OBESITY AS A RISK FACTOR FOR ENDOMETRIAL CANCER

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Summary: The epidemiology and risk factors for endometrial cancer are reviewed, with current data.

Obesity seems to be the main risk factor for this neoplasia, both because it is very common in the female population, and because the other risk factor (i.e. estrogen replacement therapy) has almost disappeared with the addition of progesterone therapy.

The pathogenesis of obesity as risk factor, although it is not completely clear and unique, is examined.

EPIDEMIOLOGY

Data on endometrial cancer are extremely varied, the incidence varying with the population examined.

There is a noteable difference not only among the peoples of the European and North American continents and those of the continents of Asia, Africa and South America, but there is also a difference among populations of the same continent.

As an example of this variability, we would refer to some of the data found in current literature.

– In Japan, the incidence is 1.3/100,000 while in the U.S.A. it is 15.3 ([1]).

– Among Japanese women who have emigrated to the U.S.A., there is a considerable increase in the incidence of endometrial cancer. Therefore, when environmental factors are varied there is also a variation in the incidence, even within the same ethnic group ([2]).

– The incidence also varies with geographical variation. In San Francisco Bay, U.S.A., it is 40.3, while in Connecticut it drops to 25.9 and in New Mexico it is only 17.9 ([3]).

– Studies have also shown that there is a difference in the incidence of endometrial cancer in terms of the races of the U.S.A. Among the white population it is 20.1 while it is 9.3 among negroes ([4]).

We can therefore safely assume that both genetic and environmental factors affect the incidence of this type of carcinoma.

When considering environmental factors, the most important element seems to be nutrition. There is, in fact, a close relationship between endometrial cancer and a diet which is rich in animal fats ([5]).

Another fact of considerable importance is the apparent increase in this type of cancer over the last decades. For example, in San Francisco Bay in 1969 it was quoted as being 24.9/100,000 while it had risen to 40.3 in 1973 ([3]). During the same period the ratio between the incidence of invasive cancer of the portio and endometrial cancer was also modified. At the beginning of the century the ratio between these two types of carcinoma was 1:10, while in 1972 it was approximately 1:1 ([6]).

Most certainly, improved diagnostic techniques have contributed to change this ratio, as too, has the increase in the average life-span (age). The majority of cases of endometrial cancer (85.5%) is found in post-menopausal patients ([7]), and, in the more advanced countries, women today live approximately one third of their lives after menopause ([8]).

RISK FACTORS

Estrogens

The relationship between the assumption of estrogens, as hormonal replacement therapy, and the increase in endometrial cancer has already been underlined by many Authors. In 1975, Smith's research ([9]) raised many questions. Smith stated that the use of estrogens increased the risk of endometrial cancer by as must as five times, while Ziel and Finkle ([10]) said that the risk was increased by 7.6 times. The data, deduced from retrospective studies, were severely criticized and, in good part, contradicted by other Authors ([11, 12, 6]).

There is no doubt that estrogens play an important role in development of endometrial cancer, but their significance has been somewhat reappraised, as can be seen if the incidence of obesity and the presence of this neoplasia are compared.

Obesity

The risk factor of obesity in connection with this carcinoma is so expected that, surprisingly, it is rarely seriously quantified in literature.

As a matter of fact, Kjellgren ([6]) only relates the weight of the patients: the average weight of the patients affected by endometrial cancer was 68 kg, while the average weight of the controls was 62 kg.

Damon ([13]) states that there was a 13% weight increase in the affected group in comparison to the control group.

Neither relates data on statistical significativeness.

Mac Mahon ([14]), on the other hand, has quantified the risk linked to excess weight. This author has divided the population in 3 groups according to their weight: in comparison with groups 1 and 2, group 3 (superior weight) was assigned a greater risk factor of 1.8. The heavier half of group 3 was assigned a greater risk factor of 2.4, always in comparison with groups 1 and 2.

On the basis of this research and the work of other Authors ([15, 16, 17]) one may therefore assume that there is a direct ratio between endometrial cancer and obesity, and that the risk coefficient increase as excess weight increases.

Pathogenic hypothesis

The best working hypothesis suggests that obesity is a risk factor as it leads to hyperestrogenism, particularly in the post-menopausal age, when ovarian hormonal secretion has ceased.

This causes an increase in estrone due to the periferic aromatization of the androstenedione - produced by the adrenals.

The estrone is 4-5 times greater in obese women in comparison to women of the same age but who are not overweight ([18]). Aromatization occurs principally at the level of the adipose tissue, but it also occurs in the liver, both in obese ([19]) and in non obese ([20, 21]).

A second mechanism, affecting the obese, is the decrease of the SHBG and a reduction in their linking capacity. There is a reduction of approximately 70% ([22]). This causes an increase in the free estrone (i.e., the active hormone) in the blood.

A third, and no less important effect of hyperestrogenism in obese women is the significant reduction of estrogen metabolism, more precisely, of hydroxylation in C-2 ([23]).

Thus, non uterotropic metabolites decrease and the 16-hydroxylated compounds increase; although weaker than estradiol, they may cronically produce endometrial alterations.

These same mechanisms are also present in the pre-menopausal age ([24]) and thus obesity may cause endometrial changes also in women who are still fertile.

Given the undeniable "hormone-dependence" of endometrial cancer ([25, 30]), there has been a frantic search to find a typical hormone pattern. Many Authors ([31-35]) see it in the action of androstenedione (and,

above all, in its products of conversion), which increases in comparison to controls.

When, however, control groups are made up of healthy women of the same age and weight ([22, 26-39]), such differences disappear.

These results would not deny the theory of hormone-dependence, but rather lay stress on the importance of obesity as a risk factor (in fact, hormonal changes are correlated to weight changes).

Endometrial cancer does not, however, have a single, unique pathogenesis. Quinn ([7]) has discovered that in 106 patients affected by endometrial cancer, there was a low incidence of obesity and also of hyperestrogenic factors — such as anovulation —, which is often seen in the history of patients affected in the post-menopausal phase ([4, 40, 41]).

Lauritzen ([42]), on the other hand, thinks that obesity does not have the same effect as hyperestrogenism action.

He states that estrogens are neither carcinogenetic nor mutagens, but they are "conditioners" of the "internal milieu" of the organism. They may, by increasing the number of cellular mitosis, increase the statistical probability that a real cancerogenic substance may damage the genetic material and decrease, for the same reason, the reparative mechanisms of the DNA.

Obesity, like diabetes, does increase the probability that cancer of the uterus and of the breast may develop, as these organs have a high metabolic turnover of carbohydrates and fats. In the case of both obesity and diabetes, this metabolism utilizes these substances in a pathological way.

CONCLUSION

The etiopathogenesis of endometrial carcinoma has not yet been exactly defined. The greatest risk factors are continuative estrogen therapy and obesity.

With regards to the former, it would seem that the risk is anulled, if the estrogen therapy is cyclic and progestins are added ([8, 43]).

With regards to obesity, it is above all necessary to admit that obesity is fairly common. In our study of women in menopause, 52.9% were overweight (IMC >23.5) and 11.8% were obese (IMC >29.5).

Lacking hormonal markers which can be regarded as absolutely reliable for the identification of the population at risk, mass screening should be based on carrying out periodic endometrial smear, which, in the case of obese and overweight subjects, should be carried out more frequently. Primary prevention may consist of a vaste and intensive campaign to educate people about correct diet and nutrition ([44]).

BIBLIOGRAPHY

1) Doll R., Muir C., Waterhouse J. (eds.): "Cancer incidence in five continents. International Union Against Cancer", Springer-Verlag, Berlin, vol. 2, 1970.
2) Haenszel W., Kurihara M.: *J. Natl. Cancer Inst., 40*, 43, 1968.
3) Weiss N. S., Szekely D. R., Austin D. F.: *N. Engl. J. Med., 294*, 1259, 1976.
4) Gusberg S. B.: *Am. J. Obst. Gyn., 126*, 535, 1976.
5) Lipsett M. B.: *Cancer, 35*, 3359, 1975.
6) Kjellgren O.: *Acta Obst. Gyn. Scand.*, Suppl. *65*, 77, 1977.
7) Quinn M. A., Kneale B. J., Fortune D. W.: *Gyn. Oncol., 20*, 298, 1985.
8) Speroff L., Glass R. H., Kase N. G.: "Clinical Gynecologic Endocrinology and Infertility", Williams and Wilkins, Baltimore, 1983.
9) Smith D. C., Prentice R., Thompson D. J., Herrmann W. L.: *N. Engl. J. Med., 293*, 1164, 1975.
10) Ziel H. K., Finkle W. D.: *N. Engl. J. Med., 293*, 1167, 1975.
11) Kistner R. W.: *Obst. Gyn., 48*, 479, 1976.
12) Lauritzen C.: "Oestrogens and endometrial cancer: a point of view". *Clin. Obst. Gyn.*, vol. 4, n. 1: "The menopause", W. & B. Saunders, London, 145, 1977.
13) Damon A.: *J. Natl. Cancer Inst., 24*, 483, 1960.

14) MacMahon B.: *Gyn. Oncol., 2*, 122, 1974.
15) Wynder E. L., Escher G. C., Mantel N.: *Cancer, 19*, 489, 1966.
16) Elwood J. M., Cole P., Rothman K. J., Kaplan S.D.: *J. Natl. Cancer Inst., 59*, 1055, 1977.
17) Davies J. L., Rosenhein N. B., Antunes C. M. F., Stolley P. D.: *Obst. Gyn. Survey, 36*, 107, 1981.
18) Siiteri P. K.: *J. Endocr., 89*, 119, 1981.
19) Siiteri P. K., Williams J. E., Takaki N. K.: *J. Ster. Biochem., 7*, 897, 1976.
20) Siiteri P. K., MacDonald T. C.: "The role of extraglandular estrogen in human endocrinology". In: *Handbook of Physiology*, S. R. Geiger, E. B. Astwood, R. O. Greep (eds.), New York, The American Physiological Society, 615, 1973.
21) Gordon G. C., Olivo J., Rafii F., Southern A. L.: *J. Clin. Endocrinol. Metab., 40*, 1018, 1975.
22) Nisker J. A., Hammond G. L., Davidson B. J., Frumar A. M., Takaki N. K., Judd H. L., Siiteri P. K.: *Am. J. Obst. Gyn., 138*, 637, 1980.
23) Schneider J., Bradlow H. L., Strain G., Levin J., Anderson K., Fishman J.: *J. Clin. Endocrinol. Metab., 56*, 973, 1983.
24) Kopelman P. G., Pillkington T. R. E., White N., Jeffcoate S. L.: *Clin. Endocr., 12*, 363, 1980.
25) Gusberg S. B.: *Am. J. Obst. Gyn., 54*, 905, 1947.
26) Gusberg S. B., Moore D., Martin F.: *Am. J. Obst. Gyn., 68*, 1472, 1954.
27) Gusberg S. B., Hall R. E.: *Obst. Gyn., 17*, 397, 1961.
28) Gusberg S. B., Kaplan A.: *Am. J. Obst. Gyn., 87*, 662, 1973.
29) Gusberg S. B., Kardon P.: *Am. J. Obst. Gyn., 111*, 633, 1971.
30) Ziel H. K., Finkle W. D.: *N. Engl. J. Med., 293*, 1167, 1975.
31) Hausknecht R. U., Gusberg S. B.: *Am. J. Obst. Gyn., 116*, 98, 1973.
32) MacDonald P. C., Siiteri P. K.: *Gyn. Oncol., 2*, 259, 1974.
33) Rubin B. L., Gusberg S. B., Butterly J., Han T. C., Maralit M.: *Am. J. Obst. Gyn., 114*, 660, 1972.
34) Twombley G. H., Schneider S., Levitz M.: *Am. J. Obst. Gyn., 82*, 424, 1961.
35) Schindler A. E., Ebert A., Friedrich E.: *J. Clin. Endocrinol. Metab., 35*, 627, 1972.
36) MacDonald P. C., Edman C. D., Hemsell D. L., Porter J. C., Siiteri P. K.: *Am. J. Obst. Gyn., 130*, 448, 1978.
37) Judd H. L., Lucas W. E., Yen S. S. C.: *J. Clin. Endocrinol. Metab., 43*, 272, 1976.
38) Davidson B. J., Gambone J. C., Lagasse L. D., Castaldo T. W., Hammond G. L., Siiteri P. K., Judd H. L.: *J. Clin. Endocrinol. Metab., 52*, 404, 1981.
39) Marchesoni D., Gangemi M., Maggino T., Mozzanega B., Di Lenardo L.: "Obesità e carcinoma dell'endometrio in menopausa". In: *Obesità e menopausa"*, Pozzi Ed., Roma, 111, 1983.
40) Wynder E. L., Escher G. C., Mantel N.: *Cancer, 19*, 489, 1966.
41) Onnis A.: "I tumori maligni del corpo dell'utero". In: *Ginecologia ed Ostetricia*, Monduzzi Ed., 311, 1982.
42) Lauritzen C.: "Problemi di peso durante il climaterio". In: *Obesità e menopausa*, Pozzi Ed., Roma, 142, 1983.
43) Onnis A., Marchesoni D., Gangemi M.: "Terapie sostitutive personalizzate". In: *La prevenzione in menopausa: strategie terapeutiche.* Monduzzi Ed., 165, 1985.
44) Onnis A.: "Prophylaxis and prevention on gynecologic oncology: new trends". SOG & SEMES Ed., Padova, 1982.