[CANCER RESEARCH 33, 1353-1367, June 1973]

A Comparison Review of Key Epidemiological Studies in Cervical Cancer Related to Current Searches for Transmissible Agents[1]

I. D. Rotkin

Department of Preventive Medicine and Community Health, University of Illinois at the Medical Center, Chicago, Illinois 60680

Summary

The search for a venereally transmissible oncogenic agent which may show relatedness to onset of cervical cancer rests upon three main evidential currents: demographic demonstration of cultural variables associated with increased risk, epidemiological focus upon sexual factors maximizing risk, and the assumption that cervical cancer begins and develops according to a multistage continuum. For this, an abbreviated model conforming multistage carcinogenesis in the human uterine cervix with the classical animal model introduces an epidemiological review. Assumptions required for this rationale include maximal biological activity in the cervical cellular matrix during adolescence, an oncogenic agent for initiation of neoplasia, and recognition of pivotal events directly related to risk. In reviewing variables and attributes described in the literature, distinction is made between those that are cultural and indirect and those that are biological and may directly transform epithelium. A set of comparison studies is presented in assessing historically described major influences upon risk and each is examined for relevance, using a comparison ratio for detection of excessive frequencies between patients and controls. It is shown that onset of sexuality before age 17 is the most powerfully discriminating variable in virtually all studies where this has been investigated and that a history of multiple sexual consorts is a supporting variable of some strength. Marital variables and those associated with sociosexual stability are cultural and relate to the biological variables of early coitus and multiple sexual partners. Coital frequencies, menstrual patterns, and gravidity seem to bear no discernible risk relationship. Noncircumcision of sexual partners is shown to have been limited in most studies to husbands and in some studies to selected or all coital mates, yet no study reveals differences between patients and controls for exposure to uncircumcised partners. Comparison studies are collected in charts to demonstrate relative strength and consistency of trends.

Cervical cancer is the only solid neoplasm for which epidemiological findings in humans have been adapted to a model developed with laboratory animals, and it is the only tumor that has been studied with regard to a full universe of possible variables and attributes that might alter risk. This has resulted in the currently espoused hypothesis that *Herpesvirus hominis* type 2 may be an initiating or promoting carcinogenic agent which can be transmitted during coitus by the male donor to the female host at risk.

[1] Presented at the American Cancer Society Conference on Herpesvirus and Cervical Cancer, December 8 to 10, 1972, Key Biscayne, Fla.

The search for venereally transmissible oncogenic agents that can endow cells of the uterine cervical matrix with carcinogenic capacity or potential, and which has led to recent seroepidemiological ventures, rests upon 3 main evidential currents emerging from more than a century of studies and speculations. These are: (*a*) demographic resolution of increased risk for women culturally identified by marriage and social deprivation; (*b*) epidemiological focus upon sexuality as the core biological association, with early coitus and multiple sexual consorts as the specifically effective components maximizing risk; and (*c*) the assumption that cervical cancer begins and develops according to a multistage sequence, from transformation of cells by an initiating influence through early detectable pathologies and into cancer after cocarcinogenesis.

A recently reported model conforming development of human cervical cancer with a multistage continuum of carcinogenesis (27) will be used here to introduce a brief historical review of epidemiological events leading to speculations derived from seroepidemiological data by Rawls *et al.* (20) and others that herpesvirus type 2 is a candidate oncongenic agent transmitted from donor male to host female during sexual intercourse. Following this review, and as a primary objective of this paper, a set of major historical studies will be presented with simple comparisons designed to provide support for the key sexual risk variables upon which the pursuit of transmissible agents is based, and perhaps demonstrating the secondary or doubtful relevance of other risk issues still being espoused.

Epidemiological Background

The epidemiology of cervical cancer has been resolved 3 times. Original studies began in the middle of the 19th century, when Domenico Rigoni-Stern (22), the precocious Italian chief physician of a Verona hospital and an instructor at the University of Padua, raised the issue of marriage in relation to risk of both uterine and breast cancers. His conclusions from mortality records were that more uterine cancers are found in married than in unmarried women, that cancer of the uterus is quite prevalent in women between ages 30 and 40, that the frequency of this cancer doubles in the following 2 age decades and then drops off,

and that it is rare among unmarried women and almost absent in certain orders of nuns. There were concomitant observations regarding an inverse incidence relationship of cancer of the breast to cancer of the uterus insofar as breast cancer frequently is a cause of death in nuns and in unmarried women.

Revival of an interest in cancer of the uterus initiated the 2nd period of epidemiological investigation, mostly with scattered reports during the 1940's, perhaps stimulated by recognition of the squamous cervical lesion as distinct and different in pathology from that of the corpus adenocarcinoma. Demographic studies generated early data on morbidity in populations and, abetted by the momentum of sociological research, risk studies were influenced by the persuasion that chronic diseases were not only environmentally but also socially and psychologically conditioned. During this period Kennaway (15) investigated morbidity of uterine cancer by race and social status, the original United States cancer morbidity study by Dorn and Cutler (9) was in process, and Levin *et al.* (16) described an association of syphilis with uterine cancer. Also at about this time, Allen and Gardner (3) announced that long-term topical administration of estrogens had induced neoplastic lesions in mice cervices. This was followed by a track of laboratory efforts to initiate murine cervical neoplasia with another presumably carcinogenic substance, smegma taken from the penises of horses and men.

Rigoni-Stern's findings in Italian nuns were confirmed by the studies of Gagnon (11), Towne (37), and Taylor *et al.* (34) during the 1950's. Since very few uterine and fewer cervical cancers were found in these large series from Canada, Chicago, and Massachusetts, it appeared evident that marriage was an effective variable in establishing risk. Additionally, a series of classical studies were conducted during this important decade in which selected risk hypotheses, some already developed in demographic surveys, were tested with case-control designs. These included the studies of Lombard and Potter (17), in which a spectrum of variables was investigated and which demonstrated excessive hazard from cervical cancer for women who were married under age 20. Other significantly associated events were marital instability, the use of coal tar douches, and syphilis. In Denmark, Brøbeck (6) published a proband study in cervical cancer genetics, without positive results; Clemmesen (8) summarized available knowledge in cervical cancer demography and epidemiology among other cancers, especially with regard to social variables. The later-recurring theme of marital status, heredity, and social class, repeated alone or woven together in so many other studies during that decade and until now, was established in this appraisal. Clemmesen denied that noncircumcision was relevant as a major variable, as also will I in this paper. The other large study was a program investigating populations in the United States and India by Wynder *et al.* (39). Presented as unresolved findings were separate associations with circumcision status, marital status, early marriage, early 1st coitus, and multiple marriages. Other contributions included the finding by Røjel (23) of cervical cancer excesses among prostitutes and again a relationship of syphilis to risk, assessment of selected psychosocial influences upon risk by Stephenson and Grace (31), and an investigation by Jones *et al.* (14) in California of selected variables known at that time. Several important demographic surveys also appeared during this decade, notably those issued by Haenszel *et al.* (12, 13) describing morbidity rates in urban and rural Iowa and in New York City, and the national survey of cancer morbidity by Dorn and Cutler (9) in which cancer incidences of 10 selected United States cities represented national rates.

At the end of this period it was well established that the epidemiology of cervical cancer had been settled. There were 2 separate explanations for excessive incidences, one of which held that the variables of early marriage and existence in low socioeconomic strata increased risk and the other associating this lesion with noncircumcision and the carcinogenicity of smegma beneath prepuces. A late paper of this series was a report by Terris and Oalmann (35) in which each of a set of variables was studied, some with more effect than others. This report treated age of coital onset as one of several variables as had also Wynder *et al.* (39). Results from most of these research programs are particularized in the comparison studies.

The 3rd current of research took place largely in the 1960's and recognized the act of sexual intercourse as the pivotal event in setting up risk (24). The hypothesis was, and still is, that a carcinogenic agent is transmitted by the coital mate to the female at risk. This is a biological event during which there is opportunity for transformation of normal but destined cells and for initiation of carcinogenesis. This also is the basis upon which the adequacy of herpesvirus type 2 was postulated, but there was precedent for the feeling that an organism, particulate or otherwise, was the effective agent. Levin *et al.* (16), Lombard and Potter (17), and Røjel (23) already had described associations with syphilis, and Reid (21) had announced his conviction that postcoital spermatozoa could be related to mutagenic change in cells of the cervix. Other speculations were concerned with specific protozoa, bacteria, and fungi known to inhabit vaginal access to the cervix, all without demonstrated result.

Contribution during the 1960's came from my laboratory in California, where I had undertaken an integrated sorting of known, surmised and possible influences upon risk in a multivariate study. The objective was to erect a plausible biological rationale for increased risk and an epidemiological model for carcinogenesis in the human uterine cervix. A series of reports concluded that onset of sexuality during adolescence and exposure to multiple sexual consorts were the 2 events most powerfully conditioning risk of this cancer. The act of coitus effectively launched risk, and an agent of some kind was passed from male to female during this time of life when cervical epithelium was most readily available for transformation. There were and are a number of candidate oncogenic agents that could be transmitted sexually by donor male to host female, an obvious one of which is a particle or organism of some kind, as suggested in an early report (24). Later speculations included a DNA virus as an adequate, but not only, possibility (25).

This 3rd resolution of cervical cancer epidemiology is particularly interesting these days when there is so much talk about renewed attacks upon cancer etiology, so many announcements favoring programs for prevention, so little information upon which to base programs, such a scarcity of money to pursue epidemiological information, and so few trained people who could participate if funding were more generously provided. The body of knowledge, the state of the art available and applicable for prevention and early detection of most prevalent cancers hardly is substantial for intervention on primary and secondary levels. It is necessary to realize that, although a few pioneering groups, captained by such investigators as Lombard and Potter, Wynder, Terris, and others, embarked upon epidemiological research involving a number of variables and directed against several cancers, the word "epidemiology" was interpreted as it was derived from infectious diseases, and the hope seemed always to be that a single truly causative influence would be found in some dramatic moment after the data were assessed. Thereafter solutions would come quickly, brilliantly, and definitively, with headline announcements.

Even those who are concerned with acute infections realize that single agents, however powerful, do not operate without some help or hindrance. As the statistician might say, it is seldom that 1 variable will contribute 100% of variance. Especially for human cancer, and probably for all chronic diseases, the search for a sole influence or agent has been utterly unsuccessful, yet there is the intuition that 1 or several variables or attributes somehow must be pivotal; i.e., however many influences conspire to initiate and develop a disease, there must be some structure and consistency to the process. It was this belief that directed research during the 1960's into a multivariate logic (28).

Limiting ourselves to cervical cancer, the important difference in research philosophy was that, whereas the investigations during the 1940's and the 1950's had been concerned with the pursuit of individual variables, taken alone or in groups and each obediently structured around a hypothesis, research in the 1960's was designed to explore at one time all possible contributions to onset. My own work began in the early 1950's, and I was unaware that the behaviorists already had worked out multivariate concepts and procedures. It seemed to me that all sources of variance, environmental, behavioral, and genetic, should be examined comprehensively in 1 program, as suggested also by the then rather new doctrines of the quantitative geneticists, to find some kind of pattern upon which resolution of the many claims could take place. Instead of single variables, I decided to work with domains of related dimensions (28). In this manner, one could take large groupings of individual subvariables and manipulate them with standard case-control procedures and with confidence that if bias were avoided a resulting set of influences might develop which could be put together into some kind of a natural history of this disease, which also could provide solid hypotheses to be tested and which might lead to a reasonable basis for control. In relatively few years this plan provided some impressive relationships, and the pivotal variables came into focus. It was evident that *adolescence* was a covering attribute of major importance, and it is to be hoped that a strong attempt will be made to understand the biology, physiology, and psychology of the developing adolescent.

As far as I know, a structured effort involving universes of variables and resolving interactions as has been done with cervical cancer has not yet been undertaken for any other cancer, including breast, colon, prostatic, pancreatic, and bronchiogenic carcinomas.

Rationale

It is necessary that this epidemiological background explaining increased risk is captured in understanding why a viral agent can be considered as an initiating or cocarcinogenic event in the cancer process. For this, it might be well to summarize from previous work (27) a profile of the candidate who is at increased hazard of cervical cancer.

She was born in deprivation and exists in a low socioeconomic stratum. There is a higher likelihood that she is Spanish, black, Puerto Rican, or East Indian in the United States and elsewhere, but the prospect also is high that she is white if poor and uneducated. The cultural commonality is a low socioeconomic status, but women from higher stations in life are not excluded. She is exposed at an early age to male sexual aggressiveness as an environmental hazard. Although she is too young to be highly arousable, early sexuality is a folkway solution for companionship and an antidote for loneliness. Onset of coitus is during adolescence or earlier. Intromission sets up risk of cervical cancer. Exposure to a plurality of sexual consorts, each with a discrete probability of conveying a carcinogenic influence to her, increases risk. The speculation now is that one of these carcinogenic influences may be herpesvirus type 2.

With this profile in mind, we may repeat a set of assumptions from the earlier report (27) that link events and attributes with sequential carcinogenesis in the cervix.

1. Biological activity in the cervical cellular matrix is at a maximal level during adolescence, and events associated with cellular replication and the uptake of substances from the cervical milieu subside after adolescence. The rise in mitotic activity during this life period increases the probability that transformation of the divisional mechanism of susceptible cells can take place following the initiating stimulus of a carcinogenic influence, and such a probability decreases as fewer divisional events take place.

2. A carcinogenic principle of some kind is required for the initiation of neoplasia in the cervix. Whether or not this is a single agent, as a virus, or several alternative agents each carrying carcinogenic adequacy alone or working together still is undetermined, as also are the sources of these agents, whether another previously encountered female, ambient contamination, or otherwise,

3. Certain variables and attributes, some sociocultural and others biological, appear more directly related to risk

of cervical cancer than others. Two *direct* events bearing relationship are early coital onset and multiple sexual consorts. Early sexual experience, with risk rising as more males are encountered, modifies a cluster of such *indirect* events as early pregnancy, multiple pregnancies, early marriage, multiple marriages, socioeconomic status, ethnic classification, and others in a domain of dimensions that are introduced by or related to the act of coitus.

Multistage Carcinogenesis

Limited to a comparison of the human events just described with laboratory work in animals, Table 1 is a time sequence following the 2-stage model originally proposed by Berenblum (4) and fully explored elsewhere (27). A specific carcinogen is applied to the young animal, and after a determinable period of latency a specific cocarcinogen is necessary to promote the lesion. The young animal is paralleled in humans for cervical cancer by the adolescent girl. The agent is brought directly to the milieu of the cervix over a venereal pathway. Latency has been determined in my own work (25) and also by Aitken-Swan and Baird (2) at about a mean span of 30 years, perhaps comparable to a mean latent period of 30 weeks in the mouse (27). That a cocarcinogenic event takes place is presumable since it is quite certain that many *in situ* lesions do not develop into cancer and also that the *in situ* and invasive lesions resemble each other only superficially. Herpesvirus type 2 currently is postulated either as the initiating agent for Step 2, as the promoting agent for Step 4, or perhaps as both. Whether any of these viral hypotheses is supportable remains to be tested. For all of us who are interested in intervention opportunity for control is implicit at each step: by short-term postponement of coitus and by curtailment of sexual consorts during adolescence, by determination of venereal agents and immunization or other alternatives, by cytological screening during the latent period, and by resolution and prevention of cocarcinogenic events.

Since there is no point to a model without a utilitarian base, the question of validity remains before I go on to the comparisons of major studies. If the model is valid it can be utilized in making decisions, in forecasting developing pathology, in avoiding needless extreme modalities, in prevention of disease, and in anticipating clinical procedures such as cytological reappraisal of pathology through time. An approach to validity depends upon several considerations outlined in Table 2. Resolution of animal work depends upon the manner in which evidence satisfies the hypothesis, achieved by replication of the experimental design and by observation of results. The nature of the human evidence is in this case the collected epidemiological risk data and also conclusions regarding the developing pathology of the lesion in the cervix, putatively from dysplasia through *in situ* to cancer.

The synthesis of both the animal and human material arrives in the assumptions given here, in the commonality of the animal model with human data, in the conclusions derived from conformance of the human information with animal experiments, and in the derivation of a rationale for the developing carcinoma which is useful for control even if it may not be totally satisfying or complete. Upon such a base we can project action steps that are available for control (27). What remains is to assess major claims in connection with increased risk of cervical cancer, and this I now will undertake with comparisons of major studies, each associated with certain specific variables.

Table 1

Comparison events, multistage carcinogenesis in time sequence (27)

Level	Animal	Human (cervix)
1	Young animal	Adolescence
2	Specific applied carcinogen	Agent (venereal pathway)[a]
3	Latent period	Latent period
4	Specific applied cocarcinogen	Cocarcinogenic event (unknown)[a]

[a] Cervical cancer, humans: herpesvirus type 2 has been postulated as the initiating agent for Level 2; or as the promoting agent for Level 4; perhaps both.

Table 2

Validity of the model

Step	Resolution
1. Animal data	Hypothesis of multistage carcinogenesis; replication of experimental design; observation of results.
2. Human epidemiological risk data	Exploratory search for hypotheses (universe of variables); inferential assessment of end results.
3. Synthesis	Assumptions derived from risk data; commonality with animal model; conclusions based upon merging of animal and human information; derivation of a rationale.
4. Action	Control of cervical cancer, based upon model. Clinical: adequate risk data base for individual patient; population; primary prevention, screening.

Table 3
Comparison studies of variables

Early marriage (C)[a]
Multiple marriages (C)
Early coitus (B)
Multiple sexual consorts (B)
Coital frequencies (B)
Abortion (B)
Broken marriage: separation (C)
Unstable sexual relationships: extramarital and premarital coitus (C and B)
Parity/gravidity (B)
Menses (B)
Contraception (B)
Circumcision (B)
Socioeconomic status (C, not compared)

[a] C, cultural variable; B, biological variable.

Table 4
Studies cited

	Refs.
Lombard and Potter (1950), Massachusetts	17
Wynder *et al.* (1954), U. S. Hospitals: New York	39
Stephenson and Grace (1954), New York City	31
Stocks (1955), England	33
Jones *et al.* (1959), Los Angeles, Calif.	14
Dunn and Buell (1959), California	10
Terris and Oalmann (1960), New Orleans, La.	35
Stern and Dixon (1961), Los Angeles, Calif.	32
Boyd and Doll (1964), England	5
Christopherson and Parker (1965), Louisville, Ky.	7
Aitken-Swan and Baird (1966), Aberdeen, Scotland	2
Terris *et al.* (1967), New York City	36
Martin (1967), New York and Baltimore	18
Rotkin (1967), California	25, 26
Abou-Daoud (1967), Lebanon	1
Moghissi *et al.* (1968), Detroit, Michigan	19
Wahi *et al.* (1969), North India	38

Comparison Studies

Before presenting individual comparison studies, it is appropriate to comment upon the differentiation of *biological* and *cultural* variables. Table 3 lists variables which will be compared, each labeled and with some overlap. Marriage is a cultural event whether legalized, repeated, or broken. Socioeconomic status, not included in comparisons because the association of higher cervical cancer frequencies with definers of low social levels is quite secure, also is cultural. The important biological component of both marriage and sociocultural status is sexuality, and the key biological sexual event related to cervical cancer is onset during adolescence. Some of the other biological variables such as menstrual patterns, frequencies of pregnancies, deliveries and abortions, and also noncircumcision seem minimal with relation to risk, as will be demonstrated.

The studies (Table 4) include major research results reported during the 2 decades from 1950 to the present, and each has been a multiple-variable or multivariate study investigating several or a full range of variables. References also are given to avoid unnecessary repetition wherever possible.

The quantitative basis for evaluation in these comparison studies is a simple ratio reflecting frequency differences between patients and controls for each variable in each study. For those variables for which data were classified on a reasonably similar system, each comparison study can be regarded as a coherent set, and a mean ratio can be taken to reflect the central tendency for all included studies taken together. For other variables, such as coital frequencies (Table 9), individual investigators classified observations according to preferential systems, and comparisons are limited to ratios for each study. Some research areas were very popular during the past 2 decades and others were avoided or overlooked, particularly those describing the more closely biological aspects of the heterosexual event. For this reason some variables are represented in more studies than are others. However, inclusion of a variable in a study may follow currents of popularity in research, or avoidance of difficult and sensitive options, more than relevance to risk variance.

In addition to tabular comparisons, a set of charts is introduced (Chart 1; Table 17) to demonstrate collective trends resulting from each table for most individual variables. These represent a simple and comprehensive basis for decisions regarding the relative consistency and effect of each variable upon risk, as determined by ratios indicating excess frequencies of patients or controls for the variable (laterality) or lack of an excess (centrality). The intent is to specify with accumulated studies the uniform strength of key variables by comparison with those showing inconsistency or nonrelevance. These will not be discussed again until the end of this paper, nor will repeated reference be made as each variable is presented.

Age at First Marriage (Table 5). Eleven of 13 studies are consistent in discovering an excess of patients with early marriage, compared to controls. These 11 studies represent 19 investigated population segments, all with more patients who married early. Since demographic and risk studies never have failed to show higher rates and greater risk of cervical cancer in the presence of marriage, an objective in these and other studies was to probe for temporal differences of marital events, and the evidence was overwhelming that accelerated marriage increases risk. However, it would be and has been ingenuous to conclude that this cultural procedure confers greater susceptibility upon cervical epithelium or influences cellular transformation. The concomitant biological component in marriage which is the direct variable is *sexuality*.

A mean excess of 40% of patients who were first married before ages 20 or 21 is calculated from all these studies, with individual excesses ranging from 20 to 90%. The Aitken-Swan and Baird data, which depart from the trend, represent *in situ* patients. Further scrutiny is required for the populations reported by Abou-Daoud, where very early marriage takes place in a substantial portion of the population, with an excess of 170% of Christian patients married under 15; and also by Wahi, where seeming equivalence for Hindu patients and controls is replaced with excesses of accelerated patient marriages when percentage frequencies are taken at ages 17 and 13. An excess of early marriages

Table 5

Comparison studies of frequencies of age at 1st marriage under 20 or 21 in cervical cancer patients and controls

Study	% frequency under age 20 or 21		
	Patients	Controls	Ratio
Lombard and Potter (1950)	45	24	1.9
Wynder *et al.* (1954)			
White	54	33	1.6
Negro	68	53	1.3
Stocks (1955)	24	13	1.8
Jones *et al.* (1958)			
Ward cases	66	56	1.2
Private cases	42	35	1.2
Total white cases	54	45	1.2
Terris and Oalmann (1960)	71	49	1.4
Boyd and Doll (1964)			
Hospitals A + B	25	16	1.6
Hospitals A	25	20	1.3
Christopherson and Parker (1965)[a]	62	48	1.3
Aitken-Swan and Baird (1966), *in situ*	31	31	1.0
Martin (1967), Jewish only	43	28	1.5
Abou-Daoud (1967)[b]			
Christian	70	48	1.5
Moslem	21	15	1.4
Terris *et al.* (1967)	55	41	1.3
Rotkin (1967)	64	42	1.5
Wahi *et al.* (1969)[c]			
Hindu	99	95	1.0
Muslim	95	93	1.0
		Mean ratio	1.4

[a] Recalculated from Christopherson and Parker data to exclude unknown and never married.

[b] Data for marriage under age 15: Christian patients, 19%; controls, 7%; ratio, 2.7. Moslem patients, 21%; controls, 15%; ratio, 1.4.

[c] Since almost all subjects were married by age 20, this population is not comparable to many of the others studied. Earlier maturity may require comparisons based on earlier ages of marriage as follows. Under age 17: Hindus, patients, 91%; controls, 72%; ratio, 1.3. Muslims, patients, 78%; controls, 68%; ratio, 1.1. Under age 13: Hindus, patients, 45%; controls, 24%; ratio, 1.9. Muslims, patients, 25%; controls, 30%; ratio, 0.8. Frequency of cervical cancer for Hindus is 2% of studied population; for Muslims it is 1% of studied population.

Table 6

Comparison studies of multiple marriages by frequencies of patients and controls

Study	% with 2 or more marriages		
	Patients	Controls	Ratio
Wynder *et al.* (1954)			
U. S. Hospitals			
White	30	14	2.1
Black	35	22	1.6
Terris and Oalmann (1960)	47	16	2.9
Stern and Dixon (1961)	51	26	2.0
Boyd and Doll (1964)			
Hospitals A + B	16	10	1.6
Hospitals A	14	9	1.6
Martin (1967), Jewish only	20	11	1.8
Terris *et al.* (1967)	35	22	1.6
Rotkin (1967)	48	27	1.8
		Mean ratio	1.8

does not hold for Muslim patients, yet this population, generally considered at very low risk, is reported as one-half of the Hindu prevalence in this screening program. There is little need for further demonstration that early marriage increases risk of cervical cancer. That the companion biological temporal event is *early onset of coitus* will be shown in a succeeding comparison study.

Multiple Marriages (Table 6). Reports covering 9 in-

vestigated populations are listed in comparing percentage frequencies of patients and controls with 2 or more marriages. All studies show excesses of patients with more than 1 marriage ranging from 60% to almost 200% in the study of Terris and Oalmann, with a mean excess over controls of 80% of patients with multiple marriages for all populations in these studies taken together. We are here considering multiple instead of single cultural events and, although the result strongly endows multiple marriages with significance, we are warranted in searching for the biological component in these marriages, which will be resolved as *multiple sexual consorts* in a later table.

Early Onset of Coitus (Table 7). It is fortunate that investigators designing the 5 major studies represented here for this variable uniformly decided to test onset of coitus before age 20 for patients and controls and that 3 of these studies continued further with age 17 as a discriminatory comparison, plus the later study of Terris *et al.* Perhaps this unanimity of option results from the trend of data which seem to accumulate similarly for all studies. In my own investigations excesses of 1st coitus for patients over controls continued to age 20, after which reversal took place. Greatest differences were found between patients and controls before age 17 in accord with all other studies. By itself, this concordance of trend for the several studies is impressive.

A mean excess of 140% of patients covering the studies shown began coitus during adolescence before age 17, with excesses for individual studies ranging from 40% to almost 200%. Wynder *et al.* provide ethnic data in 2 studies, all with results in the same direction; my own investigations (25, 26) cover 5 separate subsamples, all with a uniformity of trend which not often is encountered in epidemiological studies.

Dilution takes place as age advances but the effect remains in comparing patients against controls who entered sexual activities before age 20. The 5 comparison studies also all are uniform in trend, with a mean excess of 50% of patients who began coitus before age 20. In the studies in which both comparisons took place, under ages 17 and 20, the effect becomes intensified as the age is decreased from

Table 7

Comparison studies of onset of coitus under ages 20 and 17 in cervical cancer patients and controls

Study	% 1st coitus		
	Patients	Controls	Ratio
Before age 20			
Wynder *et al.* (1954)			
U. S. Hospitals			
White	60	35	1.7
Negro[a]	85	75	1.1
New York			
White	55	33	1.7
Negro[a]	86	72	1.2
Terris and Oalmann (1961)	79	60	1.3
Aitken-Swan and Baird (1966) *in situ*	63	38	1.7
Martin (1967), Jewish	53	31	1.7
Rotkin (1967)	82	54	1.5
		Mean ratio	1.5
Before age 17			
Wynder *et al.* (1954)			
U. S. Hospitals			
White	19	10	1.9
Negro[a]	55	36	1.5
New York			
White	17	6	2.8
Negro[a]	45	28	1.6
Terris and Oalmann (1961), total	53	26	2.0
Terris *et al.* (1967), total	53	37	1.4
Rotkin (1967)			
total samples	51	28	1.8
Subsample 1	46	32	1.4
Subsample 2	39	27	1.4
Subsample 3	57	20	2.9
Subsample 4	47	25	1.9
Subsample 5	62	32	1.9
		Mean ratio	2.4

[a] Increased ratio for Negroes with earlier age (17 against 20) reflects acceleration effect from early coitus on risk (29). Results from coital onset before age 17 for blacks perhaps should be held equivalent to 1st coitus before age 20 for whites. It is necessary in such studies also to provide data for 1st coitus in black samples before age 15 to show maximal differences between patients and controls (29).

20 to 17. The effect is strong even in results by Aitken-Swan and Baird, where *in situ* cancers are represented. This may provide some strength for the notion that the invasive stage of this disease can result from the *in situ* lesion, or at least that early sexuality initiates the process that culminates in the *in situ* as well as in the invasive stages.

The power in this comparison lies not only in the consistency of result for all represented studies but also in a quantitative comparison with the many studies in Table 5, age at 1st marriage. Not only does the coital act constitute a direct application of a carcinogenic agent to epithelium which is most susceptible during adolescence, but also a large proportion of women begin coital activies without the cultural event of marriage. It would be hazardous to propose that risk rises linearly as age at 1st coitus is increasingly earlier since relatively few women in any culture begin sexual activities before adolescence, yet my own studies seem to bear this out. It is regrettable that sexual data were not taken in the many studies where marriage was pursued as a variable.

Multiple Sexual Mates (Table 8). Although only 3 comparison studies are shown, all are in one direction, with excesses of patients who experienced coital exposure to a plural number of consorts. The demonstration that sexual intercourse with increasing numbers of partners intensifies risk of cervical cancer does not suffer from the lack of studies investigating this variable. Additional emphasis is provided by the 7 studies in Table 6, where multiple marriages are shown to increase risk to about the same degree, since in both tables multiple sexual consorts are represented whether in or out of marriage. Results in Table 8 serve to detach the biological significance of possible exposure to more than 1 contaminant-carrying male away from the cultural issue of marriage, the probability of encountering such a carrier increasing as each additional male achieves intromission. According to both Tables 6 and 8, an excess of about 70 or 80% of patients accepted more than 1 male sexual partner.

Coital Frequencies (Table 9). The proposed influence upon risk of increased numbers of sexual acts per unit of time has led to premises which are more ascribed than demonstrated. In assessment of the several studies in this table, 1 set of results is found where patients show such an increased frequency. However, against this early study of Terris and Oalmann we can compare the later study of Terris *et al.* reported in 1967, where no excess develops in an age-susceptible population. In the report by Boyd and Doll there also is a suggestion of excessive sexual frequencies for patients, but the small percentage of frequencies in both patient and control groups renders the result doubtful. Further, their data were not significantly different for patients and controls when standardized for age at marriage. Otherwise, a scan of high-frequency ratios from top to bottom of the column reveals that most studies show equivalences for patients and controls.

The several investigators pursued different designs, and direct comparability of these studies is not feasible. Data relating to coital frequencies depend upon estimates and guesswork on the part of subjects, and insecurity is inherent in all such reporting. To be convincing, extreme frequency differences would be required with levels of significance to at least 10^{-4}. However, procedural reliability is increased when milestone frequencies are collected rather than diffuse data covering long periods of time. In my own studies (26), subjects were asked to report greatest sustained frequencies during life, excluding honeymoons and reunions after absences.

The excess of studies without patient-control differences effectively rules out any serious consideration of coital frequencies as a variable which can alter risk or which can evidentially support a contaminant rationale, except in the sense that greater frequencies can provide repeated opportunity for a carrier male to convey an agent to the cervix during adolescence. For this to happen, it is necessary that (*a*) there are multiple males, (*b*) 1 male is a carrier of an agent, and (*c*) the host female at risk is in her adolescent years. The central variable in this case is *multiple sexual partners*.

Abortions (Table 10). Only 2 of the listed studies investigated this variable, with indifferent results. Martin's study involved small groups in which the large excess of induced abortions easily might be spurious or a result of concomitant cultural bias. In my own design, with more than 400 each of patients and controls and all matched in pairs, the number of abortions was taken as a percentage of total pregnancies, resulting in almost exact equivalences of both spontaneous and induced abortions for patients and controls. Pending further research, abortion frequencies would appear to have no bearing upon risk, directly or indirectly. It is doubtful that any source of direct trauma to the cervix carries cancer risk potential.

Separations (Table 11) and Unstable Sexual Relationships (Table 12). Excesses of patients generally representing social and sexual instability indicate only greater motivation and opportunity toward additional sexual consorts. Most studies

Table 8

Comparison studies of multiple sexual consorts by frequencies for patients and controls

Study	% with 2 or more sexual mates in life		
	Patients	Controls	Ratio
Terris *et al.* (1967)	78	72	1.1
Martin (1967), Jewish only	43	17	2.5
Rotkin (1967)	70	49	1.4
			Mean ratio 1.7

Table 9

Comparison studies of coital frequencies in cervical cancer patients and controls

Study	% patients	% controls	Ratio
Jones *et al.* (1958)			
Before age 30			
1-3 times/wk	57	56	1.0
4+ times/wk	33	32	1.0
Terris and Oalmann (1961)			
Daily or more often			
Age 20	43	12	3.6
20-29	41	12	3.4
30-39	32	9	3.6
40-49	5	5	1.0
Weekly or less often			
Age 20	25	51	0.5
20-29	8	33	0.2
30-39	9	48	0.2
40-49	19	64	0.3
Boyd and Doll (1964)[a]			
4-7 acts/mo.	32	40	0.8
8-11 acts/mo.	24	18	1.3
12-15 acts/mo.	6	3	2.0
More than 16 acts/mo.	5	3	1.7
Mean acts/mo.	6	5	1.2
Martin (1967), Jewish only			
Maximum acts in any wk of marriage, 7 or more	58	64	0.9
Weekly during several yr before diagnosis, 1 or more	55	58	0.9
Terris *et al.* (1967)			
Before age 20			
More than 1/wk	63	55	1.1
Rotkin (1967)			
Greatest sustained frequencies at any time in life, all ages, acts/mo.			
More than 4	79	76	1.0
More than 9	51	47	1.1
More than 14	25	23	1.1
Mean acts/mo.	12	11	1.1

[a] Ratios of O/E, with data standardized for age at marriage, all classes by number of coital acts per month. χ^2 not significant.

where this complex of variables was investigated show that patients were excessively unstable in all their relationships, with variable degrees of difference. This entire area of research deals with cultural events, the operational related biological component of which is increased numbers of sexual partners. The nature of the sexual data in Table 12 also is subject to appraisal, all reporting having been done by wives. Two of these studies report heavy excesses of patients who had unfaithful husbands. It is highly speculative that wives in general would report these categories of data with adequate precision, although the alternative suggestion is that these husbands might have been exposed to other females who were carriers of a carcinogenic agent, perhaps a virus. It also might be suggested that patients who have suffered a dread disease might be more inclined to seek solutions in responding to this type of questioning. My own studies of premarital and extramarital coital patterns showed only minor differences between patients and controls (26).

Pregnancies and Deliveries (Table 13). An assortment of frequencies and percentages is shown for the several studies, each of which is an individual comparison since different designs were used in collecting data. Ratios reflecting differences between patients and controls hover around unity for most of these studies, with minor variations favoring patients or controls. The excess of early pregnancies in the

Table 10

Comparison studies of abortion frequencies in cervical cancer patients and controls

Study	% patients	% controls	Ratio
Martin (1967), Jewish only, any induced	43	17	2.5
Rotkin (1967)			
No. of abortions as a % of total pregnancies[a]			
Spontaneous	16	16	1.0
Induced	14	15	0.9

[a] Not directly comparable to number of cases having had abortions, compared for patients and controls, but taken as a function of total pregnancies, and a better test. Not significant.

Table 11

Comparison studies of broken marriages and separations in cervical cancer patients and controls

Study	% patients	% controls	Ratio
Lombard and Potter (1950)	21	7	3.0
Stephenson and Grace (1954)	43	13	3.3
Jones *et al.* (1958)			
Married before age 20	62	58	1.1
Married at age 20 or later	39	31	1.3
Stern and Dixon (1961)	71	47	1.5
Boyd and Doll (1964)			
Hospitals A + B	45	29	1.6
Hospitals A	41	31	1.3
Terris *et al.* (1967)	41	29	1.4
Moghissi and Mack (1968)			
Inmates, House of Corrections, Detroit[a]	43	7	6.1
			Mean ratio 2.3
Omitting Detroit data			Mean ratio 1.8

[a] Controls taken from Planned Parenthood population. Patients at Detroit House of Corrections were in excess by 4 times (400%) over frequency in control groups with regard to separations. However, the control group cannot be taken as representative of the general population and is more likely to represent a low-risk segment. Also, inmates of detention facilities are known to have been strongly associated with unstable relationships, especially in marriage.

Table 12

Comparison studies of frequencies of unstable sexual relationships (extramarital and premarital coitus) by patients and controls

Study[a]	% patients	% controls	Ratio
Stephenson and Grace (1954), husbands	21	8	2.6
Terris and Oalmann (1961), wives	54	26	2.1
Martin (1967), Jewish only			
Ever wives	10	6	1.7
Ever any husband	28	8	3.5
Rotkin (1967)			
Extramarital, wives	29	23	1.3
Premarital, wives	54	47	1.1

[a] Information obtained only from wives for all studies.

study of Christopherson and Parker refers generally to early onset of sexuality. Otherwise, this same study shows excesses of multiple pregnancies for *controls*, and with no pregnancies for more patients. From my own studies mean numbers of pregnancies and deliveries are about the same for patients and controls. For excesses in higher multigravid and multiparous classes of patients, it should be remembered that these women began their coital lives earlier with more opportunity for additional pregnancies. From this table, it would be difficult to reconcile numbers of pregnancies or deliveries with increased risk of cervical cancer.

Menstrual Patterns (Table 14). A glance at the ratios comparing patients with controls in the 3 studies of this table will rule out any association of age menarche, duration menses, interval menses, and irregular menses with increased risk of cervical cancer. All studies are in close concordance and are antithetical to a hypothesis of a pubertal hormonal component with effect upon risk.

Contraception (Table 15). Several investigators have studied the effect of differential contraceptive practices upon risk of cervical cancer. In surveying this table, it is useful to search for ratios substantially under unity, indicating excesses in control groups. For the practice of douching, Martin's results are directly opposite those of Boyd and Doll, and my data show no substantial difference in frequencies of patients and controls who douched. Obstructive types of contraceptives are associated with controls in several studies, perhaps indicating protective shielding against contaminant carcinogens. The use of rhythm by more controls in my samples is not easily explainable except perhaps with relation to personality types which might eschew multiple sexual partners and begin coitus later in life. The only generalization possible from this comparison set is that a protective barrier may prevent an agent from reaching the cervix.

Noncircumcision of Sexual Consorts (Table 16). Schor (30), in his textbook on statistics, points out that from different reports wives, husbands, and physicians all appear confused in defining circumcision status and that identification of circumcision as a statistical unit is highly insecure. To this can be added the uniformly biased selection of target populations in most of the circumcision studies relating to

cervical cancer, where *husbands* rather than coital mates were studied.

Noncircumcision of cohabiting male partners was the most discussed and heralded variable announced as directly related to risk during the 1950's and into the next decade. Choice of this variable was derived by inference from low frequencies of cervical cancer in Jewish populations, where ritual circumcision is practiced, and also from a logic which assumed that, since desquamated cells and sebaceous secretion formed a smegma under the prepuce, perforce this substance was carcinogenic. There was some laboratory effort to induce neoplastic lesions in animals, with variable results which could not be extrapolated to humans. Thereafter, epidemiological studies in humans were regarded as generally having confirmed the relationship of noncircumcision of coital mates with increased risk. Assessment of these studies is interesting.

Of the 6 studies represented in the table, 4 are concerned with estimates of noncircumcision in husbands, although an attempt was made by Wynder *et al.* to determine frequencies of women exposed to sexual partners other than husbands. However, circumcision status for these partners was unknown and not considered, frequencies were approximately equivalent for patients and controls, and in any case percentages of nonhusbands appear unrealistically small. Jones *et al.* investigated the coital partner of longest duration, and Dunn and Buell studied the 1st coital partner. In my own studies all coital mates were represented as far as possible, and also the 1st coital mate. When patients and controls are compared with regard to sexual union only with uncircumcised partners, and also those who have experienced both circumcised and uncircumcised males, no appreciable differences result in any of the studies except that of Terris and Oalmann, where only husbands are studied. All other results hover around unity, indicating that frequencies of association with any uncircumcised males are the same for patients and controls in any subsegment.

When the percentage of patients and controls are further compared with regard to uncircumcised and mixed classifications, plus mates of unknown status distributed into these categories, even the result of Terris and Oalmann dwindles down to an excess which is comparatively negligible for this type of data.

It is remarkable that, for a variable which is regarded differently by wives, husbands, and individual physicians

Table 13

Comparison studies in parity and gravidity (frequencies of patients and controls)

Study	Patients	Controls	Ratio
Boyd and Doll (1964)			
Mean no. of children			
Hospitals A + B	2.9	2.5	1.2
Hospitals A	3.1	2.7	1.1
Mean age, 1st pregnancy			
Hospitals A + B	23	25	0.9
Hospitals A	23	25	0.9
Christopherson and Parker (1965)			
No. of pregnancies			
None	16%	10%	1.6
1, 2	37%	30%	1.2
3, 4	24%	24%	1.0
5, 6	9%	15%	0.6
7, more than 7	13%	20%	0.7
Total 5 or more	22	35	0.6
Age 1st pregnancy under 20	45%	24%	1.9
Abou-Daoud (1967)			
Mean no. all pregnancies			
Christian	7.6	5.9	1.3
Moslem	6.9	5.8	1.2
Rotkin (1967)			
No. of pregnancies			
None	10%	17%	0.6
1, 2	34%	32%	1.1
3, 4	30%	31%	1.0
5, 6	32%	12%	2.7
7, more than 7	12%	7%	1.7
Total 5 or more	44%	19%	2.3
Mean no. of pregnancies	3.3	2.9	1.1
Rotkin (1967)			
No. of deliveries			
None	17%	24%	0.7
1, 2	45%	43%	1.0
3, 4	24%	25%	1.0
5, 6	10%	6%	1.7
7, more than 7	4%	2%	2.0
Total 5 or more	14%	8%	1.8
Mean no. of deliveries	2.3	2.0	1.2

Table 14

Comparison studies of menses in cervical cancer patients and controls

Study	Patients	Controls	Ratio
Boyd and Doll (1964)			
Mean age menarche			
Hospitals A + B	14	14	1.0
With irregular menses			
Hospital A	7%	7%	1.0
Hospital B	7%	8%	0.9
Abou-Daoud (1967)			
Mean age menarche			
Christian	14	14	1.0
Moslem	14	14	1.0
Rotkin (1967)			
Mean age menarche	13	13	1.0
Mean days duration menses	5	5	1.0
Mean interval between menses	28	28	1.0
With irregular menses	12%	15%	0.8

Table 15

Comparison studies of contraceptive practices by frequencies of patients and controls

Study	% patients	% controls	Ratio
Terris and Oalmann (1961)			
Ever used	3	12	0.3
Never used	97	88	1.1
Boyd and Doll (1964)			
None	30	27	1.1
Ever sheath	21	26	0.8
Ever douche	5	22	0.2
Ever obstruction	7	10	0.7
Ever withdrawal	42	39	1.1
Ever chemical	6	7	0.9
Aitken-Swan and Baird (1966)			
Sheath	12	20	0.6
Martin (1967), Jewish only			
None	5	6	0.8
Condom	46	61	0.8
Diaphragm	15	14	1.1
Douche (for contraception only)	11	2	5.5
Withdrawal	23	16	1.4
Rotkin (1967)			
None	1	3	0.3
Condom	66	68	1.0
Diaphragm	29	39	0.7
Douche (all reasons)	92	83	1.1
Withdrawal	57	53	1.1
Rhythm	24	50	0.5
Jelly	32	45	0.7

Table 16

Circumcision of coital partners (comparison studies by frequencies)

	% coitus with uncircumcised and mixed			% uncircumcised, mixed and half unknown[a]		
Study	Patients	Controls	Ratio	Patients	Controls	Ratio
Wynder *et al.* (1954)[b]						
Husbands						
White	81	72	1.1	87	77	1.1
Black	71	53	1.3	82	68	1.2
Jones *et al.* (1958)						
Partner longest duration						
White ward	60	67	0.9	66	70	0.9
Black ward	54	62	0.9	60	65	0.9
White private	52	56	0.9	58	59	1.0
Combined	55	61	0.9	61	63	1.0
Dunn and Buell (1959)						
First partner	58	56	1.0	67	62	1.1
Terris and Oalmann (1960)						
Husband of longest duration	44	25	1.8	68	51	1.3
Boyd and Doll (1964)						
Husbands, ever married to	51	51	1.0	69	67	1.0
Husbands, multiple, all	51	49	1.0	68	65	1.0
Aitken-Swan and Baird (1966)						
Husbands[c] invasive and *in situ* patients	39	33	1.2	64	63	1.0
Rotkin (1967)						
All coital mates	66	58	1.1	75	66	1.1
First coital mate	42	41	1.0	59	55	1.1

[a] One-half of mates with unknown or doubtful circumcision status was taken as a correction for differences in frequencies of uncertain mates between patients and controls, on the premise that from inspection of the data about one-half might be uncircumcised. Differences in most studies were sufficiently minimal to preclude any varying results if adjustments differed by other proportions.

[b] Frequencies of women in all classes who also experienced nonhusband partners (circumcision status unknown) do not affect ratios: white, 3 patients and 4 controls; black, 7 patients and 9 controls.

[c] Percentages were recalculated by me from Aitken-Swan and Baird data to include all categories of circumcision status in the denominator, since these authors held uncertain circumcision separate in calculating percentages.

Table 17

Comparison of studies accumulated to show centrality, laterality and consistency in relation to selected variables (Chart 1)

Variable, attribute, or event	Comparison[a] score	Tables
A. Early onset of coitus related		
a. Age at 1st marriage under 20 or 21	0, 2, 17	5
b. First coitus under age 20	0, 0, 8	7
c. First coitus under age 17	0, 0, 12	7
B. Multiple sexual partner related		
d. Multiple marriages	0, 0, 9	6
e. Multiple sexual consorts	0, 1, 2	8
f. Combined *d* and *e*	0, 1, 11	6, 8
g. Unstable sexual relationships	0, 1, 5	12
h. Broken marriages and separations	0, 1, 8	11
C. Circumcision of coital mates		
i. Uncircumcised and mixed	0, 9, 3	16
j. Uncircumcised, mixed, one-half unknown	0, 11, 1	16
D. Parity/gravidity		
k. 5 or more deliveries	1, 0, 2	13
l. Mean no. grava or para	0, 2, 2	13
Coital frequencies		
m. Frequencies more than 3.5 acts/wk	0, 5, 2	9
Contraception		
n. Ever douche	1, 1, 1	15
o. No contraception	2, 2, 0	15
p. Use of condom	3, 1, 0	15
q. Obstructive (diaphragm, jelly)	3, 1, 0	15
r. Withdrawal	0, 2, 1	15

[a] The *comparison score* has 3 totals measuring in order: studies with excesses of controls, studies with equivalent frequencies (centrality), studies with excesses of patients. Example: 0, 2, 17 connotes no studies with excesses of controls, 2 studies with equivalent frequencies, 17 studies with excesses of patients, and distance from the ratio base line indicates strong positive laterality. Most comparisons are of percentage of frequencies; see indicated tables for exceptions.

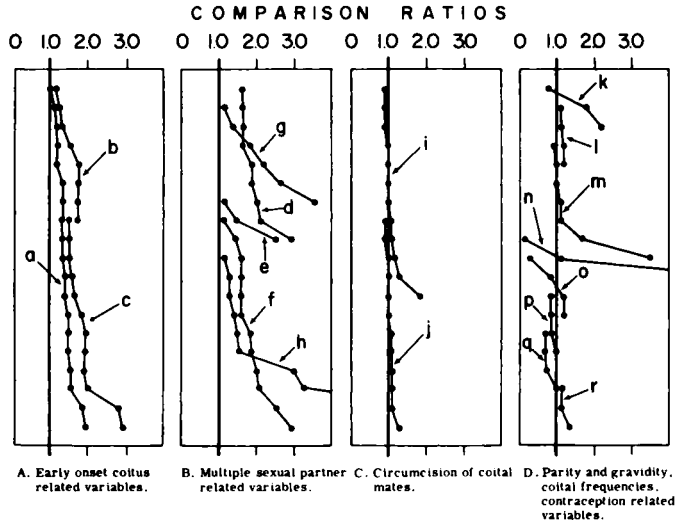

Chart 1. Comparison trends show centrality, laterality, consistency, or inconsistency of studies investigating selected variables. Each *dot* represents a ratio for patients compared to controls in a study: 1.0 is the ratio base line of equivalent patient and control frequencies (usually percentage), with 0.9 to 1.1 taken as reasonable centrality. Laterality to the *left* (under 1.0), studies showing excesses of controls; laterality to the *right* (over 1.0), studies with excesses of patients. Totals for each trend can be indicated as a *comparison score* (Table 17) with sums of studies <0.9, at or about 1.0, and >1.1, to show centrality or laterality. Lines connecting dots do not indicate any continuous distribution and are used only to show trends and relative comparison ratio distances from centrality in increasing ratio sequence. Individual sequences are independently positioned on grids for convenience in making comparisons and for no other reason. Individual t ends: *a*, early marriage; *b*, early coitus (< age 20); *c*, early coitus (< age 17); *d*, multiple marriages; *e*, multiple sexual partners; *f*, combined *d* and *e*; *g*, unstable sexual relationships; *h*, broken marriages and separations; *i*, coitus with uncircumcised partners; *j*, same as *i*, but including proportion of partners with unknown circumcision status; *k*, 5 or more deliveries; *l*, mean number grava or para; *m*, coital frequencies >3.5 acts/week; *n*, ever douche; *o*, no contraception; *p*, condom; *q*, obstructive contraception; *r*, withdrawal.

and where data are memorially or judgmentally estimated, 7 different studies representing 12 different population groups should all fail to show any substantial degree of difference with regard to excesses of patients who cohabited with uncircumcised males, yet that this belief has been very strongly espoused as the crucial influence upon differential cervical cancer risk. Our studies (28) demonstrated that circumcision as a practice is concomitant by chance with low cervical cancer frequencies in some populations, while other studies have shown that it is a separate aspect of other populations. Resolution of this situation long has been necessary because circumcision truly is a biological event. At best, it may be held that a prepuce can trap a carcinogenic contaminant in a harbor suitable for storage and transmission to the female at risk, but it hardly is likely that a prepuce is necessary in the case of a virus. From all studies there is little likelihood that noncircumcision in sexual partners increases risk to cervical cancer to any extent.

Collected Comparison Studies (Chart 1; Table 17). A simple and convenient demonstration of relative strength and consistency or inconsistency of accumulated trends for specific variables is shown in Chart 1. On the position that strong replicative concordance for a variable or groups of variables by a number of studies, however done and assessed, provides convincing support for appropriate conclusions, such a set of graphic comparisons may serve to settle ultracritical and destructive concern over differential field methodologies and statistical treatments.

The vertical line in each chart at 1.0 is the *ratio base line* of centrality, or equivalence of frequencies for patients compared to controls. Since the nature of the variables and procedures for describing them with data in the different studies invite insecurity, some skepticism is justified, and a ratio of 0.9 to 1.1 is taken as reasonable centrality. Lateral distances from the base line indicate excesses, to the right favoring patients (>1.1), to the left favoring controls (<0.9). Each study, whether separate sample, subsample, or population segment, is represented by a dot. Studies are connected to show direction of trends, but no continuities are suggested. Separate sets of studies on the same chart section are positioned for convenience and do not indicate relatedness of individual studies.

In general, centrality connotes a lack of contribution to risk variance, consistent laterality to the right indicates increased risk, and laterality to the left denotes decreased risk. A trend stretching across the chart from left to right shows inconsistency, particularly where few studies represent the variable. Consistent laterality becomes stronger with more studies.

Trends may be summarized with a *comparison score* of 3 numbers which count vertical totals for each variable, the sums of studies showing centrality or excesses to the left and right. From this, consistency also is appraisable (Table 17).

Chart 1*A* shows remarkable consistency for variables associated with early onset of coitus, including early marriage. All studies so related are lateral to the right. Earlier coitus (under age 17) is more deeply lateral than slightly delayed sexuality, an intensification effect. Only 2 of 19 early marriage studies are central; the rest show excesses of patients. From this chart, the variable early coitus is consistent and strong, conforms to the model for multistage carcinogenesis, and justifies an assumption of greater susceptibility of cervical tissue to an oncogenic agent during adolescence.

Chart 1*B* provides positive laterality to the right for all variables related to multiple sexual consorts, with the interpretation that exposure to additional males will increase the likelihood that one will contribute an oncogenic agent. This does not rule out a 1st and only sexual partner as the donor.

Chart 1*C* reveals a concordant centrality of almost all studies related to circumcision of sexual partners, resulting in a comparison score of 0, 9, 3 which reduces to 0, 11, 1 when partners with unknown circumcision status are distributed into the studies. The hypothesis that noncircumcision of sexual mates increases risk is immediately apparent as consistently nonproductive.

Chart 1*D* provides a less apparent basis for interpretation of variables related to contraception. With few studies for each trend, only 2 are consistent, both to the left (negative laterality) and both describing obstructive methods. It is possible, but not conclusive, that a barrier will prevent an agent, perhaps a virus, from reaching the cervix.

References

1. Abou-Daoud, K. T. Epidemiology of Carcinoma of the Cervix Uteri in Lebanese Christians and Moslems. Cancer, *20:* 1706-1714, 1967.
2. Aitken-Swan, J., and Baird, D. Cancer of the Uterine Cervix in Aberdeenshire. Aetiological Aspects. Brit. J. Cancer, *20:* 642-659, 1966.
3. Allen, E., and Gardner, W. U. Cancer of the Cervix of the Uterus in Hybrid Mice following Long-continued Administration of Estrogen. Cancer Res., *1:* 359-366, 1941.
4. Berenblum, I. The Mechanism of Carcinogenesis. A Study of the Significance of Cocarcinogenic Action and Related Phenomena. Cancer Res., *1:* 807-814, 1941.
5. Boyd, J. T., and Doll, R. A Study of the Aetiology of Carcinoma of the Cervix Uteri. Brit. J. Cancer, *18:* 419-434, 1964.
6. Brøbeck, O. Heredity in Cancer Uteri. Aarhus, Denmark: Universitetsforlaget, 1949.
7. Christopherson, W. M., and Parker, J. E. Relation of Cervical Cancer to Early Marriage and Childbearing. New Engl. J. Med., *273:* 235-239, 1965.
8. Clemmesen, J. On the Etiology of Some Human Cancers. J. Natl. Cancer Inst., *12:* 1-21, 1951.
9. Dorn, H. F., and Cutler, S. J. Morbidity from Cancer in the United States. USPHS Publication No. 590 (Public Health Monograph No. 56). Washington, D. C.: U. S. Government Printing Office, 1959.
10. Dunn, J. E., Jr., and Buell, P. Association of Cervical Cancer with Circumcision of Sexual Partner. J. Natl. Cancer Inst., *22:* 749-764, 1959.
11. Gagnon, F. Contribution to the Study of the Etiology and Prevention of Cancer of the Uterus. Am. J. Obstet. Gynecol., *60:* 516-522, 1950.
12. Haenszel, W., and Hillhouse, M. Uterine Cancer Morbidity in New York City. J. Natl. Cancer Inst., *22:* 1157-1181, 1959.
13. Haenszel, W., Marcus, S. C., and Zimmerer, E. C. Cancer Morbidity in Urban and Rural Iowa. USPHS Publication No. 462 (Public Health Monograph No. 37). Washington, D. C.: U. S. Government Printing Office, 1956.
14. Jones, E. G., MacDonald, I., and Breslow, L. A Study of Epidemiologic Factors in Carcinoma of the Uterine Cervix. Am. J. Obstet. Gynecol., *76:* 1-10, 1958.
15. Kennaway, E. L. The Racial and Social Incidence of Cancer of the Uterus. Brit. J. Cancer, *2:* 177-212, 1958.
16. Levin, M. L., Kress, L. C., and Goldstein, H. Syphilis and Cancer. N. Y. State J. Med., *42:* 1737-1745, 1942.
17. Lombard, H. L., and Potter, E. A. Epidemiological Aspects of Cancer of the Cervix. Cancer, *3:* 960-968, 1950.
18. Martin, E. M. Marital and Coital Factors in Cervical Cancer. Am. J. Public Health, *57:* 803-814, 1967.
19. Moghissi, K. S., Mack, H. C., and Porzak, J. P. Epidemiology of a Prison Population. Am. J. Obstet. Gynecol., *100:* 607-614, 1968.
20. Rawls, W. E., Tompkins, W. A. F., Figueroa, M. E., and Melnick, J. L. Herpesvirus 2: Association with Carcinoma of the Cervix. Science, *161:* 1255-1256, 1968.
21. Reid, B. L. Cancer of the Cervix Uteri. Review of Causal Factors with an Hypothesis as to Its Origin. Med. J. Australia, *1:* 375-383, 1965.
22. Rigoni-Stern, D. Fatti Statistici Relativi alle Mallattie Cancrose che Servirono di Base alle Poche Cose dette dal Dott. G. Servire Progr. Pathol. Terap. Ser. 2, *2:* 507-517, 1842.
23. Røjel, J. Interrelation between Uterine Cancer and Syphilis. Acta Pathol. Microbiol. Scand Suppl. 97, 1-82, 1953.

24. Rotkin, I. D. Relation of Adolescent Coitus to Cervical Cancer Risk. J. Am. Med. Assoc., *179:* 486-491, 1962.
25. Rotkin, I. D. Adolescent Coitus and Cervical Cancer Associations of Related Events with Increased Risk. Cancer Res., *27:* 603-617, 1967.
26. Rotkin, I. D. Sexual Characteristics of a Cervical Cancer Population. Amer. J. Public Health, *57:* 815-829, 1967.
27. Rotkin, I. D. Cervical Carcinogenesis: an Epidemiologic Model Adaptable to Control Programs. Recent Results Cancer Res., *39:* 165-176, 1972.
28. Rotkin, I. D., and Cameron, J. R. Clusters of Variables Influencing Risk of Cervical Cancer. Cancer, *21:* 663-671, 1968.
29. Rotkin, I. D., and Taylor, W. E. Ethnic Comparability of the Relation between Early Coital Trends and Cervical Cancer. Cancer, *23:* 458-460, 1969.
30. Schor, S. Fundamentals of Biostatistics, pp. 18-19. New York: G. P. Putnam's Sons, 1968.
31. Stephenson, J. H., and Grace, W. J. Life Stress and Cancer of the Cervix. Psychosomat. Med., *16:* 287-293, 1954.
32. Stern, E., and Dixon, W. J. Cancer of the Cervix—a Biometric Approach to Etiology. Cancer, *14:* 153-160, 1961.
33. Stocks, P. Cancer of the Uterine Cervix and Social Conditions. Brit. J. Cancer, *9:* 487-494, 1955.
34. Taylor, R. S., Carroll, B. E., and Lloyd, J. W. Mortality among Women in 3 Catholic Religious Orders. Cancer, *12:* 1207-1223, 1959.
35. Terris, M., and Oalmann, M. C. Carcinoma of the Cervix: an Epidemiologic. Study. J. Am. Med. Assoc., *174:* 1847-1851, 1960.
36. Terris, M., Wilson, F., Smith, H., Sprung, E., and Nelson, J. H. The Relationship of Coitus to Carcinoma of the Cervix. Am. J. Public Health, *57:* 841-847, 1967.
37. Towne, J. E. Carcinoma of the Cervix in Nulliparous and Celibate Women. Am. J. Obstet. Gynecol., *69:* 606-613, 1955.
38. Wahi, P. N., Saraswati, M., and Luthra, V. K. Factors Influencing Cancer of the Uterine Cervix in North India. Cancer, *23:* 1221-1226, 1969.
39. Wynder, E. L., Cornfield, J., Shroff, P. D., and Doraiswami, K. R. A Study of Environmental Factors in Carcinoma of the Cervix. Am. J. Obstet. Gynecol., *68:* 1016-1052, 1954.