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SIGNIFICANCE OF IN SITU CARCINOMA OF THE UTERINE CERVIX

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The concept that *in situ* carcinoma is a stage in the development of clinically invasive carcinoma has received widespread acceptance. Whether or not progression from *in situ* to invasive carcinoma is inevitable if the process is left undisturbed has not yet been determined. This relationship cannot be determined by direct means because the *in situ* lesion must be entirely removed before it is possible to rule out the presence of invasive elements. Therefore, indirect means, both statistical (Dunn, 1953) and morphological (Wheeler and Hertig, 1955), have been used to deduce the likelihood of progression from one type of lesion to the other. This paper deals with our experience in a large detection programme in which one of the major efforts has been to evaluate the significance of *in situ* squamous carcinoma of the cervix.

Methods and Material

(*a*) *Statistical Methods.*—Age-specific incidence rates for invasive carcinoma of the cervix in the Province of British Columbia have been collected since 1955. (Incidence rate, as incidence, is the rate at which a disease appears in a population. The number of cases of a disease that *begin*, in a stated period of time, in a specified population. This is expressed as the number of cases per thousand or hundred thousand per year.) If *in situ* carcinoma is a precursor of invasive carcinoma the discovery and removal of a large number of *in situ* carcinomas from a controlled population should produce a detectable fall in the incidence of invasive carcinoma. From these results some deductions can also be made regarding the percentage of *in situ* lesions that would become invasive if they had not been treated, and the mean duration of the *in situ* phase of cervical carcinoma.

(*b*) *Morphological studies* of step-serially-sectioned cone biopsies of the uterine cervix, in which preclinical carcinomas of both *in situ* and early invasive types have been carefully analysed with a view to studying the relationship of *in situ* carcinoma to clinically invasive carcinoma.

Between 1949 and the end of 1960, 146,833 women have had cervical smears studied on one or more occasions in the cytology laboratory. This figure represents one-third of the women over the age of 20 in the Province. The laboratory began as a small project and has steadily increased to the point where 63,575 specimens, representing 58,109 women, were received in 1960 (see Table I). These specimens came from about 1,200 physicians, representing almost two-thirds of the practising physicians in the Province. The objective is that all women over the age of 20 be examined in the next few years. The laboratory has facilities for at least 100,000 specimens per annum.

From the beginning each patient has had a case card initiated upon the first screening, and on each subsequent examination the results are entered along with pertinent clinical and pathological data. Since 1958 much of the sorting and analysis of the data has been done mechanically by the Provincial Division of Vital Statistics from coded information on each set of specimens examined.

The programme is financed almost entirely through Provincial and Federal Government grants. There is no charge to the patient for cytology or examination of biopsies, including step serial sections of cervical cones. This approach has the obvious advantages of allowing adequate cytological and histological investigation for all patients in a population screening programme.

The smears are taken with a wooden spatula by the physician as part of a general pelvic examination. While many women with signs and symptoms of disease have smears taken, most of our material is from asymptomatic women. We have emphasized to the contributing physicians that these cytological studies are to find disease where none is suspected ; invasive cancer of the cervix being best diagnosed by inspection and biopsy, and abnormal uterine bleeding suggestive of endometrial carcinoma by uterine curettage.

Results

Table I shows the expanding programme and its results in terms of preclinical carcinomas of the cervix that have been discovered. During the 12-year period 828 cases of purely *in situ* carcinoma were detected. The two stages of preclinical but invasive carcinoma that have been described and defined (Fidler and Boyes, 1959) are represented by 47 cases with discrete, scattered, micro-invasive foci (Stage 0+) and 40 with frankly invasive but clinically occult carcinoma (Fidler and Boyd, 1960). Almost all of these early invasive carcinomas have required cone biopsy for diagnosis because no significant clinical lesion was visible and/or the initial bite or wedge biopsies were equivocal.

Table II, Section A, shows the annual incidence of newly diagnosed cases of clinically invasive squamous

carcinoma of cervix uteri in the Province of British Columbia in the years 1955 to 1960, inclusive. These are accurate figures that have been prepared from the lists of notifications sent to the Division of Vital Statistics by hospitals and physicians, checked against lists of biopsy diagnoses obtained from all hospital pathologists in the Province, and again checked against lists obtained from all treatment centres in the Province. Finally, if any doubt existed regarding the exact site, histological type or stage, or whether the lesion was primary or recurrent, the contributing sources, and often the original doctors, were contacted. During the six-year period only four cases were encountered in which adequate and reliable information for classification was not available. The year 1955 was chosen as the baseline year because complete information on all cases before this time would have been difficult to obtain, and, moreover, it was felt that the cases of *in situ* carcinoma detected before this year would be insufficient to influence greatly the incidence of invasive carcinoma. *Preclinical* invasive carcinomas are purposely not included in Section A in order not to introduce a bias of increasing numbers of lesions, which, although invasive, would not ordinarily be reported during that year if cytological examination were not available.

TABLE I.—*Cases of in Situ Carcinoma and Preclinical Invasive Carcinoma Detected During* 1949 *to* 1960 *Inclusive*

Year	Cases Screened*	*In situ* Carcinoma	*In situ* With Micro-invasion	Occult Invasive Carcinoma
1949–50	904	9	—	—
1951	2,197	12	1	1
1952	4,140	26	—	1
1953	5,504	27	—	5
1954	8,843	34	4	1
1955	11,707	53	3	2
1956	15,106	77	6	3
1957	18,719	97	6	2
1958	29,875	141	12	7
1959	33,833	142	6	7
1960	58,109	210	9	11
Totals	193,942	828	47	40

* Many of these patients appear in the totals in several different years. The number of women screened to the end of 1960 is therefore not 193,942, the corrected total to the end of 1959 being 107,354 and for the entire 12-year period 146,833.

TABLE II.—*Incidence of Invasive Squamous Carcinoma of the Cervix Uteri in Women Over* 20 *Years of Age in British Columbia in the Years* 1955–60, *Showing Population of Women in Thousands and Rates Per* 100,000 *Female Population*

Year	Population in Thousands	A		B		C	
		Clinically Invasive Carcinoma		Clinically Invasive Carcinoma Plus Occult Invasive Carcinoma		Clinically Invasive Carcinoma Plus Occult and Stage 0+*	
		Total Cases	Incidence	Total Cases	Incidence	Total Cases	Incidence
1955	422·9	120	28·4	122	28·8	126	29·8
1956	436·7	119	27·2	122	27·9	126	28·9
1957	460·9	120	26·0	123	26·7	130	28·2
1958	473	112	23·7	119	25·2	132	27·9
1959	478·8	108	22·6	115	24	122	25·5
1960	486·4	96	19·7	107	22	116	23·8

* Stage 0+ is used to designate *in situ* carcinoma with scattered discrete micro-invasive foci.

The results in Section A, in which the incidence of 28.4 cases per 100,000 women in 1955 fell to 19.7 per 100,000 in 1960, are highly significant. This is a 30.6% reduction in incidence at a time when about one-third of the female population aged 20 and over had been examined.

The possibility of bias from the following sources has been studied and considered to be negligible: (*a*) An apparent falling incidence due simply to more time being given to seeking out cases diagnosed in the earlier years of the study. (*b*) A high incidence in the early stages of the programme due to an intensified educational programme. The opposite is true since the educational programme has gained increasing momentum from the beginning. (*c*) A change in the age distribution of the female population with an increase in that part of the population less likely to produce disease. Annual estimates from the Department of Vital Statistics of the female population in five-year age-groups have shown no real change in the age distribution. (*d*) A more critical and restrictive classification of invasive carcinoma in more recent years would influence the figures. This is not the case, because all of the biopsy material has been available for our study, and the criteria for *in situ* carcinoma and the stages of invasion have remained constant.

If the cases of preclinical invasive carcinoma are included in the incidence rate, despite the mounting number of these cases detected annually in the expanding programme, the downward trend seen in Sections B and C in Table II is still significant. The total decline is 23.6% and 20.0% respectively from 1955 to 1960. Whereas the more rapid fall in incidence in Section A is due to cases of preclinical invasive carcinoma in addition to *in situ* carcinoma being detected and removed, the fall-off in Section C has resulted from the removal of *in situ* carcinoma only. The figures in this latter section are totally unbiased by the possible effect of the detection of early invasive carcinoma in the screening programme. This, therefore, supports the hypothesis that *in situ* carcinoma is a significant lesion that does progress to clinically invasive carcinoma. Since the evolution from the onset of carcinoma *in situ* to clinical invasive carcinoma is of many years' duration, a rapid fall-off is not to be expected in Section C until a later stage in the detection programme. Section A is, however, the most relevant index of the value of the programme to the community.

Table III is a comparison of the various morphological aspects of *in situ* carcinoma, with mean ages of the patients from which the lesions came. It

TABLE III.—*Morphological Aspects of in Situ Carcinoma of Cervix*

		No. of Patients	Mean Age in Years
Percentage of circumference involved	25%	180	38·5
	50%	140	41·7
	75%	79	42·2
	100%	73	43
Depth of extension into glands	Superficial	346	39
	Deep	268	44·5
Histological grade (Broders)	I	177	39
	II	316	41·4
	III	121	46
Cytological grade	Differentiated	569	41
	Undifferentiated	241	44·5

This analysis is based upon 656 cases (including stage 0+) seen to the end of 1959. Total numbers of patients do not add up to this figure because the information was not available in all cases, and in the cytological grade both differentiated and undifferentiated cells were recorded in many of the cases.

TABLE IV.—*Mean Age Phases of Squamous Carcinoma of Cervix*

	No. of Patients	Mean Age in Years
Onset of *in situ* carcinoma	18	35·7
Total cases of *in situ* carcinoma	618	41·1
In situ carcinoma with microscopic foci of invasion	38	46·5
Occult invasive carcinoma	29	51
Clinically invasive carcinoma	511	52·8

These figures are up to and including the year 1959.

appears that the size of the lesion, extent of gland penetration, and histological and cytological grades all advance with the mean age of the patients in whom the lesions are found.

In Table IV the mean age at onset of 35.7 years was found by following a group who were known to have been previously cytologically negative, 18 of whom subsequently developed *in situ* carcinoma. Those patients with the earliest microscopical foci of invasion were found to have an average age of 46.5 years, and the more-advanced lesions—namely, the occult preclinical invasive group—were found in patients with the mean age of 51 years. Finally, the mean age of overt invasive cancer in our series is 52.8 years.

These observed data suggest that this lesion is progressive and that the average duration from the onset of *in situ* carcinoma to clinically invasive carcinoma is 17 years.

Another inference of the duration of the *in situ* phase can be drawn from comparing the mean age of the 618 *in situ* cases (41.1 years) with the mean age of the invasive group (52.8 years). In the series of 618 *in situ* cases, while many of the lesions would have just begun, and many would be nearing the end of the *in situ* phase, the mean should represent the mid-point of normal distribution. If clinically invasive carcinoma represents the top end of the distribution, the lower end should be at about age 30 years—a span of some 20 years or more.

An incidence rate of *in situ* squamous carcinoma was found by establishing a group of women known to be cytologically and clinically negative and following them to see how many became positive. Because the women in this group have been followed for varying periods of time, and because one patient followed for 10 years should have the same risk as 10 patients followed for one year, we have used the number of cases developing *in situ* carcinoma per patient-years of risk as our incidence figure. By the end of 1959 this group consisted of 20,424 patients and they contributed 39,245 years of risk, or are equal to 39,245 patients followed for one year. Eighteen of these patients developed *in situ* carcinoma, representing an annual incidence of 46 per 100,000 women.

The prevalence of *in situ* squamous carcinoma is a more straightforward figure. (Prevalence is the number of cases of the disease in question that exist in a specified population at a specified time. This is expressed as the number per thousand or per hundred thousand.) Among 107,354 women examined until the end of 1959, 618 cases of *in situ* carcinoma were found, resulting in a prevalence rate of 578 per 100,000 women. The mean age of these patients was 41.1 years.

These statistics may be used as another means of estimating the duration of *in situ* squamous carcinoma and the number that became invasive carcinoma. If the *in situ* phase lasted only one year, the prevalence rate should be equal to the annual incidence. Therefore, if one divides the prevalence by the incidence the result should be the duration—that is, $578/46 = 12.6$ years. Furthermore, if all *in situ* carcinomas went on to become invasive, the incidence of these two should be identical. However, the incidence of *in situ* squamous carcinoma is 46 per 100,000 while the incidence of clinically invasive carcinoma is 28.4 per 100,000. One may speculate that about 60% ($28.4/46 \times 100 = 61.5\%$) of *in situ* squamous carcinomas go on to become invasive cancer. This all-important figure will require observation of many more *in situ* incidence cases before it becomes statistically sound. Furthermore, correction for expected death from other causes during the long period of preclinical disease would tend to raise the percentage becoming invasive.

Summary

During a 12-year period approximately one-third of the women aged 20 and over in British Columbia, Canada, have had cervical cytology examinations. There has been a reduction of the incidence of clinically invasive squamous carcinoma by 30.5%, from 28.4 cases per 100,000 in 1955 to 19.7 cases per 100,000 in 1960.

When all cases of invasive squamous carcinoma, including those preclinical lesions that have been detectable only because of the cytology screening programme, are used for an incidence rate, the rate still falls significantly from 29.8 to 23.8 per 100,000 women, a drop of 20% between 1955 and 1960. It is concluded that this drop in incidence is due to the removal of *in situ* carcinoma from the population. It is expected that the fall-off in clinically invasive carcinoma will be increasingly evident and perhaps precipitous in the next few years, as it reflects the increasing number of *in situ* carcinomas that have been removed each year to date.

Studies of the incidence and prevalence rates of *in situ* and invasive lesions suggest that about 60% of *in situ* carcinomas may go on to become invasive cancer, and that clinical invasion is, on the average, preceded by about 13, 17, or 20 years of *in situ* carcinoma, depending on which of three methods are used in the calculation. More incidence cases of *in situ* carcinoma must be studied before these figures become statistically reliable.

Morphological studies of cone biopsies of *in situ* and early invasive carcinomas of the uterine cervix suggest a progression of *in situ* to clinically invasive carcinoma.

We believe that a population-screening programme, such as that described, is capable of virtually eliminating invasive carcinoma of the cervix.

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REFERENCES

Dunn, J. E., jun. (1953). *Cancer*, **6**, 873.
Fidler, H. K., and Boyes, D. A. (1959). Ibid., **12**, 673.
—— and Boyd, J. R. (1960). Ibid., **13**, 764.
Wheeler, J. D., and Hertig, A. T. (1955). *Amer. J. clin. Path.*, **25**, 345.

The Chadwick Medal for 1961 for "excellence in Public Health engineering" has been awarded to Mr. M. L. H. Creasey, of Stratton Road, Merton Park, London S.W.1, in recognition of his being the best student of the year in the Chadwick Department, University College, London.