ESTROGEN THERAPY IN MENOPAUSE AND ENDOMETRIAL CANCER

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SUMMARY

The hormone dependency of endometrial cancer and the increase of its incidence seem to be generally accepted. The Authors expose the results of a four year retrospective epidemiological research aiming at verifying the possible role of menopausal estrogen assumption in the etiopathogenesis of the above mentioned disease. Two groups of post-menopausal patients were examined, who underwent total abdominal histerectomy and bilateral salpingo-ooforectomy: 168 were endometrial cancer free, 50 were affected. The percentages of estrogen users, the exposition time and type of therapy were carefully analised in them. No correlation could be found between estrogen consumption, which resulted much lower than in the U.S.A., and endometrial cancer incidence. The relatively short assumption times, the different drug associations, and the hypoestrogenic origin of the most disturbing menopausal symptoms can help to explain this finding which is, however, in agreement with what emerges from studies carried out in different countries by several Authors.

Endometrial carcinoma increasing incidence, both as an absolute remark and when compared to cervical cancer, seems to be an object of general agreement ([1]).

Menopausal assumption of exogenous estrogens, which trebled in the last years in the U.S.A. ([2]), probably deserves a prominent role among the several hypotheses proposed to explain the event. The endocrine theory in endometrial cancer pathogenesis is based on the observation that a long-lasting estrogen stimulation, unopposed with progesterone, can induce a precancerous lesion in the endometrium, such as cystic or adenomatous hyperplasia. Besides, the high fat tissue conversion rate of androstenedione to estrone ([3, 4, 5, 6, 7]) makes obesity a sure risk factor for endometrial cancer so as, otherwise, are chronic liver diseases which, preventing androstenedione conversion to ketosteroids, enhance the blood levels of this estrogen-precursor. The endocrine theory is furtherly supported with data reported on the occurrence of endometrial cancer in an ovariectomized patient after a 25 year estrogen treatment ([9]), in a patient affected with a Sheehan's syndrome after a 17 year stilbestrol treatment ([10]), and after a long-lasting estrogen therapy for gonadal dysgenesis ([11]).

Though no certainty exists about menopausal estrogen assumption ability to increase endometrial cancer incidence, we report in this note the results of a four year retrospective study, aiming at verifying, from an epidemiological point of view, if estrogen supply can be properly charged for a higher risk of endometrial cancer.

MATERIAL AND METHODS

A retrospective study on two groups of in-patients has been carried out in our Department. The first group consists of 168 post-menopausal patients who underwent total abdominal histerectomy and bilateral salpingo-ooforectomy: no endometrial cancer was found at histology (five had a glandulocystic hyperplasia, two an adenomatous one). The second group consists of 50 post-menopausal patients affected with a histolo-

gically proved endometrial cancer at different clinical stages (fresh cases).

Every patient was carefully inquired whether she submitted to a post-menopausal hormonal therapy, and its type and lenght were determined if possible. Though our cases are not all consecutives, no random criteria were followed in our study.

RESULTS

Table 1 shows the results of our epidemiological study: 31 patients of the control group (18.4%) and 8 patients of the cancer group (16%) said they used hormones in menopause; two of the 31 control users showed a histologically proved endometrial hyperplasia; five of the 137 control non-users had an endometrial hyperplasia too. The most frequent therapy lenght was 1 to 3 years both in the control (51.6%) and in the cancer (50%) group. In both groups the hormone assumption was more frequently started between the ages of 45 and 55, when menopausal symptoms are more likely to appear. The estro-androgen association was the most often prescribed therapy, while sequential estrogens and progestins were only scarcely utilized. We considered « unknown » the type of therapy, when showing the patient the most used and common commercial confections couldn't help her to remember it. We point out, lastly, that one non-user cancer patient was simultaneously affected with a breast cancer.

DISCUSSION AND CONCLUSIONS

Endometrial cancer is generally considered to be hormone-dependent; higher estrone ([8, 12, 13]) and estradiol ([3, 4, 15, 31]) levels are found in the affected patients when compared to controls; menopausal endogenous hyperestrogenism, unopposed with progesterone, makes the endometrium become hyperplastic and, sometimes, neoplastic. It seems, thus, reasonable to associate the increasing incidence of endometrial cancer and the greater use of estrogens in menopausal therapy. The interdependency, however, between exogenous estrogens and endometrial cancer is far from being demonstrated, and the problem is still open: if some Authors ([2, 16, 17, 18, 19, 21, 22]) claim a close relation, others, on the contrary, deny it ([23, 24, 25, 26]).

The results we obtained show a much lower menopausal estrogen consumption in our casuistry than in other Authors' (Tab. 1): our user percentages, 18% in the control and 16% in the affected patients, are very different from Ziel and Finkle's ([2]), 15% in the control and 57% in the affected patients. The epidemiological situations are quite different, even because in the U.S.A. the most used estrogens are the conjugated ones.

In our casuistry, on the contrary, the mostly used, perhaps because of their wider prescription, products are the estro-androgen associations, both in the control (38.7%) and in the affected (50%) group, while the respective percentages for conjugated estrogens are 16.2% and 25%.

The mean estrogen exposition time is very important too: while in our casuistry it most often ranged from 1 to 3 years (51.6% of the controls and 50% of the affected patients), several Authors ([2, 17, 19, 21, 22]) state that the risk increases proportionally with the assumption time and that the relative risk is four times greater ([19]) in patients whose exposition time ranged from 5 to 9 years, and eleven times greater when estrogen assumption lasted more than ten years.

Only six (19.4%) of control and one (12.5%) of cancer patients who were on therapy assumed the hormone for more than 3 years.

These data furtherly confirm that our therapeutic approach to menopause is different from that in the U.S.A., even if data from Rendina and Donadio ([27]) resemble those from U.S.A. casuistries: in their retrospective study 663 out of 912 (73%) cancer patients had been users, while in the controls the percentage was 66%.

Table 1. — *Estrogen therapy in menopause.*

	CONTROLS (168)	N.	%	CANCER (50)	N.	%
Users		31 *	18,4		8	16
Non users		137 **	81,6		42 ■	84
Exposition time	less than 1 Yr	9 •	29	less than 1 Yr	3	37,5
	1 to 3 Yrs	16	51,6	1 to 3 Yrs	4	50
	more than 3 Yrs	6 • •	19,4	more than 3 Yrs	1	12,5
Age when therapy was started	less than 45 Yrs	11	35,5	less than 45 Yrs	2	25
	45 to 55 Yrs	18 •	58	45 to 55 Yrs	6	75
	more than 55 Yrs	2 • •	6,5	more than 55 Yrs	0	—
Type of therapy	Conjugated estrogens	5 •	16,2	Conjugated estrogens	2	25
	Natural estrogens	2 • •	6,5	Natural estrogens	1	12,5
	Synthetic estrogens	1	3,3	Synthetic estrogens	0	—
	Estrogens-progestins	3	9,5	Estrogens-progestins	0	—
	Estrogens-androgens	12	38,7	Estrogens-androgens	4	50
	Unknown	8	25,8	Unknown	1	12,5

* 1 adenomatous hyperplasia - 1 glandulocystic hyperplasia
* * 1 adenomatous hyperplasia - 4 glandulocystic hyperplasia
• 1 adenomatous hyperplasia
• • 1 glandulocystic hyperplasia
■ 1 breast cancer simultaneous with the endometrial cancer.

Anyway, the «risk ratio» emerging from our data, between menopausal patients on estrogen therapy and not, is 0.043 (Tab. 2): no correlation is found between menopausal estrogen assumption and endometrial cancer.

This finding could be due to the low estrogen assumption rate in our patients, to the type of therapy and its lenght; we underline, however, that the menopausal symptomatic therapy is usually needed by patients with low estrogen plasma levels and consequently at low risk for endometrial cancer, independently on the therapy.

Table 2. — *Risk ratio between estrogen therapy and no-therapy in the two groups of post-menopausal examined patients.*

	Therapy	No-therapy
Controls	31 (18,4%)	137 (81,6%)
Cancer	8 (16%)	42 (84%)

Risk ratio = 0,043

We can at last state, in agreement with others ([28, 29, 30]), that estrogen therapy doesn't increase the risk of endometrial cancer: Koller ([29]) didn't find a higher incidence of it in women on estrogens for a long time because of unoperable breast cancer; Kullander ([28]), in an epidemiological study carried out in Sweden, affirms that endometrial cancer higher incidence occurs only in some age groups and is not in correlation with menopausal estrogen assumption; likewise Rosol and Coll. ([30]) show that in Czechoslovakia the endometrial cancer increasing occurrence is limited to women from 70 to 80 years of age who couldn't surely dispose of estrogens at their menopauses in their country.

Anyway, beyond the different results emerging from the several epidemiological researches we examined, we like to underline the opportunity of a general agree-

ment on the need of associating progesterone to estrogens in the prescription of menopausal therapies: it would counter balance the hyperplastic action exerted by estrogens on the endometrial cell. Recent data by Studd and Coll. ([32]) and by Upton ([33]) evidence a significant lowering of endometrial cancer risk when progestins, cyclically administered, are given to integrate estrogen therapies: and this is a fact none can ignore.

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