KEY MESSAGES

- Pap smear screening in the Western Cape, South Africa is limited.
- The limited Pap smear screening programme reduces the risk of cervical cancer.
- The risk of cancer of the cervix declines with increasing number of smears.
- An organized screening programme might reduce incidence of cervical cancer by 70%.

References


Commentary: Case-control studies of screening should carry a health warning

AE Raffle

In 1991 George Knox published an unequivocal condemnation of misuses of case-control methods for evaluating screening.1 Noel Weiss countered some of Knox’s criticisms, arguing that carefully conducted and cautiously interpreted case-control studies may be the only option in circumstances where other evidence is unavailable.2 Whilst Weiss’s arguments are valid, Knox’s criticisms were justifiable given the poor scientific rigour of many publications that had claimed to elucidate the outcomes of screening. Faced with Hoffman et al.’s paper3 it is hard not to have a sense of déjà vu.

Not only are there theoretical concerns. Experience with nationwide quality assured programmes shows that mortality reduction achieved by ‘true life’ screening is less than predicted by randomized controlled trials (RCT), which in turn is less than...
the estimates from case-control comparisons. The breast cancer mortality reduction in women aged 55–69 attributable to the England and Wales mammographic screening programme introduced in 1989, is estimated by 1998 based on cohort specific trends, as 7%. When the service was planned the predictions from RCT evidence were far more optimistic—that breast cancer deaths in the screened age band would be reduced by ‘a third or more’. Estimates from case-control studies of breast screening are higher still. The conclusion of the authors of the Health Technology Assessment report are that ‘case control estimates of effectiveness should therefore be interpreted with extreme caution’.

A case-control study of screening takes cases who suffer the adverse outcome that screening is intended to avert, and controls drawn from the population giving rise to the cases, then compares past participation in screening amongst both groups. If screening makes a difference, by virtue of positive tests correctly identifying those destined to become cases, coupled with intervention that reduces risk of the adverse outcome, then some potential cases will have become non-cases because of participation in screening and will have switched to the control group. The screening rate amongst controls is essentially the same as that in the total population, since the number of averted cases joining the controls is too small to make any impact on the overall participation rate.

The South African study found that 50% of 524 cases of invasive cervical cancer reported prior participation in cervical screening compared with 73% of 1540 controls. The authors interpret this as showing that even the limited screening service in the Western Cape, with no quality standards or assurance processes, leads to a reduction in cervical cancer incidence of 70%. This assumption that the association between being a control and reporting past screening is explained by the efficacy of screening alone is invalid. In Weiss’s paper about maximizing the reliability of case-control studies of screening he stresses the importance of validating screening histories from records. Hoffman et al.’s study does not do this but instead depends totally on women’s recollection. The unreliability of these data is betrayed by the implausibly high 73% reported participation amongst the controls, who the authors describe as disadvantaged women. It is highly likely that women tended to report to the interviewer what they perceived as the ‘correct’ health-related behaviour. Achievement of 73% participation in cervical screening amongst disadvantaged groups in England has needed major publicity, multiple written and verbal invitations and reminders, highly accessible services, and incentive payments for providers linked to uptake rates. Weiss also stresses the importance of ascertaining all cases of advanced disease during the 6 months they were captured, and of whether fatal cases were included. These two factors alone are sufficient to raise serious doubts about the validity of this study, but there is a third concern. The difficulty of ruling out ‘healthy screenee’ bias has been repeatedly commented on. The odds ratio in a case-control comparison will be distorted if there is a relationship between an individual’s risk of an adverse outcome, and their likelihood of participating in screening. The authors attempt to remove any potential bias by matching for decade of age, urban/rural residence, race, education, parity, age at first sexual activity, use of contraceptives, and cigarette smoking. This may reduce the bias but it cannot rule it out. This healthy-screenee effect bedevils all studies that incorporate comparisons between those who self-select to participate and those who self-select not to.

In England and Wales, despite nationwide provision of cervical screening from the 1960s, it was not until the late 1980s following re-launch of the programme that a measurable and substantial fall in incidence and in cohort-specific mortality occurred. The relaunch introduced strict quality standards, lowering of thresholds for classifying and treating abnormalities, and meticulous follow-up and failsafe to ensure all identified abnormalities received treatment. This adds further weight to the conclusion that the difference between screening history recollected amongst cases and controls in the South African study is the result of weaknesses in the method and not because limited screening is uniquely effective in the Cape.

Two other factors cannot go unmentioned. First, as the UK National Screening Committee emphasizes, all screening programmes do harm, and some do good as well as harm. Poor quality screening brings harmful outcomes—anxiety for normals, iatrogenic harm from invasive investigations and treatments, and anger for those who develop disease despite screening—with little or no benefit. Second, screening is a relatively expensive form of preventive medicine because of the large numbers of tests and treatments needed. Data from Bristol, UK, show that 1000 women need to be screened for 35 years to prevent a death from cervical cancer. This needs substantial resources. In South Africa, with higher incidence, the number needed to screen to prevent a death may be less, but the positive outcome will only be achieved in a properly resourced and quality assured programme.

References