Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies

IARC WORKING GROUP ON EVALUATION OF CERVICAL CANCER SCREENING PROGRAMMES

Abstract

A collaborative study of screening programmes in eight countries was performed to estimate the risks of cervical cancer associated with different screening policies. Most of the data came from centrally organised screening programmes. Relative protection was higher in women who had had two or more negative results of screening tests than in those who had had only one negative smear, particularly in the first five years after the last test. There was little difference in the protection afforded by screening every year compared with every three years, but screening only once every five or 10 years offered appreciably less protection. The age of the women did not affect the sensitivity of the test or the sojourn time of the disease (the length of the detectable preclinical phase during which abnormal cytology could be picked up if a smear were taken); invasive cancer in women under 25 was rare. Centrally organised screening programmes were more effective than uncoordinated screening.

Screening programmes should be aimed principally at women aged 35-60 but should start some years before the age of 35, and the intervals between screening should be three years or less.

Introduction

Well organised screening programmes can substantially reduce mortality from cervical cancer and the incidence of invasive disease in the target populations. Much of the evidence for this comes from studies comparing the incidence rates of cervical cancer in a given area before and after the rapid introduction of screening, or between areas with different intensities of screening. Few data have been available, however, on the effect of different screening patterns on individual women at risk. These data would be required to compare screening strategies quantitatively. Despite this several organisations have recommended various screening policies,[1-4] and parts of Europe and north America have operated screening programmes for 20 years or more. In the absence of controlled trials to evaluate different screening policies the data accumulated by these programmes are a valuable source of information.

A collaborative study has been conducted under the aegis of the International Agency for Research on Cancer to estimate the risks of invasive cervical cancer associated with different screening histories. Data were obtained from the medical records—mainly those from organised screening programmes. The material on which this paper is based comes from the programmes in Aberdeen, north east Scotland[5-7]; British Columbia, Canada[8,9]; Iceland[10-12]; Manitoba, Canada[13]; Maribo county, Denmark[14-16]; Ostfold county, Norway[17-19]; and Sweden[20,21]; and from case-control studies conducted in Geneva, Switzerland[22]; Milan, Italy[23]; and Toronto, Canada.[24] The results of the collaborative study will be published in detail elsewhere.[25] Although a common approach was used in summarising the results from the different centres, certain disparities in definition, especially of a negative result of a screening test, were inevitable.

The aim of screening for cervical cancer is to identify and treat preinvasive lesions, thus preventing the progression to invasive cancer. The question of whom to screen is a question of whom to invite initially for screening, and how often to screen those with only negative test results. Apart from the problem of ensuring that a high proportion of those targeted for screening are actually screened there are two major questions to be considered. Firstly, how often to screen women who have either not been screened before or have no history of positive results of screening tests in the past, and secondly, how to treat women in whom suspicious or positive results are obtained. This study concentrated on the first of these issues and tried to estimate the risk of invasive cervical cancer among women who had had one or more negative results and how their risk of developing invasive cancer was related to the time elapsed since the last negative result and the number of previous negative results. Different screening strategies were compared to assess the reduction in risk of invasive disease that each strategy might be expected to produce. The lifetime risk associated with a particular screening pattern is given by the cumulative incidence of invasive disease between screenings together with the risks that accumulate before the age scheduled for the first screening test and after that scheduled for the last screening test.

Immediately after a single negative result the incidence of clinical cancer reflects the sensitivity of the test—that is, sensitivity is derived from the number of false negative results. As time elapses after the test the incidence of cancer will increase, reflecting the development of de novo cancers. After a series of negative test results within a relatively short interval most false negatives should have been removed, and the incidence will be due almost entirely to de novo cancers. The evolving incidence curve is then simply the rate at which cases that were not detectable when last screened start occurring in a screened population. In effect, this curve describes the cumulative distribution function of the duration of the detectable preclinical phase, which can be estimated from either cohort[26] or case-control studies.[27] The duration of the detectable preclinical phase is the period during which abnormal cytology would be detectable if a smear were taken and is known as the sojourn time.[26]

In this study the incidence of invasive cervical cancer after a series of negative test results was estimated by identifying all cases occurring in a defined population and relating their screening history to the corresponding denominators derived from the whole

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population. The results were expressed as the ratio of incidence rates corresponding to different screening histories. Because exfoliative cytology is aimed principally at detecting precursors of squamous cervical cancer attention was confined to the incidence of squamous tumours.

Method

Several centres in Europe and Canada collaborated. The data came from areas with centralised cervical cytology screening programmes where most smears passed through one laboratory (Aberdeen, British Columbia, Iceland, Maribo county, Manitoba, and Ostfold county); areas with a centralised programme that was responsible for only a fraction of the screening (Sweden); areas where screening was not centrally organised but where all smears were evaluated by a single central laboratory (Geneva); and areas where most screening was performed in private practice, with several cytopathology laboratories responsible for cytological evaluation so that screening histories had to be obtained from many sources (Toronto and Milan).

Considerable attention was paid to the definition of a negative result of a screening test. Operationally, a negative test result is one that does not lead to any further action, but the cytological criteria used for deciding that further action was not required depended partly on how the screening programme was organised—for instance, whether it was possible to repeat the screening of women yielding doubtful results within a few months. The definitions of negative and positive smears finally adopted were based on the original Papanicolaou classification rather than on more recent classifications, as 20 years or more are covered by this study. A negative smear was thus one reported as being: (*a*) class I (normal); (*b*) class II (atypical) followed by a class I smear; or (*c*) class II followed by a class II smear within 10 months, followed by a class I smear.

A positive smear was one reported as being: (*a*) class III (suspicious), IV, or V; (*b*) class II followed by a smear of class III or worse; (*c*) class II followed by histological proof of dysplasia or a more advanced lesion; (*d*) class II followed by a class II smear after more than 10 months; or (*e*) three consecutive class II smears, irrespective of the time interval.

These definitions were adapted from those used in the cohort study in British Columbia[9] and were agreed on at the first meeting of the investigators in December 1979 in Copenhagen. Some centres, however, used the basic operational definition and only considered a test result to be negative if it did not lead to any further action.

Table I shows the material included in the study, the study designs from the various centres, and indicates that most of the data came from the screening records of centrally organised programmes. Two approaches were adopted—namely, cohort and case-control. In the cohort studies all women entering the screening programme were identified, and those with an initial negative smear were followed up. Cases of invasive cervical cancer, often identified through the appropriate cancer registry, were recorded and incidence rates calculated in relation to age, time elapsed since the last negative smear, and the number of previous negative smears. In the case-control studies, originally used in areas without a centralised screening programme, cases of invasive cervical cancer were ascertained, several controls were selected for each case and the screening history of the women up to the time of diagnosis of the case in each case-control set was determined. Age was used for matching in each study, but additional matching criteria were used in some centres (table I). Relative risks were calculated from the time elapsed since the last negative smear and from the number of previous negative smears.

During the study it became apparent that even in areas with a centralised screening programme the approach used by case-control studies provided a concise method of summarising the results. It also had the advantages that it did not require the entire screening records to be computerised (provided that they existed in a form that permitted rigorous sampling) and that updating the results entailed simply adding new case-control sets and not completely recalculating the tables of woman years at risk. This type of approach was, therefore, also adopted for Iceland and north east Scotland, where the complete screening records were available for all women.

The results from Aberdeen have been reported separately,[7] and a detailed description of the methods is given there. The methods used in Iceland in the present study are similar to those used in Aberdeen. Briefly, the two studies were confined to women who were listed in the records of the respective screening programmes. Controls for cases arising spontaneously were chosen from among women who were resident in the population when the case was diagnosed and who had been previously screened. Controls for

TABLE I—*Study designs of participating centres*

Area	Extent of centrally organised screening programme	Year started	Population covered	No of women screened	Records computerised	Type of study	Years of diagnosis of cases	No and source of invasive squamous cancer cases	Choice of control or comparison group	Source of information on screening history
Toronto, Canada	None	—	—	—	No	Case-control. Institution based	1973-76	156, diagnosed between 1/10/73 and 30/9/76 at Princess Margaret Hospital, Toronto	Five per case. Matched for age (±10 years), place of residence, and type of dwelling	Interview of cases and controls. Treating physician
Iceland	One central screening clinic and cytopathology lab. Women recalled every 2-3 years with personal invitation	1964	Icelandic citizens; women aged 25-70 (25-59 until 1969)	c 50 000	Yes	Case-control within a cohort	1969-84	101 cases from the Iceland cancer registry who appeared in the screening programme records	Five per case. Matched for age (±5 years). Appeared in screening records before date of diagnosis of matched case	Records of screening programme
Aberdeen, Scotland	One central cytopathology lab. Screening reminders sent to women and their family doctors	1959	Women aged 25+ in the Grampian region, NE Scotland	c 200 000	1 in 10 sample between 1960-80. All records since 1980	Case-control within a cohort	1968-83	85 cases from the Grampian cervical cancer register who appeared in screening records	Five per case. Matched for age (±5 years). Appeared in screening records before date of diagnosis of matched case	Records of screening programme
Geneva, Switzerland	Central cytopathology lab. No organised screening	1970	Geneva residents	—	Cytology records computerised	Case-control. Population based	1970-76	186 cases from the Geneva cervical cancer registry	One per case. Geneva residents chosen from population lists. Matched for age (±5 years), origin (Swiss or not), and marital status	Records of cytopathology laboratory
Milan, Italy	None	1968	—	c 150 000	No	Case-control. Population based case series—hospital controls	1978	121 cases newly diagnosed from resident Milan population 1978	Three per case. Milan residents admitted to hospital in same year matched for age and hospital	Linkage to records of the six main cytology laboratories covering over 95% of all smears
Sweden	Centralised cytopathology. Individual letters of invitation	1967	Increasing number of Swedish counties 1967-73, women aged 30+	930 127	Computer file for years 1967-75	Cohort	1967-80	446 cases appearing in Swedish cancer registry after negative result of screening test	Situation before screening was widespread	Records of mass screening programme
Maribo county, Denmark	Central cytopathology lab. Individual letters of invitation	1967	Maribo county residents, women born 1918-52	29 452	Yes	Cohort	1966-82	53 cases from screening programme computer records and cancer registry	Situation before screening was widespread in Maribo and surrounding counties	Records of screening programme and all privately taken smears
Ostfold county, Norway	Central cytopathology lab. Individual letters of invitation	1959	Ostfold county residents aged 25-59	38 546	Yes	Cohort	1959-82	79 cases from national cancer registry	Seven surrounding counties	Records of screening programme
British Columbia,* Canada	Central cytopathology lab	1949 as diagnostic service, late 1950s as mass screening programme	British Columbia residents born 1914-18 and 1929-33	121 806	Yes*	Cohort	-1969	68 cases from screening file of women with negative result of screening test	Unscreened part of the population	Records of screening programme
Manitoba, Canada	Central registry of cytology	1963-74	All adult women	335 220	Yes	Cohort	1963-74	86 cases appearing in Manitoba cancer registry after negative result of screening test	Situation before screening was widespread	Records of screening programme

*Cohort study described by Boyes *et al* (1982). Computerised records were available only until 1969.

TABLE II—*Relative protection against cervical cancer by time elapsed since last negative smear (figures in parentheses are No of women with cervical cancer)*

Months since last negative smear	Aberdeen	Iceland	Sweden	British Columbia	Manitoba	Ostfold county	Maribo county	Toronto	Geneva	Milan
				(i) *After one previous negative smear*						
0-11	*	*	14·5 (17)	2·5 (10)	3·6 (15)	12·2 (1)	*	1·7 (7)	8·3 (2)	3·6 (1)
12-23	*	4·9 (1)	6·7 (37)	2·1 (10)	4·0 (10)	1·7 (7)	3·2 (2)	1·8 (5)	2·0 (5)	2·8 (1)
24-35	5·7 (2)	1·7 (6)	5·7 (43)	7·5 (2)	14·5 (2)	0·5 (12)	2·0 (3)	2·7 (2)		0·6 (5)
35-47	3·5 (2)	1·1 (5)	4·6 (51)	5·8 (2)	3·7 (6)	0·8 (5)	2·7 (2)	0·2 (3)	3·1 (6)	1·0 (2)
48-59	2·5 (13)	1·3 (13)	3·4 (56)			4·0 (1)		2·3 (1)		
60-71				1·9 (12)		0·9 (4)	1·7 (10)			1·3 (4)
72-119	1·6 (7)	2·6 (5)				2·1 (41)		1·4 (4)	2·1 (4)	
120+	1·3 (13)	0·6 (12)				0·7 (16)				
Never screened	1·0 (26)	1·0 (42)	1·0	1·0	1·0	1·0		1·0 (117)	1·0 (150)	1·0 (100)
				(ii) *After two or more previous negative smears*						
0-11	*	9·6 (2)	*	8·8 (7)	9·6 (13)	23·7† (1)	8·5§(2)	10·0 (4)	5·5 (7)	11·1 (1)
12-23	10·9 (2)	11·3 (3)	18·7 (3)	4·6 (7)	19·6 (3)	7·6† (3)	7·1§ (2)	8·1 (2)	5·5 (3)	*
24-35	7·0 (3)	8·1 (4)	8·2 (7)	14·1 (1)	14·1 (2)	5·4† (4)	2·1§ (5)	1·8 (3)		2·4 (1)
36-47	3·5 (6)	10·3 (3)	4·5 (2)	3·9 (2)	8·5 (2)	2·2† (8)	3·4§ (2)	3·6 (1)	1·9 (6)	2·0 (1)
48-59	8·0 (5)	4·6 (7)	2·9 (10)	1·6 (3)				0·5 (4)		
60-71						3·3† (10)	2·9§ (5)			0·4 (2)
72-119	1·7 (3)	1·5 (3)		1·6 (5)				0·4 (3)	1·6 (2)	
120+	1·7 (3)	0·4 (4)				0·8† (3)				
Never screened	1·0 (26)	1·0 (42)	1·0	1·0	1·0	1·0		1·0 (117)	1·0 (150)	1·0 (100)

*Relative protections not estimated as no cases were observed.
†Data for three or more negative smears.
§Data for two to four negative smears.

TABLE III—*Geometric mean relative protection against cervical cancer in women with two or more previously negative smears participating in centrally organised screening programmes*

Months since last negative smear	Relative protection (No of cases)	95% Confidence limits
0-11	15·3 (25)	10·0 to 22·6
12-23	11·9 (23)	7·5 to 18·3
24-35	8·0 (25)	5·2 to 11·8
36-47	5·3 (30)	3·6 to 7·6
48-59	2·8 (30)	1·9 to 4·0
60-71	3·6 (16)	2·1 to 5·9
72-119	1·6 (6)	0·6 to 3·5
120+	0·8* (7)	0·3 to 1·6
Never screened	1·0	

*Based on figures from Aberdeen and Iceland only.

contact increased; these results were therefore truncated four years after last contact. In the three case-control studies in the other centres selection biases (equivalent to losses during follow up) were considered to be small.[22-24]

For comparison the final tabulations of the results from each centre were given as the inverse of the relative risk, the so called relative protection. Where appropriate, statistical methods for matched case-control studies were used, the program PECAN being used for matched regression analyses.[28] The results given refer explicitly to squamous cancers.

Results

The main results were for women aged 35-64, as little screening of women over 65 took place and only a small proportion of cases occurred in women under 35. This younger group was considered separately to determine

TABLE IV—*Relative protection* (No of cases) against cervical cancer in women under 35 years in Sweden, British Columbia, and Manitoba after one or more negative screening tests*

	Years since last negative smear								
	<1	1<2	2<3	3<4	4<5	5<6	6<7	7<8	≥8
One previous negative smear	11·7 (9)	4·9 (18)	4·9 (16)	2·5 (29)	2·7 (18)	1·7 (16)	2·1 (9)	1·2 (10)	1·50 (5)
Two or more previous negative smears	16·8 (4)	10·9 (3)	10·6 (2)	3·8 (4)	2·3 (5)				

*Assuming an incidence of $20/10^5$ in unscreened women. Most woman years refer to the age group 30-34, and incidences have been taken from *Cancer Incidence in Five Continents* Vols II and III.

cases detected by screening were chosen from among women screened and classed as normal within three months of the case being diagnosed (as for these cases the ratio of prevalence rates was being estimated).

At each centre the resulting rates or relative risks were compared with the incidence rate in a comparable unscreened population to determine the decreased risk associated with a particular screening history. The choice of a comparable unscreened population varied among the centres. Table I indicates the groups used for comparison in the cohort studies in British Columbia, Manitoba, Maribo county, Ostfold county, and Sweden. For the case-control studies from Geneva, Milan, and Toronto the baseline category comprised those women who had never been screened. For the studies in Aberdeen and Iceland, in which the populations under study were all women who appeared at least once in the records of the screening clinic, there were two series of cases (those detected by screening and those diagnosed clinically) with corresponding controls. The baseline category was taken to be those women in the first of these series who had never previously been screened.

Losses during follow up were small in Iceland, Denmark, Norway, and Sweden, due to the completeness of national coverage, and in Aberdeen[7] and British Columbia,[9] where specific measures were taken to reduce such losses. Only in Manitoba might losses have become appreciable as time since last whether there was a substantially greater proportion of fast growing cancers among younger women.

Table II summarises the results for women aged 35-64 who had (*i*) one negative smear and (*ii*) two or more negative smears. Two features are noteworthy. Firstly, the heterogeneity among centres was considerably greater in the results shown in table II (*i*) than in those shown in table II (*ii*). Secondly, table II (*ii*) the results from areas with centrally organised programmes were similar, the differences being no greater than could be attributed to sampling variation, but were in contrast with the three studies from areas with no centralised mass screening programme. In these three studies the relative protections tended to be substantially lower, especially two or more years after the last negative smear.

The protection given by one negative smear is influenced largely by the sensitivity of the screening test, especially in the first two or three years after the negative smear. In the results in table II (*ii*), however, the effect of false negatives should have been largely removed by the repeat screening. The values in the first few years after the last negative screen were appreciably higher in table II (*ii*) than in table II (*i*) for most centres. The decreasing protection with time since the last negative smear reflects the increasing incidence of cases whose precursor lesions became detectable only after the last screen. Thus the data in table II (*ii*) indicate the protection given against

the development of new invasive cancers and are relevant to those women who have already entered a screening programme.

Table III summarises the values given in table II (*ii*) for the centres with centrally organised screening programmes as the weighted geometric mean—that is, the arithmetic mean of the logarithm weighted by the respective person years, estimated for the case-control studies—together with the number of cases on which each value is based and the 95% confidence intervals. For the first year after a negative screen, for which some infinite values appear in table II, an average incidence was calculated from the sums of the numerators and the denominators and divided by an average baseline incidence to give the pooled value for relative risk.

The relative protection remained high for the first three years after the last negative smear and then declined steadily towards the null value of unity. Even six to nine years afterwards, however, substantial protection was probably still achieved, which is consistent with the generally accepted concept that many dysplastic and in situ lesions remain preinvasive for at least 10 years. More than 10 years after a negative smear the data were sparse but suggested that little if any protective effect remained.

Table IV gives the results for women aged under 35, mainly for the age group 30-34. The results are very similar to those shown in tables II and III.

Discussion

To draw conclusions from studies of cervical screening performed in eight different countries with widely varying approaches to early detection by mass screening and contrasting study designs and dissimilar approaches to ascertaining screening histories requires caution. But the disparate nature of the sources of information does strengthen any common conclusions.

Most previous work estimating the variables of the clinical course of lesions that are precursors of invasive cervical cancer has been based largely on the prevalence of in situ and other preinvasive lesions at first and subsequent screenings. Because it is uncertain what proportion of these lesions would progress to invasive cancer in the absence of screening, and whether this proportion is the same at the first and subsequent screening tests, it is unclear how applicable these estimates are to precursors of the invasive disease. It is the clinical course of precursor lesions that do lead to invasive cancer that should affect decisions on screening policies. As the emphasis in this study has been on the interval between negative results of screening tests and the development of invasive disease, inferences concerning the sojourn time apply only to those lesions that will become invasive.

The results in table II (*i*), which give the relative protection after a single negative smear, are the primary source of information on false negative rates, and those in table II (*ii*), the relative protection after two or more negative smears, are the primary source of information on the distribution of the sojourn time of precursor lesions. A striking feature is the considerably greater heterogeneity seen among centres in table II (*i*) than in table II (*ii*) particularly in the first two or three years after screening. The inference is that the sojourn time distribution varies little from one centre to another and is a basic component of a common process of development of disease, whereas the sensitivity of screening depends on how each programme is conducted and varies appreciably. This variation may derive from the cytological classification used, the definition of a negative test, the way in which doubtful smears are handled, and the different methods of taking smears in the different regions. It would also be surprising if, between the early 1960s and the early 1980s, cytological techniques for both taking and interpreting smears had not improved.

The comparison between the results in table II (*i*) and table II (*ii*) shows, as expected, that women derive considerably greater protection from two or more negative smears than from one alone, particularly in the first five years afterwards. For some centres—for example, British Columbia and Manitoba—the difference is consistent with a squaring of the false negative rate, suggesting that the first and second tests are independent. Thus for British Columbia table II indicates that, with a relative protection of about 2·5, the incidence of cervical cancer in women in group (*i*) in the first two years is some 40% of that in unscreened women, suggesting a false negative rate of about 40%. After two independent tests only 16% of lesions would be negative on both occasions, giving a relative protection of 6·25, which is close to the value for group (*ii*).

We found that age did not affect appreciably either the sensitivity of cytological screening or the distribution of the sojourn time of the disease. In particular, there was no evidence that younger women (under 35) were more at risk of developing fast growing tumours. The detailed results do not indicate that sensitivity is appreciably lower in older women (over 50), at least up to the age of 65, beyond which the data are sparse.[25] Although the follow up at some centres ended before the recent increase in cervical cancer among young women became evident, other centres (Aberdeen, Iceland, Maribo, and Ostfold) continued follow up until the end of 1982 or later.

In interpreting these results two other issues must be considered. Firstly, other variables might have influenced the results. Most of the studies reported were based solely on the records of the respective screening programmes so information on, for example, sexual history or socioeconomic state was not available. It is unlikely, however, that any appreciable effect may be attributed to unrecorded confounding variables. The relative protection observed is much larger than that normally associated with confounding, and the "dose-response" curve—that is, the decreased protection as years elapse—would require a very strong association, in women who had been screened, between the time elapsed since the last smear and the hypothesised risk factors for it to be substantially flattened. In addition, in studies where such information was available adjustment by variables relating to sexual experience or socioeconomic factors had little effect.[24 29 30] Berrino *et al* showed that there was no relation between screening history and sexual variables.[23] Furthermore, all the studies shown in tables III-VII were based on the records of screening clinics and so refer to women who had presented for screening at least once. The high risk women, who had never presented for screening, were therefore not included.

Secondly, some of the invasive tumours on which the results are based were asymptomatic and detected by screening. In the studies in Aberdeen and Iceland these cases formed a substantial proportion of the case series, and controls were chosen accordingly from women who were screened and found to be negative when the case was detected. In other studies where information on the clinical stage of the tumour was available only a small proportion of cases were preclinical or occult. The inclusion of asymptomatic cases, however, should if anything reduce estimates of the duration of the sojourn time because for these cases more time elapses before they become clinical. Their inclusion, therefore, would mean that the values in table III would be based on underestimates of the duration of the full preclinical phase.

The results given here may be compared with those reported in two case-control studies recently published from Milan[29] and Cali, Colombia.[30] In the Milan study the adjusted relative protection for an interval of less than three years was 8·33 after the exclusion of positive smears and adjustments for age, socioeconomic state, sexual history, oral contraceptive use, and other medical history. In the Cali study an estimate of 9·9 was obtained by comparing women who had been screened with those who had never been screened. Although not explicitly stated, most of the smears on which this estimate was based were taken within three years of cancer being diagnosed or the corresponding time point for controls. These results are clearly similar to those given in table II.

IMPLICATION OF THE RESULTS FOR SCREENING POLICIES

The results in table III suggest that the same relative protection is given by the cytological smear whatever the underlying incidence of the disease. Participating centres were not in countries with particularly high incidences, such as parts of Latin America, or countries with particularly low incidences, such as Spain or Israel, but the results may be taken as a starting point.

The success of different screening policies can be assessed from their effect on the cumulative rate of cervical cancer. For example, if the cumulative rate among unscreened women in a given five year period is given by CR(5), with roughly constant incidence during

this period, then among women who had a second negative smear at the start of the period the cumulative rate from the figures in table III would be

$$CR(5)\left(\frac{1}{15{\cdot}3}+\frac{1}{11{\cdot}9}+\frac{1}{8{\cdot}0}+\frac{1}{5{\cdot}3}+\frac{1}{2{\cdot}8}\right)\Big/ 5=0{\cdot}16\ CR(5).$$

Table V gives the percentage reduction in the cumulative rate among women aged 35-64 who were screened at differing time intervals and who had a second negative smear at the age of 35. In many countries the incidence of cervical cancer remained at a plateau in this age range.

TABLE V—*% Reduction in cumulative rate of invasive cervical cancer in women aged 35-64 with different frequencies of screening*

Interval between screening (years)	% Reduction in cumulative incidence	No of tests
1	93·5	30
2	92·5	15
3	90·8	10
5	83·6	6
10	64·1	3

*Assuming that a woman is screened at age 35 and that she had also had at least one screen previously.

TABLE VI—*Incidence of cervial cancer in women who have not been screened*

Age group (years)	20-24	25-29	30-34	35-64
Incidence=	$1/10^5$	$15/10^5$	$25/10^5$	$45/10^5$

not take non-compliance into account. If the incidences are different from those in table VI but in the same proportion the proportional reduction in risk, or cumulative incidence, will remain the same. There would have to be major discrepancies between the proportional values in table VI and the real values before the relative reduction in risk suggested by table VII would be seriously wrong.

Thirdly, the incidences in table VI are based on those from Norway (volumes III and IV of *Cancer Incidence in Five Continents*), a population which at that time would have had incidence rates apparently little affected by screening.[31] The percentage reduction in risk is little altered by replacing the incidence rates with those from other populations, either high risk such as in Cali, Colombia, or low risk such as in Spain. The absolute reduction in risk and the number of cases prevented/10^5 tests depend on the underlying incidence in the population.

Fourthly, the incidence for those under 30 in table VI has been increased to allow for the recent increase in cervical cancer among the young. Because screening every five years rather than every three reduces the protection appreciably, starting screening at age 35 is considerably less effective than starting at age 25, which is marginally less effective than starting at age 20. Repeating the first screening test is of only slight benefit.

CONCLUSIONS

The results given in table VI reinforce the point that the aim of screening is to prevent invasive cervical cancer, not simply to detect preinvasive lesions. The greatest protection against a lesion surfacing as a clinical cancer is provided by taking a smear in the years immediately preceding the date at which it would otherwise appear. Screening should thus be aimed at the age groups in which cervical cancer is common and start a few years before the incidence becomes appreciable. Invasive cancer is exceedingly rare in women aged less than 25. After this the incidence increases until a plateau is reached, either at age 35-40 in populations of moderate incidence or some 10 years later in populations of high incidence. The plateau continues until age 60 or over, after which some decline may occur. Regular screening of women aged 35-60 should therefore form the core of organised screening. In contrast, frequent screening of the age group 18-25 floods the cytology and treatment facilities with numerous possible precursor lesions—many of which would probably regress. This causes undue anxiety among the women affected and has little effect on the overall morbidity from cervical cancer.

The two specific aspects of mass screening for cervical cancer discussed here—namely, how often and at what age women with no evidence of cytological abnormalities should be screened—have been the subject of much debate, but attention should not be diverted from the two major determinants of a screening programme's success—that is, proper clinical follow up of abnormal cytological findings and a high rate of compliance.

TABLE VII—*Effect of different screening policies on incidence rates of cervical cancer in women aged 20-64*

Screening programme	Cumulative rate/10^5 women	% Reduction in incidence	No of tests	No of cases prevented/10^5 tests
No screening	1575			
Screening every five years:				
Ages 20-64	258·6	84	9	146
Ages 25-64	287·8	82	8	161
Ages 35-64	480·9	70	6	182
Screening every year ages 20-34, then every five years ages 35-64	233·4	85	21	64
Screening at ages 25, 26, and 30, then every five years	275·4	83	9	144
Screening every three years:				
Ages 20-64	138·9	91	15	96
Ages 25-64	161·8	90	13	109
Ages 35-64	354·9	78	10	122
Screening every year ages 20-34, then every three years ages 35-64	132·0	92	25	59
Screening at ages 25, 26, and 29, then every three years	157·4	90	14	101
Screening every year ages 20-64	105·2	93	45	33

Several comments on these results can be made. Firstly, little is gained by screening every year rather than every two or even every three years. Screening every five years also offers a high degree of protection but appreciably less than that given by screening every three years. Screening every 10 years—not a policy recommended in any country with adequate resources but of interest in areas where resources are scarce—is still associated with a reduced risk of nearly two thirds. In the context of public health this reduction should be compared with that achieved by screening 30% of the population every three years, an approach that screens the same number of women each year but reduces the incidence rate by less than 30%.

Secondly, when comparing screening policies throughout life up to the age of 65 the age specific incidences in the absence of screening must be considered. Assuming that the rates are as shown in table VI, the effect of different screening policies on the cumulative rate can be evaluated as shown in table VII. We should emphasise that the figures in this table, as in table V, refer to women who complied with the relevant screening schedule; they do

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SHORT REPORTS

Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long term diuretic treatment

Dyckner and Wester carried out an uncontrolled study to investigate the effects of magnesium supplementation on electrolyte concentrations in 39 patients receiving long term treatment with diuretics.[1] Though no changes were found in electrolyte concentrations, a significant reduction in systolic and diastolic pressures occurred. We conducted a multicentre, double blind randomised study of supplementation with magnesium in patients treated for hypertension with potassium depleting diuretics for more than six months.

Patients, methods, and results

Patients were recruited from five general practices. Criteria for entry were hypertension treated with potassium depleting diuretics for more than six months; diastolic blood pressure <105 mm Hg; serum creatinine concentration <200 μmol/l (<2·3 mg/100 ml); no evidence of cardiac failure; no chronic diarrhoea; and no regular use of drugs containing magnesium. Patients were seen at time 0; at one week, when treatment was started; and one, three, and six months after the start of treatment. At each visit systolic and diastolic pressures were measured. Serum potassium, sodium, creatinine, and magnesium concentrations were measured at time 0 and at three and six months. The lowest values of systolic and diastolic pressures recorded at one week were taken as the pretreatment blood pressure, and patients fulfilling the entry criteria were randomised blindly to treatment with magnesium oxide 500 mg (301 mg magnesium) or placebo tablets of identical appearance and instructed to take one tablet daily. Statistical analysis was by the two tailed *t* test (paired and unpaired) and the χ^2 test.

Forty one patients were admitted to the study, of whom 20 were randomised to receive placebo and 21 to receive magnesium supplementation. One patient was withdrawn from the magnesium group after one month because of hypokalaemia. There were no differences in age, sex, duration of diuretic treatment, serum electrolyte concentrations, or systolic blood pressure between the two groups at entry. The mean age in both groups was 62, and three quarters of the patients had been taking diuretics for more than two years. Diastolic blood pressure at entry was significantly lower in the group given magnesium (87 mm Hg *v* 93 mm Hg in the placebo group; p=0·02, unpaired *t* test; 95% confidence interval 1 to 10 mm Hg). The table shows electrolyte concentrations and blood pressures before and after treatment.

The diastolic blood pressure in the group given magnesium was extremely stable, being 87 mm Hg before entry to the study, 86 mm Hg after three months'

Mean (SD) blood pressure, serum electrolyte concentrations, and creatinine concentrations before and after three and six months' treatment in patients given placebo (n=20) and those given magnesium supplementation (n=20)

	At entry to trial		After 3 months		After 6 months		
	Placebo group	Magnesium group	Placebo group	Magnesium group	Placebo group	Magnesium group	Significance
Creatinine (μmol/l)	98 (24)	95 (17)	100 (21)	97 (18)	101 (21)	95 (18)	NS
Potassium (mmol/l)	3·7 (0·5)	3·9 (0·4)	3·8 (0·3)	3·8 (0·3)	3·8 (0·4)	3·9 (0·4)	NS
Sodium (mmol/l)	141 (3)	141 (3)	140 (3)	141 (3)	141 (3)	141 (3)	NS
Magnesium (mmol/l)	0·81 (0·07)	0·78 (0·10)	0·79 (0·07)	0·81 (0·10)	0·79 (0·08)	0·81 (0·09)	NS
Blood pressure (mm Hg):							
Systolic	157 (24)	154 (19)	155 (19)	148 (19)	154 (22)	150 (20)	NS
Diastolic	93 (8)	87 (6)	92 (7)	86 (8)	92 (6)	88 (7)	*

*Difference in diastolic blood pressure between groups before treatment: p=0·02 (unpaired *t* test).
Conversion: SI to traditional units—Creatinine: 1 μmol/l≈11·3 μg/100 ml. Potassium: 1 mmol/l=1 mEq/l. Sodium: 1 mmol/l=1 mEq/l. Magnesium: 1 mmol/l≈2·4 mg/100 ml.