo-oophorectomy.[12-15]

ENDOMETRIAL CANCER SCREENING

It is interesting to note that despite an appreciation, for more than 80 years, that women with carbohydrate metabolism abnormalities and obesity are at a significantly increased risk of the development of endometrial cancer, an exact risk profile has not been ascertained for such women, probably because no single test has proven adequate in terms of sensitivity and specificity due to the relatively infrequent nature of the disease. A recent prospective ultrasound study of over 1,000 patients has elicited only 1 case of Stage Ib endometrial cancer, with a second cancer being diagnosed 3 years after a negative screening result. The down side was that an endometrial biopsy was taken from 27% of patients. From this study it was clear that colour Doppler sonography offered little in addition to ultrasound as a screening test.[15] This study certainly corroborated the findings of Gull et al, which involved 827 post-menopausal women.[16]

Patients who are at a substantially increased risk of endometrial malignancy, such as those with mismatch repair gene defects, should undergo surveillance as their lifetime risk of developing this disease is in the order of at least 50%. There are currently no strong data to support this recommendation, but it seems a reasonable approach to offer women in the pre-menopause endometrial biopsy and transvaginal scan, together with a CA125 test, and post-menopausal, women an annual transvaginal ultrasound. This would detect an endometrial thickness of 5 mm or more, whereupon an endometrial biopsy could be undertaken.

An exact age for commencing this strategy has not yet been satisfactorily validated. There are certainly families where the disease can occur as early as the third decade of life, and most practitioners would recommend screening within 5 years of the diagnosis of the youngest index case in each family.

The exact role of screening women who are taking Tamoxifen remains controversial. The American College of Obstetricians and Gynaecologists recommends that women using Tamoxifen receive a yearly gynaecological examination, education about the risks of Tamoxifen, and encouragement to promptly report any vaginal bleeding.[17] A consensus meeting in Brussels in 1997 recommended a pre-treatment transvaginal ultrasound with a 'wait and see' policy for those

women with an endometrium thickness of less than 5 mm, with a hysteroscopy and biopsy being recommended for those with an endometrial thickness of 5 mm or more. Subsequent endometrial scans, with intervention, were to be commenced at 3 years based on the endometrial thickness. It is clear that endometrial oedema in Tamoxifen users is extremely common - up to 90% - which gives an over-estimation of the uterine lining thickness, and it now seems quite clear that hystero-ultrasonography, with installation of normal saline into the cavity, is by far the most accurate diagnostic tool.

CERVICAL CANCER SCREENING

It is quite clear that more than 95% of cases of invasive carcinoma of the cervix are associated with "high risk" HPV viruses, particularly subtypes 16, 18, 31 and 33. Because of this it has been suggested that HPV testing might be usefully introduced as a population screen. It has become obvious that about 5 - 15% of "normal" women, whose Pap smears have no abnormal cells will have HPV detected by currently available tests, and that such an approach would lead to unnecessary community anxiety and a huge demand on colposcopy services. Conversely, the combination of a negative Pap smear and a negative HPV test may allow a longer interval for screening, and such an approach has recently been adopted in the Netherlands.

Risk factors for cervical dysplasia, and cancer, include sexual activity as the predominant actor, with young age at first intercourse and multiple sexual partners, having a consistently strong association with the risk of developing dysplasia. Parity as a risk factor, independent of HPV status, is now apparent.[18] In addition to this are, cigarette smoking, with a useful profile for a "high risk" person being obvious. It is probably timely that education of young women in our community takes place about the risks of human papilloma virus infections and the benefits of barrier contraception.

It has long been recognised that women who are immuno-suppressed, such as those on transplant programmes, have a higher than average incidence of cervical dysplasia,[19] so it is important that these women undergo more frequent screening. Likewise, women who have HIV infections are also susceptible - a recent study of 375 HIV positive women[20] revealed that two-thirds were HPV positive, particularly younger, non-white women, and the overall risk of high risk types was about 35%. Such women obviously need more frequent Pap smears and colposcopic assessments.

The concept of a "high risk male" is an attractive one in that the identification of such males, with appropriate treatment, might provide an effective tool for reducing the incidence of cervical disease. Male sexual activity, HPV[21] and circumcision stati are important in this regard.[22]

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