Selective screening: theory and practice based on high-risk groups of cervical cancer

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SUMMARY Using data taken from the organised mass screening system in Finland, risk indicators of cervical cancer were identified in order to define a high-risk group which could then be used for selective screening of cervical cancer. Single risk factors classified at best 39% of the cases into a high-risk group of 8%. A combination of risk factors by different statistical methods was applied, but the results were essentially the same. In order to find a high-risk group small enough to yield a reduction in costs, the number of cases originating from the low-risk group was increased. Theoretical calculations showed that for selective screening to be effective, the risk of disease in the high-risk group relative to that in the low-risk group must be greater than that implied by current knowledge of cervical cancer epidemiology. It was concluded that selective screening has only a limited applicability.

Because of the costs involved in screening programmes the screening of a disease is sometimes restricted to the high-risk groups of the population. In principle, different methods of finding a high-risk group are available. If it is the prevention or treatment of the disease which is of primary importance any cut-backs in expenditure should be viewed against the yield. The process of selection of a high-risk group for selective screening should be such that a substantial proportion of all cases of the disease in the total population is detected. The purpose of this paper is to discuss the possibilities and limitations of selective screening.

Material and methods

The experience gained from mass screenings for cervical cancer in Finland is used as an example to show the possibilities and limitations of selective screening. The general organisation of the screening programme has been described (Hakama *et al.*, 1975) and a short description only will be given here. All Finnish women are screened every five years at the age of high risk of preclinical cervical lesions. A personal letter of invitation is sent to women eligible for screening. The results of screening and follow-up are reported to the mass screening registry, which operates at the Finnish Cancer Registry.

The data were taken from screening carried out during the period 1963–71. Both attenders and non-attenders were followed up through the cancer

registry, and subsequent screenings were carried out to estimate the subsequent risk of both cervical cancer and preinvasive lesions after the first screening up to the end of 1972.

The notification card attached to the mass screening results included data on marital status, number of pregnancies, any bleeding, electrocoagulation of the cervix, and data based on the smear, such as the Papanicolaou class and occurrence of trichomonas vaginalis. Histological confirmation of the diagnosis was found either from the reports to the Finnish Cancer Registry or directly from the notification of the screening results.

The lesions confirmed at surgery or biopsy were divided into five histological groups: low-degree dysplasia, high-degree dysplasia, carcinoma in situ, microinvasive carcinoma, and frankly invasive carcinoma. This classification is subjective (Hulme *et al.*, 1968), and both high-degree dysplasia and carcinoma in situ lesions are operated on in Finland. A detailed description of the diagnostic criteria and procedures has been given (Kauraniemi, 1969).

Values for risk indicators were taken from the data on personal history or diagnostic results at the first screening. Only those with a negative smear or negative histology at first screening were accepted and all the cases were diagnosed more than four months after the first Papanicolaou smear.

The high-risk groups were originally identified by a single risk factor. Incidence rates were estimated for each high-risk group. The rates were given per

100 000 person-years and were adjusted for age to the European standard population (Doll *et al.*, 1970). Because few women outside the age group 30–54 were examined, the age-adjusted rates were based on five-year age groups within this range.

In the next step the risk factors were combined and the combination was based on a multiple discriminant function and on a successive application of conditional probabilities provided by Bayes's formula (Ledley and Lusted, 1959).

For the purposes of multivariate analyses it was impracticable to utilise all the non-malignant cases at the end of follow-up as a control group. Instead, a random sample with a ratio 1 to 400 was drawn from the normal cases for purposes of control.

Finally, the relationship between the determinants of the efficacy of the screening programme was theoretically estimated. Given the size of the high-risk group (p % of the total population) and the ratio of the risks in the high- to the low-risk group (relative risk, RR), the yield (the percentage of cases detected at screening of all cases, y) can be estimated from

$$y = \frac{RR}{RR + (100 - p)/p}$$

Results

By the end of 1972 more than 400 000 women had attended the mass screening programme and 78 000 women had been screened more than once. The size of the random sample of healthy controls used in the multivariate analyses was 1165. Table 1 shows the

Table 1 Total number of cervical lesions by diagnosis after the first Papanicolaou smear

Diagnosis	Cases	
	No.	Per 10 ⁴ person-years
Dysplasia levis	49	15
Dysplasia gravis	100	30
Carcinoma in situ	123	36
Microinvasive carcinoma	22	6
Frankly invasive carcinoma	109	8

Table 2 Incidence rates (per 10⁴ person-years) after initial screening of preinvasive and frankly invasive cervical lesions by risk indicators defined at the initial screening, and numbers detected after initial screening from the high-risk groups defined by the risk indicators

Risk factor	Incidence		No. of cases	
	Dysplasia gravis or carcinoma in situ	Frankly invasive	Dysplasia gravis or carcinoma in situ	Frankly invasive
Bloody discharge	44	4	6	4
Coital bleeding	0	46	0	8
Cytol. class IV	3878	78	11	4
Cytol. class II-V	134	15	85	42
Total	27	3	224	109

number of cases and incidence rates by different groups of malignancy.

COMBINING RISK INDICATORS

Because of the failure to detect a large proportion of all cases from the high-risk groups defined by a single risk indicator (Table 2), a combination of risk indicators was analysed.

A discriminant function score based on 14 risk indicators was estimated. The risk indicators included in the model were age, number of pregnancies, parity, continuous leucorrhoea, bloody discharge, coital bleeding, irregular bleeding, postmenopausal bleeding, electrocoagulation, uterine surgery, cytological diagnosis, colpitis, vaginal mycosis, and trichomoniasis. The analysis was carried out separately for all positive diagnoses (dysplasia levis, dysplasia gravis, carcinoma in situ, microinvasive carcinoma and invasive carcinoma) and controls, for frankly invasive cases and controls, and for cases of carcinoma in situ or dysplasia gravis (preinvasive lesions operated on in Finland) and controls. Table 3 shows the values of the estimated parameters for risk indicators with estimates significantly different from zero.

Cytological diagnosis was the most powerful single variable related to a cervical lesion; diagnoses of vaginal colpitis and mycosis were associated with a high risk of cervical cancer during the follow-up period. Of the anamnestic data, electrocoagulation was correlated with a low risk of preclinical lesions whereas coital bleeding was indicative of invasive carcinomas. The number of pregnancies or parity was associated with an increased risk of cervical cancer. The risk of cervical cancer increased with increasing age, whereas the risk of preclinical lesions decreased with increasing age.

The cumulative distributions of the discriminant function scores for cases and controls are shown in Fig. 1 and Table 4. Screening of 15% of the population would result in the detection of about 55% of both invasive and preinvasive lesions. Increasing the proportion of cases diagnosed in the high-risk group also implied an increase in the size of

Table 3 Discriminant analysis with 14 risk indicators. Estimates of significant ($P < 0.05$) coefficients for the standardised variables and correlations with the discriminant function

Variable	Discrimination between healthy controls and					
	All non-normal lesions		Frankly invasive lesions		Dysplasia gravis or carcinoma in situ	
	Coefficients	Correlations	Coefficients	Correlations	Coefficients	Correlations
Age	—	—	0.31	0.39	-0.21	-0.09
No. of pregnancies	—	—	—	—	0.24	0.27
Parity	0.23	0.35	0.19	0.36	—	—
Cytological diagnosis	0.79	0.86	0.76	0.82	0.87	0.89
Continuous leucorrhoea	—	—	—	—	—	—
Bloody discharge	—	—	—	—	—	—
Coital bleeding	—	—	0.31	0.38	—	—
Irregular bleeding	—	—	—	—	—	—
Postmenopausal bleeding	—	—	—	—	—	—
Colpitis	0.22	0.52	0.23	0.44	—	—
Vaginal mycosis	0.22	0.40	—	—	0.33	0.36
Trichomoniasis	—	—	—	—	—	—
Electrocoagulation	-0.25	-0.28	—	—	-0.22	-0.23
Hysterectomy	-0.17	-0.15	-0.16	-0.10	-0.11	-0.13

Table 4 The proportion (%) of cases diagnosed from the high-risk group by size of group, malignancy of lesion, and method of defining the high-risk group

Diagnostic group	Method of defining high-risk group	Size of high-risk group						
		8%	15%	25%	30%	55%	65%	70%
All non-normal lesions	Cytol. class II-V	36	—	—	—	—	—	—
	Bayes's probabilities	42	50	57	61	84	90	93
	Discriminant function	43	56	60	63	78	84	88
Frankly invasive cases	Cytol. class II-V	39	—	—	—	—	—	—
	Bayes's probabilities	42	55	64	67	83	88	91
	Discriminant function	45	55	67	69	89	93	96
Dysplasia gravis and carcinoma in situ	Cytol. class II-V	38	—	—	—	—	—	—
	Bayes's probabilities	36	49	59	65	85	91	93
	Discriminant function	44	54	64	68	86	90	92

the high-risk group. Application of Bayes's probabilities gave essentially similar results (Fig. 2, Table 4).

GENERAL EVALUATION

Table 5 shows the relationship between the proportion to be screened (size of the high-risk group), the proportion of cases found in the high-risk group, and the relative risk of cervical cancer in the high-risk group in terms of unit risk in the low-risk group.

If more than half of the cervical cancer cases are to be diagnosed from the high-risk group of 10% of the total population, a relative risk of more than 10 has to be assumed. On the other hand, with a relative risk of 10 and a yield of 90%, about 50% of the population were assumed to belong to the high-risk group. Detecting almost every case (for example, 90%) of cervical lesions in the high-risk group implies a very

high risk of the disease if any reduction is to be obtained in the costs of the screening programme.

Discussion

In principle, the screening of those with a high risk of disease only is recommended because of the reduction in cost, or because this helps to avoid the adverse effects of screening. Successful selective screening is based on the assumption that there is a subpopulation with a high risk of the disease and that these people can be identified. Furthermore, the subpopulation should be small enough to make the cost of the programme less than that for unselective screening. Finally, the screening programme should be designed to yield a large proportion of all cancers present in the total population—that is, few cases should be found in low-risk groups not subjected to selective screening. Thus, the definition of a high-risk

Table 5 Proportion of cases diagnosed from the high-risk group by size of group and risk of disease in the high-risk group relative to that in the low-risk group (relative risk)

Size of high-risk group (%)	Relative risk							
	1	2	5	10	20	50	100	1000
1	0.01	0.02	0.05	0.09	0.17	0.34	0.50	0.91
5	0.05	0.10	0.21	0.26	0.51	0.72	0.84	0.98
10	0.10	0.18	0.36	0.53	0.69	0.88	0.92	0.99
20	0.20	0.33	0.56	0.71	0.83	0.93	0.96	1.00
50	0.50	0.67	0.83	0.91	0.95	0.98	0.99	1.00
70	0.70	0.82	0.92	0.96	0.98	0.99	1.00	1.00
90	0.90	0.95	0.98	0.99	0.99	1.00	1.00	1.00

group for the purposes of selective screening should take into account not only a group with a high incidence of the disease, but also the size of the group; in other words, the reduction in cost, and the proportion of cases originating in the high-risk group, that is, the yield, should be considered.

Population groups with a high incidence of cervical cancer were identified from those attending the organised mass screening programme for cervical cancer in Finland. The high-risk groups were small enough to yield a substantial reduction in the population to be screened. However, a large proportion of cancer patients originated from the low-risk population.

An attempt was made to improve the power of selective screening by combining the risk indicators. The methods used have two advantages. Firstly, the size of the high-risk group can be continuously

changed by changing the cut-off point of the discriminant or probability score, which classifies the cases and controls into those with a positive diagnosis (indicating a cervical lesion) and those with a negative diagnosis (indicating normal women). Together with the increase in the proportion to be screened, the number of cases found also increased. This allows several alternative combinations of specificity and sensitivity. Secondly, it may be assumed that different risk indicators take into account different aspects of the aetiology of the disease, thus better characterising the patients. Combining the risk indicators may provide better coverage of the aetiology, and thus a large proportion of cases may be detected in the high-risk group.

It appeared, however, that discriminant analysis with 14 independent variables representing fertility symptoms, and cytological diagnosis did not

Fig. 1 Cumulative distribution of discriminant function scores for cases of frankly invasive cervical cancer and controls.

Fig. 2 Cumulative distribution of Bayes's probabilities for cases of frankly invasive cervical cancer and controls.

characterise the high-risk group essentially better than analysis based on a single risk indicator. Because the discriminant analysis assumes risk indicators to be continuous and preferably normally distributed (Anderson, 1964) Bayes's method, which was based on the assumption of statistical independency of the risk indicators, was also applied (Ledley and Lusted, 1959).

Depending on the method and the lesion, the maximum difference between the estimated specificity and false negative rate was found when 15–30% of the total population belonged to the high-risk group. The difference between specificity and false negative rate was 42% or less and it was less dependent on the selection of the cut-off point when Bayes's probabilities were used than when the discriminant function score was utilised.

The conclusion based on all the different approaches was essentially the same. If the population to be screened was considerably reduced, then a substantial proportion of cases was found in the low-risk group. Similar results were found for screening for breast cancer (Shapiro *et al.*, 1973; Farewell, 1977; Soini and Hakama, 1978). General calculations showed that in order to find 90% of the cases of disease in a high-risk population of 10%, the risk in the high-risk group should be almost 100 times higher than in the low-risk group. According to the present epidemiological evidence no such risk indicators have been identified for cervical cancer. Both multivariate methods defined a 5- to 10-fold risk of cervical lesion in the high-risk group, irrespective of the cut-off point.

On the other hand, the small correlation between the risk of the disease and screening activities may be due to a low attendance rate and a high risk of the disease among the non-attenders. If only every second woman attends the programme and the relative risk is two for the non-attenders in terms of unit risk for attenders, and if screening prevents every second clinical case of the disease, then the reduction in the risk of disease in the total population is about 17%. This low figure is in contrast with the effect of 50% and it may be difficult to detect in the presence of random effects.

The risk indicators were associated with fertility (number of pregnancies, parity, marital status), signs and symptoms (leucorrhoea, bleeding symptoms), interventions (hysterectomy, electrocoagulation), other diseases (trichomoniasis, vaginal mycosis) or other characteristics of cytological diagnosis (colpitis, Papanicolaou class). Because the risk factors considered in this study relate to most of the known aetiological factors for cervical cancer it is likely that a proportion of cases with cervical cancer are

diagnosed from a group without any high-risk characteristics.

On the basis of the present empirical experience and theoretical calculations it seems unlikely that powerful methods of selective screening will be found in the immediate future. Selective screening is likely to be applicable only in situations where obtaining a screening diagnosis may produce adverse effects, such as radiation hazards in mammography, or when the cost of the unselective screening programme is too high.

The present results imply that the decision whether to introduce a screening programme is usually between to organise an unselective programme (within reasonable age limits) or not to organise a screening programme at all. If the efficacy of an established programme is to be increased, better results are likely to be obtained by improving the attendance rate, or sometimes by affecting the time interval between the screenings (Hakama and Pukkala, 1977), than by limiting the activities to the high-risk groups of the disease.

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