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Journal Title: Acta Endocrinol Suppl
Journal Vol: 233
Journal Issue:
Journal Year: 1980
Article Title: Pathophysologic consideration in the treatment of menopausal patients with oestrogens. The role of estriol in the prevention of mammary cancer
Article Author: Lemmon
Article Pages: 17-27

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11 pp scanned 11/15/05

Acta Endocrinologica 1980, Suppl. 233: 17–27.

Pathophysiologic considerations in the treatment of menopausal patients with oestrogens; the role of oestriol in the prevention of mammary carcinoma

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Abstract. At menopause, several abnormalities in oestrogen metabolism have been reported, which may increase the likelihood of cancer development in the breast or uterus following oestrone or oestradiol-17β supplementation. Occult hypothyroidism reduces the rate of oestrogen inactivation by C2 hydroxylation, and 15–20% of women have low rates of C16 hydroxylation to oestriol. Reduced sex hormone binding globulin concentration occurs in association with obesity, thereby increasing the biologically active unbound fraction of oestradiol in plasma. Since oestriol undergoes minimal metabolism after absorption, does not bind to sex hormone binding globulin, and has an anti-oestradiol action by decreasing the duration of nuclear binding of oestradiol-receptor proteins, it is less likely to induce proliferative changes in target organs of cancer-prone women than oestrone or oestradiol. Intermittent non-conjugated oestriol treatment has demonstrated the most significant anti-mammary carcinogenic activity of 22 tested compounds as well as anti-uterotropic activity in intact female Sprague Dawley rats fed either of two dissimilar carcinogens (7, 12 dimethylbenz(a) anthracene, procarbazine) and followed for their natural life span. The protective effect was specific for mammary carcinomas only and has been decreased in rats with a 20% increase in growth curves. Clinical experience thus far with oral oestriol therapy of post-menopausal women has indicated little hazard of cancer development.

Key words: oestriol, oestrogen therapy, breast carcinoma.

Oestriol metabolism during and after the menopause is an intriguing area of endocrinology. As ovarian oestradiol and oestrone productions wane, urinary oestradiol excretion continues at widely varying rates in different women, which reflects the parity previously experienced by each (Gross et al. 1977; Cole et al. 1976). Nulliparity enhances the risk of breast and endometrial cancer development in the years after menopause, and pregnancy completed prior to age 25 reduces the subsequent risk of breast cancer during and after menopause (Klopper & Farr 1978; MacMahon et al. 1978). The majority of investigations of urinary oestriol/oestrone + oestradiol quotients in healthy populations of pre-menopausal or post-menopausal women with varying historical risks of breast cancer development have substantiated an inverse correlation between this ratio and breast cancer risk (Table 1). Since the incidence of endometrial cancer tends to parallel the risk of breast cancer, these data may also have etiologic significance for this less frequent tumour.

A review of pre-menopausal oestrogen excretion data which have been reported over the past 20 years from healthy Caucasian women also emphasizes the wide variation in the ratio of oestriol recovered by any of several methods, to the recovery of oestrone and oestradiol (Lemon 1972). Oestriol produced in the follicular phase of the menstrual cycle is entirely derived by 16α hydroxylation from oestrone and oestradiol secreted by the ovary, as shown by double isotope dilution studies (Barlow & Logan 1966).

During the luteal phase of the cycle when oestriol production often rises (Flood et al. 1976), 15–48% of excreted oestriol originates from non-oestrone

Table 1

Urinary oestriol excretion quotients of different populations in relation to risk of breast cancer.

Author	Location	(Population) Ratio oestriol/oestrone + oestradiol, follicular; luteal			
		High risk	Intermediate	Low risk	Significance
Briggs 1972	Zambia pre-men.	(European Cauc.) 0.83–0.64	(African) 1.02–0.76	(Indian) 1.16–1.48	< 0.01 (luteal)
Dickinson et al. 1974	Honolulu pre-men. 15–24 years	(Caucasian) 0.57–0.71	(Chinese) 0.84–1.21	(Japanese) 0.76–0.98	< 0.001
MacMahon et al. 1971, 1974	North America Honolulu vs., Japan, Hong Kong Taiwan pre-men. 15–24 years	(Caucasian) 0.59–0.74	(Asian descent) in Honolulu 0.80–. . . (Caucasians) in Honolulu 0.61–. . .	(Asian) 1.43–1.41	< 0.01
Bulbrook et al. 1976	United Kingdom vs. Japan pre-men. 17–30 years	(Caucasian) 0.97 ± 0.6–0.9		(Japanese) 1.2 ± 0.6–0.9	n.s.
Hayward et al. 1978	United Kingdom vs. Hawaiian Japanese vs. Japan under 32 years	(Caucasian) 0.46	(Japanese in Hawaii) 0.46	(Japanese) 0.51	n.s.
Gross et al. 1977	Israel post-men. 50–59 years	(European caucasian) 1.19 *	(African, Asiatic origin) 2.16–2.17 *	(Yemeni) 2.54 *	< 0.001
	Median	0.58–0.71	0.82–. . .	1.18–1.41	

* E_3/E_1

or oestradiol sources. The ratios of urinary oestriol to oestrone + oestradiol calculated from metabolism of administered ^{3}H-oestradiol-17β tracer, or from simultaneously excreted non-radioactive steroids are in agreement during the follicular phase, but the radioactive method underestimates the quotient in the luteal phase by about 20% (Eren et al. 1967). This quotient is persistently elevated in parous women after delivery for 1–2 years, in both phases of the cycle (Dove et al. 1971). The source of this additional oestriol production is unclear. After menopause an increased share of urinary oestriol is derived from adrenocortical precursors, which are increased by ACTH therapy and various types of stress (Barlow 1964). These non-oestradiol precursors to oestriol production are reduced in women with endometrial carcinoma, even though no significant differences have been noted in the mean urinary oestriol quotients from post-menopause controls (Hausknecht & Gusberg 1969). Menopausal women therefore may have highly variable metabolism of oestrogens from ovarian and adrenocortical sources, as a result of postulated genetic factors (Lemon 1972), previous pregnancy inducing a lasting increase in mixed function oxidase activity producing oestriol (Cole et al. 1976), dietary and environmental changes (Dickinson et al. 1974; MacMahon et al. 1973) or drug exposure which can alter hydroxylase activity (Wattenberg 1975).

The high variability of one aspect of oestrogen metabolism before and after menopause is illus-

trated by the ratio of simultaneous blood production rates calculated for oestrone, oestradiol and oestriol (Table 2). It is, therefore, unlikely that women will respond similarly in their metabolic response to oestrogenic supplementation at the time of the menopause.

The inverse correlation between breast cancer risk and the average oestriol excretion quotient for healthy populations shown in Table 1 also appears to be predictive of benign breast disease. The majority of patients with fibrocystic disease excrete a low ratio of oestriol to oestrone and oestradiol, but further evaluation would be desirable (Lemon 1972). However, by the time breast or endometrial carcinoma has developed in women decades later, when they are post-menopausal, it is harder to obtain convincing proof of significantly reduced oestriol excretion ratios. Initial reports of reduced oestriol excretion in breast carcinoma (Schweppe et al. 1967; Bacigalupo & Schubert 1966; Lemon 1966) have not been substantiated by others (Cole et al. 1978; Thijssen et al. 1975; Tominaga et al. 1975; Arguelles et al. 1973; Gronroos et al. 1968; Olina 1964; Ukai 1964). Abnormal urinary oestriol quotients have not yet been observed in endometrial carcinoma compared to women with benign uterine disease (Hausknecht & Gusberg 1969; Brown et al. 1959). As Longcope & Pratt have pointed out, urinary oestriol excretion quotients may reflect peripheral glucuronide metabolism rather than oestriol blood production rate (Longcope et al. 1978; Pratt & Longcope 1978). However, several disorders of oestrogen metabolism have been demonstrated which appear related to increased cancer risk at the menopause.

Biochemical disorders of oestrogen metabolism associated with obesity, hypothyroidism and breast pre-cancer and cancer increasing sensitivity to administered oestrone/oestradiol

Administration of pharmacologic pulse-doses of oestrone or oestradiol to women with benign breast disease or breast cancer has led to a reduced excretion of oestriol during the ensuing 3–6 days (Table 3). When tracer doses of radioactive oestrogens were administered in one study, a reduction in radioactive oestriol metabolites was not found in breast cancer patients, so that dosage may be an important factor producing a reduction in the rate of 16α hydroxylation of oestrone to oestriol. In Bacigalupo & Schubert's investigations (1966) about one-half of the women with pre-malignant breast disease who were pre-menopausal and one-half of the menopausal women with breast cancer demonstrated a reduced metabolism of orally or parenterally administered oestradiol-17β or oestrone to oestriol.

Reduced oestrogen metabolism can also result from decreased hydroxylation of C2, which has

Table 2

Heterogeneity in oestriol blood production rates

	Ratio P_B oestriol/oestrone + oestradiol						
	< 0.050	0.051–0.100	0.101–0.150	0.151–0.200	0.201–0.250	0.251–0.300	> 0.301
Pre-menopause aged 21–40 foll. phase	3*	6	9	1			
luteal phase	6	10	3				
Post-menopause			1	1		1	2
Post-menopause with breast cancer		2	1	1	1		

* Number of subjects in each group. Longcope & Pratt 1978, 1977; Pratt & Longcope 1978.

Table 3

Conversion of pharmacologic doses of oestrone or oestradiol-17β to oestriol

	Group	Dose	Urinary oestriol/oestrone + oestradiol		
			Pre-Rx	24–48 h	24–72 h
Schubert & Bacigalupo 1961	3 non-pregnant women 21–27 years	oestradiol benzoate 5 mg/d × 3	1.10		0.93
	8 non-pregnant women with fibrocystic disease 19–48 years		0.82		0.36
Bacigalupo & Karlapp 1962	5 non-pregnant women 22–68 years	oestrone 2.5 mg iv	0.94	3.0	
	7 non-pregnant women with fibrocystic disease, good oestriol excretion 14–48 years		2.7	2.9	
	6 non-pregnant women with fibrocystic disease, low oestriol excretion 25–50 years		0.46	0.91	
Beer & Gallagher 1955	1 Hodgkin's disease 28 years	^{14}C-oestradiol 140–350 mg im			0.73*
	2 ca. breast 53–62 years				0.15–0.41
Hellman et al. 1971	6 normal women 63–80 years	^{3}H-oestradiol 5 μCi iv			0.40**
	10 breast cancer 47–76 years				0.55

* As cumulative percent of ^{14}C in oestrone, oestradiol and oestriol fractions over 96 h.
** As cumulative percent of ^{3}H in oestrone and oestriol fractions after 72 h.

seldom been measured in clinical studies. Catechol oestrogen metabilites constitute an equally large portion of urinary metabolites as 16 hydroxy derivatives from normal women. Thyroxine catalyzes the formation of 2-OH oestrone and oestradiol, leading to a reciprocal relationship between variations in thyroid metabolism and in oestriol biosynthesis (Hellman et al. 1971; Brown & Strong 1965). In hypothyroidism decreased excretion of total oestrogen metabolites per unit time may occur, as well as a reduction in catechol oestrogen metabolites and a relative increase in oestriol and its epimers. Thyroxine reverses these changes.

It has recently been reported that of the women coming in for mammograms at a large mid-western USA clinic, those having received thyroid supplementation for more than 10 years have a 3–6 fold increase in breast cancer compared to untreated patients (Kapdi & Wolfe 1976). Those who were nulliparous and longest on thyroid medication had the highest cancer risk. Over one-half of newly diagnosed breast cancers at another mid-western USA institution have subnormal tri-iodothyronine concentrations in their plasma by radioimmunoassay and an excessive response to thyrotrophin-releasing hormone, confirming earlier observations (Rose & Davis 1978; Mittra et al. 1974). These observations would be in accord with earlier reports of simple thyroid atrophy in two-thirds of breast cancer patients at autopsy compared to only

16% of control autopsies in the north-eastern United States (Sommers 1955). Occult hypothyroidism, therefore, may be a contributing factor to the risk of breast cancer. It also could readily confound interpretation of urinary oestriol ratios by markedly increasing the proportion of oestriol excreted in breast cancer.

Obesity is a common disorder in menopausal and post-menopausal women, and has been associated in many epidemiologic investigations with a higher risk of breast and endometrial carcinoma (Cole et al. 1976; MacMahon et al. 1973). Most often this increased risk has been attributed to increased oestrone synthesis by fat cells in these patients. However, impaired synthesis of sex hormone binding globulin (SHBG) has been reported in both sexes in obese individuals (O'Dea et al. 1979; Glass et al. 1977). Since over 97% of plasma oestradiol is carried on SHBG or albumin in inert biologic form, any reduction in these transport mechanisms might increase the biologic activity per millimole of dose administered of oestradiol and oestrone (Wu et al. 1976). Since some menopausal women (including many with endometrial hyperplasia and/or fibrocystic breast disease) (Grattarola 1978) still have high testosterone secretion from the ovaries, additional oestradiol may be displaced from SHBG, owing to the higher association constant of testosterone for SHBG than oestradiol.

Therefore, at least three disorders of oestrogen metabolism may be present in menopausal women, which may render a subset of individuals especially likely to manifest excessive proliferative activity in the breast or uterus from a given supplemental dose of oestrone or oestradiol – disorders of mixed function oxidase reducing 2-OH and 16α-OH hydroxylation and reduced SHBG synthesis. Few, if any, menopausal women receive laboratory studies appropriate for these disorders prior to treatment.

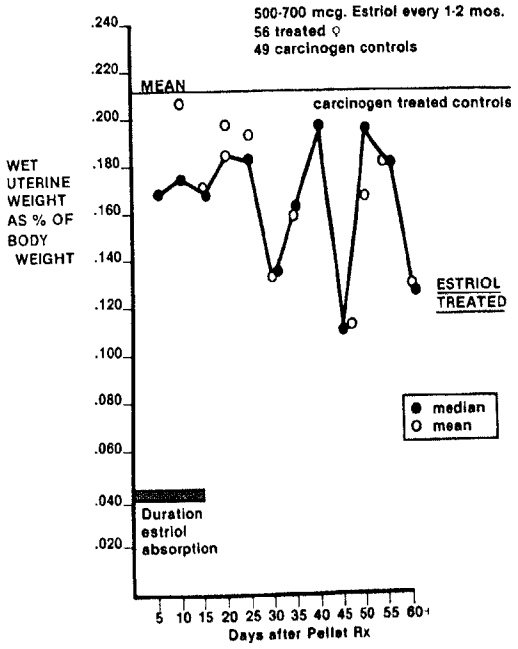

Fig. 1

Mean uterine weight (as percentage of body weight) at time of sacrifice because of malignant neoplasia, in control rats fed carcinogen, and in oestriol-treated carcinogen-fed rats. Oestriol 500–700 μg in NaCl pellets was implanted subcutaneously every 2 months for the life span of the treated females.

Physiologic and pharmacologic properties of oestriol contributing to its safety in clinical use

Is oestriol a partial answer in providing a safer oestrogen for menopausal hormone therapy with less risk of mammary or uterine carcinogenic activities per se, or is it primarily a marker reducing breast cancer risk? Although there has not yet been adequate reporting of the safety of long-continued oestriol therapy in post-menopausal women, several properties of oestriol suggest that it may indeed be a safer drug for administration to menopausal women.

1. *Anti-oestradiol activity*

Although the chief oestrogen produced in menopausal and post-menopausal women is oestrone, intracellular reduction to oestradiol-17β occurs prior to its intranuclear incorporation with its receptor protein in the uterus (Thijssen et al. 1978). Oestriol is one of a group of 2, 6 and 16 carbon hydroxylated oestradiol derivatives that are weakly uterotropic and in addition possess anti-oestradiol uterotropic activity in biologic testing (Clark et al. 1978; Huggins & Jensen 1955). As a single agent in rats or mice, oestriol readily induces proliferation of mammary epithelium, and on continuous therapy has a similar uterotropic activity to oestradiol, provided an 8 × larger dose/24 h is

administered (Clark et al. 1978). In the intact rat intermittently treated with 100–200 μg/kg/24 h, anti-uterotropic activity can be demonstrated up to 6 weeks after all exogenous oestriol has been cleared from the blood (Lemon 1978) (Fig. 1). In the rat uterus, and in human breast cancer cells in tissue culture, simultaneous oestriol + oestradiol therapy leads to accelerated 'wash-out' of oestradiol bound to protein receptors from the nucleus or cell respectively, along with oestriol bound to receptor proteins, which are well known to bind more briefly than oestradiol receptors to nuclear chromatin (Strobl et al. 1979; Clark et al. 1978). Oestriol, therefore, under appropriate conditions, acts as an oestradiol uterotropic antagonist, a property which may be exploited some time in cancer prevention, and which may be of value where prior neoplastic transformation of breast or uterine cells increases the risk of neoplasia by oestrogenic stimulation of tissue growth.

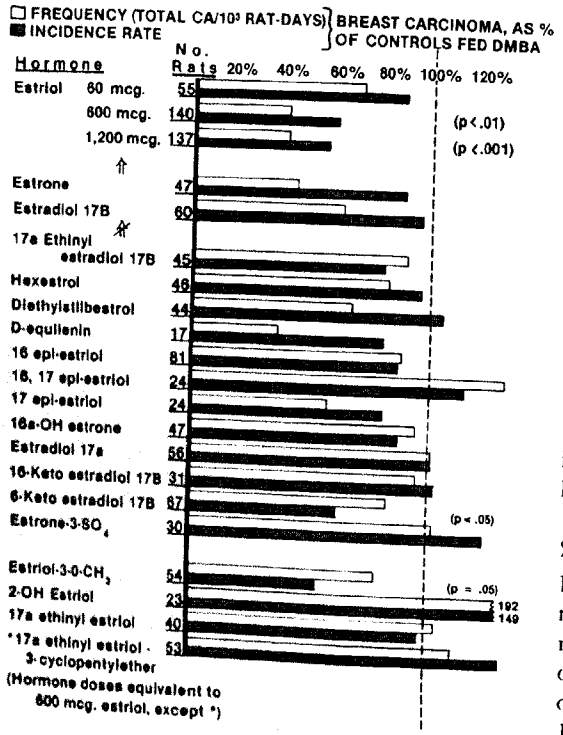

Fig. 2

Incidence rate and frequency of breast cancers in intact Sprague Dawley female rats fed 7,12-dimethylbenz-(a)anthracene (DMBA), after implantation sc every 2 months with pellets of various oestrogenic hormones. The results are expressed as percentages of the incidence rate and frequency of breast cancers observed in simultaneous control group only receiving DMBA, during their natural life span. *P*-values calculated by χ^2 from incidence rates, using Yates' correction (Lemon 1978, 1975).

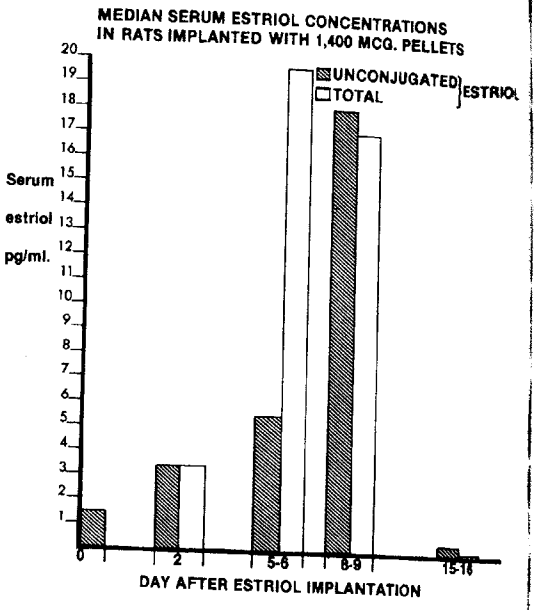

Fig. 3

Radioimmunoassay of serum oestriol concentrations in heart's blood from rats implanted sc with 1400 μg oestriol in NaCl pellets, using a specific anti-serum for oestriol. Confirms Lemon (1978) in the brevity of elevated serum oestriol concentrations.

2. *Minimal carcinogenic activity of oestriol*

Prolonged intermittent oestriol therapy during the natural life span of Sprague Dawley virgin female rats has led to a low, 3–4%, incidence of breast cancer, which has also been observed after periodic oestrone therapy sc in equimolar doses (Lemon 1978, 1975). Most investigators have not been successful in inducing malignant neoplasms in intact oestriol-treated rats or mice unless large doses, in the order of 200–500 μg/kg/24 h, have been chronically and continuously administered (Noble et al. 1975; Rudali et al. 1975). Castration may sensitize experimental animals to oestriol-induced breast proliferation (Rudali et al. 1975). Oestriol glucuronides, which are the principal entity transported in plasma, have never been shown to be carcinogenic in any organ for animals, nor have

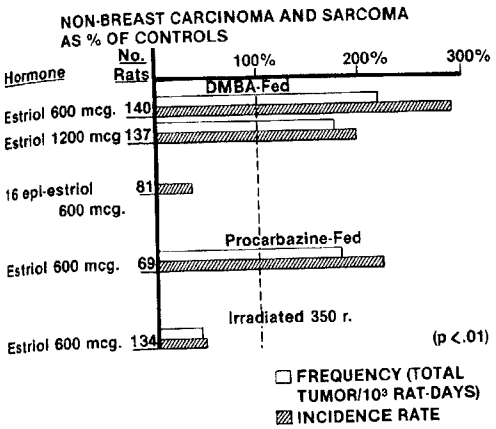

Fig. 4

Incidence rate and frequency of non-breast carcinoma and sarcomas, as percentage of carcinogen-treated controls, in intact Sprague Dawley females. The increased incidence and frequency of non-breast tumours in oestriol-treated females was not significant and represents greater longevity from the absence of breast lesions requiring biopsy.

there been any reports as yet suggesting carcinoma induction in women receiving post-menopausal hormonal therapy with oestriol (Salmi 1979).

3. *Anti-mammary carcinogenic activity of oestriol*

In systematic testing of various hormones for their potential anti-mammary carcinogenic activity in intact female rats fed mammary carcinogens and observed for their natural life span, only unconjugated oestriol, oestriol-3-methyl ether, and 6 keto oestradiol have significantly reduced breast cancer incidence (Lemon 1978, 1975). Highly uterotropic oestrogens, such as 17α-ethinyloestradiol, hexestrol, and diethylstilbestrol, none of which can be metabolized to oestriol after absorption in the rat, do not alter experimental breast cancer incidence administered in doses equimolar to oestriol (Fig. 2). In addition to these oestrogenic derivatives, testosterone, corticosterone and progesterone have not demonstrated any anti-mammary carcinogenic activity (Lemon 1975). Oestriol protects against breast carcinomas induced by two highly dissimilar carcinogens (DMBA and procarbazine), and the prophylactic action is dose-dependent up to a point. Thus far, significant protection has not been observed against radiation-induced breast cancers. Repeated but intermittent therapy is required for protective activity during the entire life span of the animal. Oestriol was administered subcutaneously in NaCl pellets every 1–2 months. Pellet absorption was complete after 2 weeks, yielding transient high concentrations of unconjugated oestriol (Fig. 3). Oestriol derivatives with prolonged biologic action, such as 17α-ethinyloestriol-3-cyclopentyl ether, were ineffective in reducing breast cancer incidence in equimolar concentrations and demonstrated increased uterotropic activity. The incidence of non-breast neoplasms was not significantly altered by oestriol in DMBA and procarbazine fed rats, but has been reduced thus far in irradiated rats (Fig. 4).

With increasing animal growth curves, probably a result of better breeding conditions in the rats prior to experimental study, the protective activity of oestriol is markedly reduced – an obvious analogy to the role of obesity and tallness increasing human breast cancer risk (de Waard et al. 1974) (Figs. 5 and 6). This reduction was observed at two different dosage levels of oestriol. Diet and housing conditions remained constant during the ten-year period of these investigations.

The mechanism of this anti-mammary carcinogenic activity of oestriol against two of the most potent experimental chemical carcinogens known is under investigation. Unlike the atrophic effects oestriol has upon the uterus of the intact adult female rat, oestriol actively stimulates growth of breast ducts in the rat (Fig. 7). Oestriol markedly increases the rate of incorporation of tritiated thymidine into mammary tissues on a per mg wet weight and per mg DNA basis, compared to DMBA fed controls. Wotiz has reported reduction in short-term DMBA-induced mammary carcinogenesis by continuous oestriol administration to intact female rats (Wotiz et al. 1978).

4. *Minimal variations of metabolism of oestriol in vivo*

Orally administered oestriol is almost completely conjugated with glucuronic acid in the gut and circulates after absorption in this form. Oestriol undergoes minimal metabolism following absorption, does not bind to SHBG and binds to serum albumin considerably less avidly than oestradiol, so that variations of SHBG or albumin concentrations in patients will affect its biologic activity only slightly, less than oestrone or oestradiol, as a result of its minimal intravascular protein binding. In conjugated form its biologic activity is probably considerably less than in non-conjugated form.

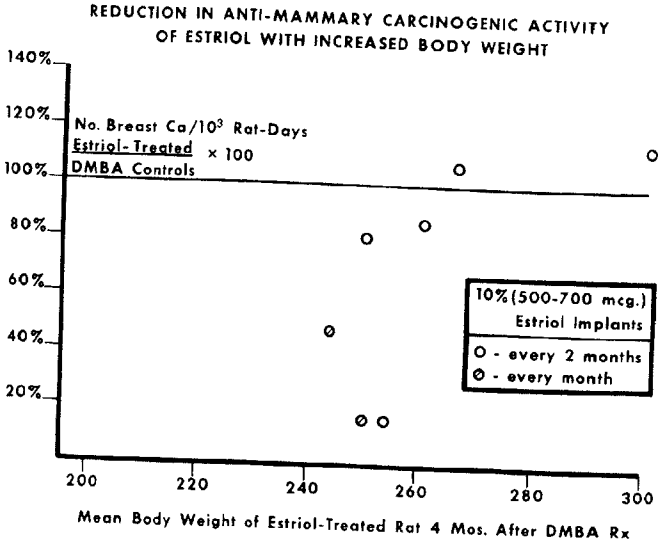

Fig. 5

Decreased effectiveness of oestriol in 10% concentration (500–700 μg) in NaCl pellets re-implanted every 1–2 months sc in rat experiments with increased growth curves. Results are plotted as percentage frequency of breast cancers in treated/control groups, according to mean body weight of treated groups 4 months after carcinogen exposure. Diet and housing were identical in all experiments.

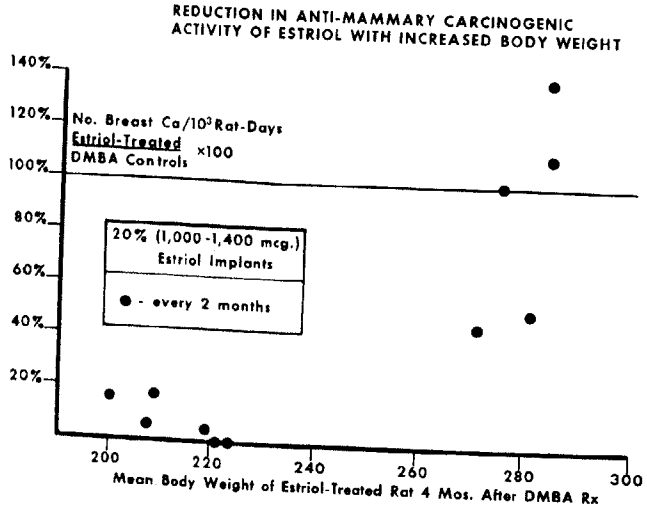

Fig. 6

Decreased effectiveness of oestriol in 20% concentration (1000–1400 μg) in NaCl pellets re-implanted every 2 months sc, in rat experiments with increased growth curves. Results are plotted as percentage frequency of breast cancers in treated/control groups, according to mean body weight of treated groups 4 months after carcinogen administration. Diet and housing were identical in all experiments.

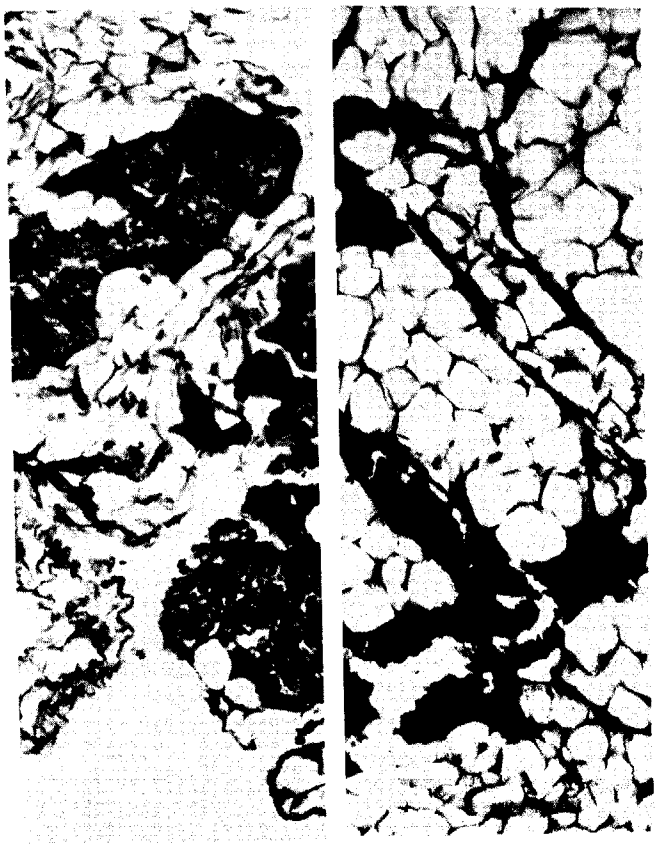

Fig. 7

Comparison of breast morphology of mammary fat pads in intact females implanted with 10% pellet of oestriol sc 7 days before, and fed 20 mg DMBA 5 days before (left), with another 50–55-day-old rat from same batch fed only 20 mg DMBA (right). Note extensive development of ducts and terminal lobules in oestriol treated (× 40).

However, absorption of oestriol from the vagina gives rise to a higher initial percent of unconjugated oestriol, with increased biologic action and quite possibly increased anti-mammary carcinogenic activity, if our experimental investigations prove to have human application.

Oral therapy with oestriol in breast cancer patients

Our own experience with oral oestriol therapy 5–15 mg daily in 24 evaluable patients with breast cancer has indicated that oestriol-3-glucuronide has definite activity in initially inducing increased growth of metastases in some 25% (6/24) of patients, who were apparently hormone dependent. No adverse changes were observed in the contralateral uninvolved normal breast in over 15 patient years of experience. However, 2 of the 24 patients developed adenomatous endometrial hyperplasia after 8–40 months of therapy, which along with intermittent vaginal bleeding experienced by 5 other patients, indicated that in these doses, in this population of patients with breast cancer, the uterus would respond to prolonged oestriol therapy with hyperplastic changes in some cases. Prolonged oestriol therapy did raise serum total lipids in 2 patients, but the effect upon serum cholesterol and triglyceride concentrations was minimal. These observations suggest caution in the amount of dose

and duration of oestriol administration for menopausal symptoms, even though its risk of inducing breast or endometrial cancer is slight. As a result of recycling through the entero-hepatic circuit, a single dose of oestriol raises urinary oestriol excretion for as long as four days afterwards.

Since intermittent oestriol therapy appears more promising as a possible anti-mammary carcinogenic therapy than continuous therapy, we are now testing alternate day treatment with 2.5–10 mg for menopausal symptoms.

Summary

It is clear that much more needs to be learned about the oestrogen physiology of ageing women, and how one may safely increase oestrogen metabolites to improve menopausal symptomatology. Breast and endometrial cancer (and probably ovarian cancer as well) are the most feared potential complications of oestrogenic treatment. There are several lines of investigation which suggest reduced 2-hydroxylation and 16α hydroxylation of oestrogens in women predisposed to or developing breast cancer, which are consistent with decreased mixed function oxidase activity in some women. Obesity commonly complicates menopause, providing increased extragonadal synthesis of oestrone, and in some women paradoxically decreasing sex hormone binding globulin to subnormal levels. Administration of oestrone or oestradiol would be anticipated to have excessive proliferative action on targets such as breast duct epithelium or uterine endometrium, if decreased sex hormone binding capacity were present, or reduced hydroxylation rates at the 2 or 16 carbon atom. Oestriol undergoes minimal degradation after absorption and its biologic action would not be affected either by altered mixed function oxidase activity or changes in sex hormone binding globulin; only glucuronide conjugation in the gut reduces considerably the biologic action of oestriol, which can be avoided by intravaginal administration. Unconjugated oestriol has demonstrated anti-mammary carcinogenic activity in intact female rodents against two dissimilar chemical carcinogens, supporting the epidemiologic thesis which has developed, indicating an inverse relationship between urinary oestriol excretion relative to oestrone and oestradiol in human populations and breast cancer risk. This inverse correlation may fact reflect how early in maturity pregnancy h permanently induced increased 16α hydroxylati of oestradiol or adrenocortical precursors of o triol to increase the production of this physiolo anti-oestradiol antagonist in some women.

Acknowledgment

The author wishes to acknowledge and thank Carnri Laboratories of Cedar Knolls, New Jersey, for the partial support of this research.

References

Arguelles A E, Poggi U L, Saborida C, Hoffman C Chekherdemian M & Blanchard O (1973): Lancet 1 165.

Bacigalupo G & Karlapp H D (1962): Arch Geschwulst forsch 19: 304.

Bacigalupo G & Schubert K (1966): Eur J Cancer 2: 75.

Barlow J J (1964): J Clin Endocrinol Metab 24: 586.

Barlow J J & Logan C M (1966): Steroids 7: 309.

Beer C T & Gallagher T F (1955): J Biol Chem 214: 355.

Briggs M (1972): Lancet 1: 324.

Brown J B & Strong J A (1965): J Endocrinol (Oxf) 32: 107.

Brown J B, Kellar R & Matthew G D (1959): J Obstet Gynecol 66: 177.

Bulbrook R D, Swain M C, Wang D Y, Hayward J L, Kumaoka S, Takatani O, Abe O & Utsunomiya J (1976): Eur J Cancer 12: 725.

Clark J H, Peck E J Jr, Hardin J W & Eriksson H (1978): In: O'Malley B W & Birnbainner L (eds). Receptors and Hormone Action, p 1. Academic Press, New York.

Cole P, Brown J B & MacMahon B (1976): Lancet 2: 596.

Cole P, Cramer D, Yen S, Paffenbarger R, MacMahon B & Brown J (1978): Cancer Res 38: 745.

Dickinson L, MacMahon B, Cole P & Brown J B (1974): New Engl J Med 291: 1211.

Dove G A, Morlay F, Batchelor A et al (1971): J Reprod Fertil 24: 1.

Eren S, Reynolds G, Turner M E, Schmidt F H, Mackay J, Howard C M & Preedy J R (1967): J Clin Endocrinol Metab 27: 1451.

Fishman J, Hellman L, Zumoff B & Gallagher T F (1962): J Clin Endocrinol Metab 22: 389.

Flood C, Pratt J H & Longcope C (1976): J Clin Endocrinol Metab 42: 1.

Glass A R, Swerdloff R S, Bray G A, Dahms W T & Atkinson R L (1977): J Clin Endocrinol Metab 45: 1211.

Grattarola R (1978): Cancer Res 38: 3051.

Gronroos M & Aho A J (1968): Eur J Cancer 4: 523.

Gross J, Modan B, Bertini B, Spira O, de Waard F, Thijssen J H H & Vestergaard P (1977): J Natl Cancer Inst 59: 7.
Hausknecht R U & Gusberg S (1969): Am J Obstet Gynecol 105: 1161.
Hayward J L, Greenwood F C, Glober G, Stemmerman G, Bulbrook R D, Wang D Y & Kumaoka S (1978): Eur J Cancer 14: 1221.
Hellman L, Zumoff B, Fishman J & Gallagher T F (1971): J Clin Endocrinol Metab 33: 138.
Huggins C & Jensen E V (1955): J Exp Med 102: 335.
Kapdi C & Wolfe J N (1976): J Am Med Ass 236: 1124.
Klopper A & Farr V (1978): In: Lauritzen C & van Keep P A (eds). Frontiers of Hormone Research, vol 5: Estrogen therapy – the benefits and risks, p 89. Karger, Basel.
Lemon H M Wotiz H H, Parsons L & Mozden P J (1966): J Am Med Ass 196: 1128.
Lemon H M (1972): J Surg Oncol 3: 255.
Lemon H M (1975): Cancer Res 35: 1341.
Lemon H M (1978): In: Lauritzen C & van Keep P A (eds). Frontiers of Hormone Research, vol 5: Estrogen therapy – the benefits and risks, p 155. Karger, Basel.
Longcope C & Pratt J H (1977): Steroids 29: 483.
Longcope C & Pratt J H (1978): Cancer Res 38: 4025.
MacMahon B, Cole P & Brown J B (1973): J Natl Cancer Inst 50: 21.
MacMahon B, Cole P & Brown J B, Aoki K, Lin T M, Morgan R W & Woo N C (1971): Lancet 2: 900.
MacMahon B, Cole P & Brown J B, Aoki K, Lin T M, Morgan R W & Woo N C (1974): Int J Cancer 14: 161.
Mittra I & Hayward J L (1974): Lancet 1: 885.
Noble R L, Hochachka B C & King D (1975): Cancer Res 35: 766.
O'Dea J P K, Wieland R G, Hallberg M C, Herena L A, Zorn E M & Genuth S M (1979): J Lab Clin Med 93: 1004.
Olina A (1964): Acta Un Int Cancer 20: 1120.
Pratt J H & Longcope C (1978): J Clin Endocrinol Metab 46: 44.
Rose D P & Davis T E (1978): Cancer 41: 666.
Rudali G, Apiou F & Muel B (1975): Eur J Cancer 11: 39.
Salmi T (1979): Lancet 2: 360.
Schubert K & Bacigalupo G (1961): Arch Geschwulstforsch 17: 207.
Schweppe J S, Jungman R A & Lewin I (1967): Cancer 20: 155.
Sommers S C (1955): Lab Invest 4: 160.
Strobl J, Monaco M & Lippman M (1979): Proc Endocrinol Soc: Abst 816.
Thijssen J H H, Poortman J, Schwarz F & de Waard F (1975): In: van Keep P A & Lauritzen C (eds). Frontiers of Hormone Research, Vol 3: Estrogens in the post-menopause, p 45. Karger, Basel.
Thijssen J H H, Wiegerinck M A H M, Mulder G & Poortman J (1978): In: Lauritzen C & van Keep P A (eds). Frontiers of Hormone Research, Vol 5: Estrogen therapy – the benefits and risks, p 220. Karger, Basel.
Tominaga T, Tei N, Kitamura T M et al (1975): Gann 66: 305.
Ukai M (1964): Nagoya J Med Sci 27: 37.
de Waard F & Baanders-van Halewijn E A (1974): Int J Cancer 14: 153.
Wattenberg L W (1975): Cancer Res 35: 3326.
Wotiz H H, Chattoraj S C, Kudisch M & Muller R E (1978): Cancer Res 38: 4012.
Wu C H, Motohashi T, Abdel-Rahman H, Flinckinger G & Mikhail G (1976): J Clin Endocrinol Metab 43: 436.