High-risk groups and cervical cancer

Screening for cervical cancer continues to cause controversy despite its long history. In many ways the test matches up to the ideal criteria for screening proposed by Wilson and Jungner—in particular, cervical cancer has a recognisable latent stage and treatment is effective. Since, however, no control trial was done early on, how best to apply the procedure has been left to a futile debate between “evangelists” and “snails.” There is just enough in the jigsaw of information to make withdrawal of screening unethical, but insufficient for unassailable recommendations. The arguments arise principally because of the failure to distinguish decision making for individual patients (by the clinical evangelist) from decision making for communities (by the policy snails).

The decisions on the most effective use of health service resources for the benefit of the community are usually made on inadequate data. The basic principle, however, is that the policy should, firstly, benefit the community as a whole and then, secondly, the individual, implying that the goal for screening will most often be less than 100%, detection. How far less and at what cost in illness is a matter of judgment.

The size of the benefit for the community from screening for cervical cancer may be assessed from mortality. In 1963, for example, 2465 women of all ages died from cervical cancer; 2153 died in 1978. The total death rate since 1970 has shown a modest downward trend. There has been a steady reduction in mortality for women aged 45-54 and, until 1976, for women aged 35-44. In part these declines may have been a result of screening; but, with no relaxation of screening, the rates in 1977 and 1978 for the younger women rose to the 1970 levels. Mortality in women aged 25-34 has risen since 1970, but the actual numbers of deaths per year have been small: about 35 during the ’60s, rising to 93 in 1978. Between 1970 and 1976 the number of deaths in the under-25-year-olds rose from five to nine a year but the total dropped to two and one in the next two years.

The distribution of the screening effort in England, even allowing for lead time, has failed to reflect the magnitude of mortality in each age group. In 1977 (and previous years were similar) 2-5 million cytological tests were carried out, of which 24% were for women under the age of 25, in whom less than 0.5% of deaths occurred, and 53% of tests were on women aged 25-34, in whom less than 15% of deaths occurred. If resources are restricted, is this a reasonable way of spending them?

Expenditure could clearly be reduced by screening fewer women and selecting only those at high risk. Hakama and his colleagues1 5 have examined this possibility using data from the Finnish mass screening system. All Finnish women at an age of high risk (roughly between 30 and 54) are invited to screening every five years. On the first visit information is collected on the known risk factors for cervical cancer. The group of women with bleeding or with class II-V smears without positive histological results were found to make up less than 10% of the responders but accounted subsequently for 20-40% of the invasive carcinomas. Hakama et al suggested that these women might be screened selectively more often than the standard interval of five years, a recommendation which would increase the cost of the programme—in England it might mean roughly 30 000 extra smears each year if the selective screening were done every two and a half years instead of every five.

An alternative is to set an arbitrary target for detection. At the community level this might be 90% of all carcinomas. Again, Hakama et al6 have examined the Finnish data, to see whether a high-risk group could be defined which would substantially reduce the size of the group requiring screening. By applying statistical scoring methods to data on the levels of each woman’s risk factors at first screening they found that about half of those with all non-normal lesions—and of those with frankly invasive carcinoma or with dysplasia gravis or carcinoma in situ—were in the 15% of the screened population with the highest scores. Important risk factors were age, parity, cytological diagnosis, and coital and postmenopausal bleeding. Nevertheless, not until the high-risk group was defined as the 70% of the whole screened population with the highest risk scores did it include 90% of cases.

The size of the high-risk group could be substantially reduced while still maintaining a 90%, detection rate only if the risk factors were associated with relative risk of 15 or more, a very unlikely event. The conclusion must be that the concept of high-risk screening for cervical cancer does not seem valid, partly because of the penalty paid in missed cases and partly because of the effort required to determine who should be excluded.

Knop4 has calculated the frequency of screening needed to detect cervical cancer before it becomes inoperable. Making a number of assumptions, including the length of time a detectable lesion takes to become inoperable and that the cytology service could handle no more smears than currently, he then showed that by carrying out the first smear at age 35 and repeating the test roughly every five years until 80 years of age 77%, of all deaths might be prevented.

Given the mortality pattern, the experience of screening systems, the application of our limited knowledge of the natural history of cervical cancer to models for the delivery of health services, community restraint and clinical demands might best be balanced by the recommendations published three years ago in the BMJ.7 Screening should begin at 25 for women presenting for contraception, pregnancy, or venereal disease, or at 30 if they were sexually active and had not been tested. The interval between smears should be five years (three years after 35 if resources permit); and screening could cease at 70. If those recommendations were applied to every eligible woman mortality ought to decline by well over half. At present too much effort is spent in trying to detect cervical cancer in too young an age group where, even with 100% coverage and effectiveness, fewer than 10 of over 2000 deaths would be prevented.

Inhibitors of angiotensin I converting enzyme for treating hypertension

The available antihypertensive agents are not so consistently potent or free from side effects as to preclude interest in a new type of drug. Two compounds recently studied are competitive inhibitors of the enzyme responsible for converting the inactive decapeptide angiotensin I to the vasoactive octapeptide angiotensin II. One of these, the nonapeptide teprotide, is of limited clinical use because it has to be given intravenously; but the proline derivative captopril is active by mouth and can be given long term. Both teprotide and captopril lower lower plasma concentrations of angiotensin II, and this fall is sustained during prolonged treatment. Aldosterone, largely regulated by angiotensin II, is also lowered. Concurrently, components of the renin-angiotensin system proximal to the enzyme blockade—renin and angiotensin I—are increased.

The initial reduction in blood pressure from teprotide or captopril is proportional to the pretreatment plasma activity of renin. While the immediate drop in pressure is closely related to the extent of the fall in plasma angiotensin II this does not necessarily confirm a simple cause-effect mechanism. If exogenous angiotensin II is infused after administration of teprotide or captopril a higher plasma concentration of angiotensin II has to be attained than before treatment in order to restore the blood pressure to control values. Hence there are components of the antihypertensive action in addition to the effect on angiotensin II. Further evidence is provided by the lowering of blood pressure by captopril in sodium-depleted anephric patients, though the significance of this finding has been disputed. Converting enzyme is one of the enzymes which metabolise the vasodilator peptide Bradykinin, and hence inhibitors of converting enzyme might in part lower blood pressure by prolonging the survival of bradykinin. Nevertheless, whether or not these drugs do cause a rise in circulating kinins is disputed.

None of the reports excludes the possibility of an accumulation of vasoactive kinins in other tissues. Another possible component of the hypertensive effect of captopril is an increase in production of prostaglandins. Whatever the cause may be, in addition to the initial effect related directly to angiotensin II, the arterial pressure often drops slowly over the first one to three weeks.

The fall in plasma concentration of aldosterone will promote excretion of sodium, but this is partly countered by a diminution of the natriuresis related to blood pressure and by a reduction in the direct natriuretic action of angiotensin II. An initial loss of sodium has been found by some workers but not others, while long-term changes have not been detected in exchangeable sodium. The serum potassium concentration rises fairly consistently, with no doubt reflecting the fall in aldosterone; even in patients with renal impairment, however, dangerous increases have been rare. Most reports have commented on an absence of reflex tachycardia and of postural hypotension, though both have been described.

Captopril would be expected to control those forms of hypertension associated with high peripheral blood levels of renin (and hence of angiotensin II). Benefit has been seen in hypertension with renin-secreting tumour, in renal failure with hypertension resistant to haemodialysis, and in malignant hypertension. But captopril can control blood pressure not only in renovascular hypertension with high plasma renin: it is effective also in the preoperative treatment of patients with renal artery stenosis and normal renin. The pathogenic role of the renin-angiotensin system in such cases remains uncertain; nevertheless, the correction of hypertension with a drug which (among other actions) lowers plasma concentrations of angiotensin II is noteworthy. Even more interesting is the effectiveness of captopril long term in patients with essential hypertension without raised plasma renin.

When a diuretic is given alone as treatment for hypertension plasma concentrations of angiotensin II rise, limiting the hypotensive effect. In theory, therefore, there is a good case for combining captopril with diuretic treatment. In practice, this combination has been strikingly effective in patients with refractory hypertension, even in the presence of renal impairment; while the fall in aldosterone not only helps to lower the blood pressure but also limits the hypokalaemia induced by the diuretic. Hitherto, captopril has been given long term in a dose of 150 mg by mouth three times daily; administration might possibly be less frequent. Lower doses have recently been recommended by the manufacturers for patients with renal impairment; how effective these reduced doses will be in suppressing angiotensin II and controlling blood pressure remains to be seen.

A steep initial fall in arterial pressure is to be expected when an inhibitor of converting enzyme is given to a patient with very high plasma activities of renin. In these circumstances serious hypotension has been countered by giving saline; but this is an imprecise method of regulating blood pressure and may not be safe in patients with heart disease. An alternative approach, which may be of value when earlier treatment with a diuretic was unavoidable, is to give a carefully regulated infusion of angiotensin II after the captopril, so titrating blood pressure up or down as needed. Saline can then be more safely replaced and the patient’s condition stabilised under controlled conditions.

Early reports suggested that captopril was relatively free from toxic effects, those most frequently reported being rashes, fever, and myalgia. With greater experience, however, more frequent and sometimes serious adverse reactions have emerged including disturbance of taste, aphthous ulcers, leucopenia, serum sickness, and nephrotic syndrome. More recently, renal biopsy specimens from patients taking captopril and who may have neither renal symptoms nor proteinuria have shown immune-complex deposits along the glomerular basement membrane. The implications of these findings remain uncertain.

The converting enzyme inhibitors are a new and exciting group of antihypertensive agents with undoubted potency. Captopril is the only one available for oral use but it has proved to have frequent adverse effects, some serious.