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STATISTICAL EVALUATION OF THE INVESTIGATIONS CONCERNED WITH THE AETIOLOGY OF CANCER OF THE UTERINE CORPUS*

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A considerable number of the investigations into the aetiology of cancer of the corpus uteri has been engaged with the hormonal aspects of the problem. During the past 10 years we, too, have tried to approach the problem in this way. The principal feature investigated has been the correlation between the development of cancer of the corpus and the follicle hormone. The studies comprised clinical observations and animal experiments [4, 5, 6].

In the clinical studies we examined the correlation between glandular cystic hyperplasia, a condition commonly known to be associated with high, or protracted oestrogen levels, and cancer of the corpus. The results obtained for many series of different patients showed that at our department hyperplasia was associated with cancer of the corpus in 1.9, 2.1 and 3.4 per cent, respectively. In view of the average incidence of cancer of the corpus (0.03 per cent), the above values were considered to be extremely high and the high incidence of cancer of the corpus in the presence of glandular cystic hyperplasia was thought to be a proof of the existence of some not quite clear correlation between the genesis of hyperplasia, oestrogen production and cancer of the corpus.

The results of animal experiments seemed to confirm this view, insofar as treatment with dibenzanthracene induced tumour formation considerably more often in oestrogen-treated animals (12 tumours in 20 animals) than in those not treated with follicle hormone (5 tumours in 20 animals). It is of particular interest that in the animals treated with oestrogens dibenzanthracene induced tumour not only more often, but that the rate of tumour growth was also faster than in the control group. For example, when in the control group the first tumours appeared, 30 tumours had already developed in the oestrogen-treated group. It was also found that castration, too, had an influence on carcinogenesis (10 tumours in 20 animals), and the highest incidence of tumour

* This work is a statistical completion of the article published in the 7th volume of the Acta Morph. Hung. (1957)

was noted in castrated animals brought into constant oestrus by oestrogen treatment (14 tumours in 20 animals) *(Table I)*.

Table I

Number of animals	Group	Dibenzanthracene 15 mg	Oestrogen 0.2 mg	Number of tumours	Percentage of tumours
20	non castrated	0	0	0	0
20	non castrated	+	0	5	25
20	castrated	+	0	10	50
20	non castrated	+	+	12	60
20	castrated	+	+	14	70

Results of our series 2.

Since we had reported our results, many confirmatory and conflicting data have been published in the literature.

Without exaggeration, the aetiology of cancer of the uterine corpus is one of the most outstanding problems in gynaecological oncology. The problem is still far from being solved and the wide variety of conflicting views makes it difficult properly to appraise the evidence available. For this reason, as matters now stand, a more exact definition of the different views and the presentation of reliable proofs in support of them seem to be of paramount importance. This applies also to our own investigations. There are only two ways in which we can confirm the reliability of the results obtained and the validity of the conclusions drawn from them. Notably, the animal experiments should be reproduced critically and the clinical results should be subjected to statistical analysis. To support our claim that there exists a correlation between hyperplasia and cancer of the corpus, we must confirm the reliability and validity of our results. The only way to achieve this is statistical analysis.

The results of our animal experiments have been confirmed by the recent investigations of LIPSCHÜTZ, who reproduced our experiments in groups of 30 animals each and obtained following data.

Table II

Number of animals	Group	Dibenzanthracene 15 mg	Oestrogen 0.2 mg	Number of tumours	Percentage of tumours
30	non-castrated	0	0	0	0
30	non-castrated	+	0	7	23
30	castrated	+	0	12	40
30	non-castrated	+	+	16	53
30	castrated	+	+	20	67

Results of the investigations by LIPSCHÜTZ.

The data in *Table II* show that the results obtained by LIPSCHÜTZ are in complete agreement with ours. Thus, we can rest assured that the studies by LIPSCHÜTZ fully corroborate our findings, which therefore appear to be of unquestionable validity.

In the light of this fact it seemed doubly important exactly to verify the results of the clinical studies which had been the starting point of our investigations.

At the time the studies were conducted, lack of pertaining statistical evidence for Hungary prevented us from making the statistical calculations required. Meanwhile, the necessary data have been made available by the Central Bureau of Statistics Budapest, and by the National Oncological Institute of Hungary, thus it has become possible to carry statistical analysis and make the additional investigations.

The only aim of this report is to describe these investigations and the results they have yielded.

Apart from what has been mentioned above, these new investigations were justified also by the fact that the problem in question has recently been the subject of extensive arguments and discussions throughout the world. Thus, any new contribution may have great significance and may help further to clarify the issue.

The data supplied by the Central Bureau of Statistics, and the National Oncological Institute show, that in Budapest in 1954 there were about 15 to 16 cases of cancer of the corpus among the 100 000 females over 35 years of age examined, and in 1955 about 12.

On the other hand, we found cancer of the corpus in 2.1 per cent of the cases of hyperplasia. In statistical terms this would mean that in Budapest 2100 cases of cancer of the corpus should have occurred among the 100 000 females over 35 years of age, instead of the actual average of 15 to 16. Thus in our material, the incidence of cancer of the corpus in association with hyperplasia was several times the incidence for Hungary and the difference was statistically very highly significant.

Accordingly, its stands beyond doubt that the incidence of cancer of the corpus we have found in cases of hyperplasia was not due to chance.

It is only natural to ask what accounted for the high incidence of cancer of the corpus in the presence of hyperplasia? Three possibilities may be taken into consideration.

(i) An aetiological relationship exists between hyperplasia and cancer of the corpus.

(ii) As it is known, both cancer of the corpus and hyperplasia occur mainly during menopause. It is therefore conceivable that the high simultaneous incidence is ascribable to the period in which both conditions tend to occur more frequently.

(iii) Clinical selection. There is namely no doubt that in clinical material the incidence of cancer of the corpus is much higher than the average for the country as a whole. This, too, may account for the high incidence of the two diseases in association.

To elucidate these possibilities, the following investigations have been carried out.

ad (ii) To clarify the role of associated incidence during the menopause, we have examined the incidence of cancer of the corpus among 1000 women in menopausal age, free from haemorrhagic and tumorous disease, who, as far as our present knowledge of cancer of the corpus goes, were suffering from indifferent conditions, such as prolapse, descensus, etc. They had been treated at this Department in 1946 and 1950, *i. e.* at the time we had made our earlier studies. In this material the incidence of cancer of the corpus was 0.3 per cent, although the above diseases, too, tend to occur in the menopause. The difference between the present 0.3 per cent and the 2.1 per cent value found in the cases of hyperplasia is highly significant. *(Table III).*

Table III

	Cancer of the corpus		
	present	absent	total
Hyperplasia	12	563	575
Indifferent disease	3	997	1000
Total	15	1560	1575

$x^2 = 10 \cdot 54$ $p < 1$ per cent

Statistical analysis of the results of studies aimed at the elucidation of the role of simultaneous occurrence

Thus, the fact that both hyperplasia and cancer of the corpus occur mainly in the menopause does not explain the high incidence of cancer of the corpus in association with hyperplasia. Therefore, the arguments put forward by some authors in this respect are unacceptable.

ad (iii) The role possibly played by clinical selection has been approached in the following way. In the period between 1946 and 1950, 4797 patients with gynaecologic disease were treated at this Department. During that period 205 cases of hyperplasia and 24 of cancer of the corpus were encountered. Cancer of the corpus was associated with hyperplasia in 8 cases. Subtracting the 205 cases of hyperplasia from the total number of patients gives 4592, the number of patients from which the effect of clinical selection for cancer can be determined. Naturally the 8 cases in which cancer of the corpus was associated with hyperplasia were also subtracted from the 24 cases of cancer of the corpus and thus our calculations are based on 16 cancers of the corpus

occurring in 4592 patients. It is known, however, that cancer of the corpus is a disease of late menopause and if we want to determine the selective effect of the Department on cancer of the corpus, the 16 cases of cancer of the corpus should be related only to the number of menopausal patients. As in clinical material menopausal patients make up about 50 per cent of the total, 2400 is the number to which the 16 cases of cancer of the corpus should be related. This means that 16 cases of cancer of the corpus occurred among the 2400 menopausal patients with no hyperplasia in the period mentioned above at our department, representing an incidence of 0.8 per cent. As it has been pointed out, however, 4 per cent of the patients with hyperplasia had also cancer of the corpus during that same period. Statistical analysis *(Table IV)* shows the difference between the two data to be highly significant.

Table IV

		Cancer of the corpus		
		present	absent	total
Hyperplasia	present	8	197	205
	absent	16	2179	2195
	total	24	2376	2400

$x^2 = 19 \cdot 34$ $p \leqslant 0{,}1$ per cent.

Statistical evaluation of the investigations aimed at the elucidation of the effect of clinical selection

These investigations and calculations prove that, notwithstanding the fact that in clinical material the incidence of cancer of the corpus is several times higher than the country-wide average, the value found is so small in comparison with the incidence of cancer of the corpus in association with hyperplasia that clinical selection cannot explain it.

The above investigations and calculations have thus excluded two of the three possibilities that might have explained the remarkably frequent association of cancer of the corpus and hyperplasia. From this it follows that the significantly higher incidence of cancer of the corpus in cases of hyperplasia is based on an unclarified relationship between the two diseases.

The calculations have thus offered statistical proof of our opinion voiced for 10 years that a correlation exists between hyperplasia developing during the menopause and cancer of the corpus, a correlation which cannot be ignored or ascribed to chance.

Recent data in the literature appear to confirm our view. For example, NOVAK has stated recently that hyperplasia developing during the menopause and cancer of the uterine corpus would be different grades of the same condi-

tion. In his recent report, MÜLLER, analysing 129 cases of cancer of the corpus, stated that atypical hyperplasia occurred in all of them. He concluded that such a high common incidence cannot be attributed to chance.

Nevertheless, the problem is still far from being solved. At any rate, I think the role of hyperplasia must not be ignored or neglected. Apart from one's individual and personal opinion, I think it is now undeniable that shortly before and during the menopause hyperplasia should be considered a most serious change. For this reason it is essential that such patients be subjected to general treatment (hormones, vitamins) after abrasion. This therapeutic schedule should be followed in every case of menopausal hyperplasia, irrespective of one's view concerning the relationship between hyperplasia and cancer of the corpus. And let us leave it to future research to decide which of the two opposite views is true. I am certain that sooner or later this problem, too will find its final solution.

Summary

Investigations carried out during the past 10 years have shown that in the material of the 2nd Department of Gynaecology Budapest Medical University the associated incidence of hyperplasia and cancer of the uterine corpus was 2,1 per cent. In the present report studies and calculations aimed at finding the causes of this common incidence have been described. It has been found that the high incidence cannot be ascribed either to the period in which both diseases are most frequent or to the clinical selection of cancer. Thus, it must be some unclarified relationship between hyperplasia and cancer of the uterine corpus that may explain the high incidence of cancer of the corpus in association with glandular cystic hyperplasia.

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СТАТИСТИЧЕСКАЯ ОЦЕНКА ИССЛЕДОВАНИЙ, СВЯЗАННЫХ С ЭТИОЛОГИЕЙ РАКА ТЕЛА МАТКИ

Л. ВАЦИ

Проведенные в течение последних десяти лет исследования показали, что среди больных II. женской клиники гиперплазия совместно с раком тела матки встречается в 2,1% случаев. В настоящей статье автор сообщает результаты новых исследований и статистические вычисления, при помощи которых он пытается выяснить причину совместного появления этих болезней. Результаты исследования показали, что причиной этого большого процентного совпадения не является ни идентичность времени самой большой встречаемости этих двух болезней, ни влияние клиники на разпознавание рака. Согласно исследованиям причиной совместной встречаемости может быть только до сих пор еще не выясненная связь между гиперплазией и раком тела матки.

STATISTISCHE AUSWERTUNG VON UNTERSUCHUNGEN DER ÄTIOLOGIE DES GEBÄRMUTTERKÖRPERKREBSES

L. VÁCZY

Die während der letzten 10 Jahre durchgeführten Untersuchungen ergaben, dass im Krankengut der II. Frauenklinik Hyperplasie gemeinsam mit Gebärmutterkörperkrebs in 2,1% der Fälle vorkamen. In der vorliegenden Mitteilung werden die Resultate neuerer Untersuchungen veröffentlicht, zusammen mit statistischen Berechnungen, zur Klärung der Ursache des gemeinsamen Vorkommens. Laut Ergebnissen ist die Ursache des häufigen gemeinsamen Vorkommens weder die Übereinstimmung des Erscheinungsalters bei den beiden Krankheiten, noch der krebsselektierende Einfluss der Klinik. Der Grund des gemeinsamen Vorkommens dürfte ein zwischen der Hyperplasie und dem Gebärmutterkörperkrebs bestehender, einstweilen noch ungeklärter, Zusammenhang sein.

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