THE CANADIAN MENOPAUSE CONSSENSUS CONFERENCE

This document has been reviewed and approved by the Executive and Council committees and is a Policy Statement of the Society.

This consensus document, prepared by an ad hoc committee, on behalf of the Society of Obstetricians and Gynaecologists of Canada, will be appearing as a continuous series in subsequent issues of the SOGC News. (Part 2 of 4)

CARDIOVASCULAR DISEASE AND HORMONE REPLACEMENT THERAPY

In Canada, cardiovascular disease (CVD) is the leading cause of mortality. In 1990, CVD killed 36,266 Canadian women. This represents 41 percent of deaths in women and is greater than all deaths due to cancer. On average, Canadian women outlive men by seven years. During this period, CVD is second only to joint and bone disease in limiting activities and reducing the autonomy of these women. Cardiovascular disease is a major health risk facing women.

Women develop CVD ten years later than men and this ten years is temporally related to the onset of the individual woman's menopause. There are recognizable risk factors for men and women. Table 1 shows those risk factors common to men and women, some of which are modifiable in attempts to prevent and delay CVD. There is one factor unique to women which increases their risk after the menopause. This factor is estrogen deficiency.

Postmenopausal estrogen replacement therapy (ERT) can reduce the risk of coronary heart disease to approximately 50 percent. The protection applies at any age, being higher in current estrogen users and maximal with more than 15 years of use. Contrary to previous beliefs that ERT was contraindicated in women with risk factors such as diabetes, hypertension and dislipidemia, even with known coronary artery disease and prior myocardial infarction, it is now evident that ERT, especially in this group, exerts a protective effect. In fact, women with pre-existing coronary heart disease enjoy the greatest benefit of estrogen use.
TABLE 1

CARDIOVASCULAR DISEASE RISK FACTORS

NON MODIFIABLE
- Gender (male sex)
- Age
  - Family history of coronary artery disease
    (age less than 60 - 65 years for women)
    (age less than 55 - 60 years for men)

MODIFIABLE
MAJOR
- Cigarette smoking
- Hypertension
- Hypercholesterolaemia
- Diabetes Mellitus

MINOR
- Hypertriglyceridaemia
- Low HDL - cholesterol
- Obesity (mainly abdominal)
- Physical inactivity
- Psychosocial factors

Cerebrovascular disease and ERT have been evaluated in a small number of studies. The findings are inconsistent but limited evidence supports a protective effect. The term "stroke" is applied to different pathological events (subarachnoid haemorrhage, cerebral infarction, cerebral haemorrhage) which may evolve differently with estrogen. Only the risk of cerebral infarction (thrombo-embolic stroke) may be reduced by ERT.

The mechanisms by which estrogens are believed to exert their beneficial cardiovascular effect are multiple, one of them being the modification of the serum lipid composition (Table 2). The changes in the lipoprotein profile explain partially the lower incidence of arteriosclerosis in users of ERT. Other mechanisms are possibly involved in the decreased progression of arteriosclerosis. Moreover, direct effects of estrogens on the arterial wall may well contribute to improved vascular function (Table 3).

Concerns have been raised that the effects of progestins added to ERT might affect the lipoprotein profile and have a detrimental effect. Is there an effect, and if so, is it significant? The debate is still open. However, as the relative importance of the different cardioprotective mechanisms of estrogen are being studied, it becomes evident that whatever effect progestin supplementation may have on lipids, it does not attenuate the cardiovascular benefit induced by estrogen.

It must be acknowledged that the compelling evidence for the cardioprotective effect of ERT is based on cohort observational studies from the last decade. In the United States, supported by the National Institute of Health, three randomized double blind controlled-clinical trials are under way. The Postmenopausal Estrogen/Progestin Intervention Trials (PEPI), will examine over a three-year period the effect of non-opposed and opposed ERT on CVD risk factors. It is expected...
to be published in late 1994. A secondary prevention trial, the Heart and Estrogen/Progestin Replacement Study (HERS) is observing postmenopausal women with known atherosclerotic heart disease, randomly assigned to combined continuous HRT or placebo. Results should be available in 1999. Finally, the Women's Health Initiative (WHI) will evaluate fifty thousand women for eleven years from March 1993. There will be three planned treatment protocols and a placebo arm. It is hoped that these three ambitious experimental studies will help to resolve the effect of combined HRT on cardiovascular risk.

For the present, the evidence available for a strong cardioprotective effect of HRT/ERT is well recognized. Cardiovascular disease is the main cause of death in women after the menopause and estrogen has been shown to have a major impact.

### Table 3

**Cardioprotective Mechanisms of ERT**

- Modification of the serum lipid profile
- Decreased oxidation of LDL-cholesterol particles
- Induction of vasodilation
- Prevention of abdominal fat deposit
- Prevention of thrombosis
- Reduction of insulin resistance

## Executive Summary

1. Estrogen deficiency is a major cause of CVD in postmenopausal women.
2. Estrogen replacement is demonstrably protective against CVD.
3. Contrary to prior belief, the beneficial effects should not be withheld from smokers or women who have diabetes, hypertension, angina or a history of coronary thrombosis.
4. While the Committee endorses the use of ERT/HRT in the prevention of CVD, the important roles of diet, exercise, stress reduction, and smoking cessation cannot be overemphasized.
5. The addition of recommended low dosages of progestin does not appear to alter the cardioprotective effect of estrogens.
REFERENCES

OSTEOPOROSIS AND HORMONE REPLACEMENT THERAPY

Bone production increases with age, attaining a maximum at about age 35. Subsequently, there is a gradual loss of bone which is accelerated after the menopause. In many women, this normal aging process is exacerbated, leading to a high incidence of fracture occurring after minimal trauma.

In her lifetime, a woman is exposed to a risk of one in six that she will sustain a fracture of the hip and a risk of one in four for vertebral fracture. Twelve to 20 percent of women who sustain a fracture of the femur will be dead within six months. Twenty to 30 percent of women who survive will require long term nursing care. In 1990, in Canada approximately 18,000 women sustained femoral fractures. The negative social effects of fractures include pain and suffering, decreased functional ability and quality of life, and loss of independence.

The accumulated evidence of many well performed clinical trials amply confirms the profound protective effects of exogenous estrogen on bone density. Because of perceived risks of cancer or compliance difficulties, not all women are willing to take estrogen. It would be helpful if only those women at risk (as not all women are) could be identified so that their physicians could offer them increased support and guidance. Total identification is not possible, however some guidance can be found by paying attention to some recognized risk factors (Table 1).

Bone densitometry is the single most accurate test for the prediction of fracture. Universal bone mass screening remains controversial. There is a lack of prospective data about what effect screening may have on fracture incidence. In Canada where the availability of dual x-ray absorptiometry (DEXA) is limited, bone densitometry can only be done on a selective basis. This Committee recommends selective use of DEXA and this is discussed in detail in the section on evaluation.

If the only beneficial effect of universal bone mass screening were to encourage more women to take HRT, it would probably be to the advantage of Canadian women.

Women should consider the use of estrogen as soon as they have become menopausal, particularly as there is an increased bone turnover at the beginning of menopause. Fortunately, there is a two to three year window of opportunity during which estrogen use can repair bone loss. While these are the recommendations of this Committee, not all women will present early after the onset of menopause. Estrogen treatment begun later in life preserves remaining bone density and can be shown to reduce fracture risk even at a late stage.

All forms of estrogen administration are, in principle, effective for the prevention of bone loss, provided that an adequate tissue concentration of estrogen is obtained. In 1990, an International Conference on Osteoporosis was held in Copenhagen. In the following 1991 Consensus report, the minimum fully effective dosages of estrogens for prophylaxis and treatment of osteoporosis are seen in Table 2. Adequate estrogen replacement should be continued for a minimum of ten years beyond the age of 50 for maximum bone protection. This does not mean that estrogen therapy should be discontinued at that time. More studies are necessary to determine the optimal duration of therapy.
TABLE 1

<table>
<thead>
<tr>
<th>RISK FACTORS ASSOCIATED WITH POSTMENOPAUSAL AND AGE-RELATED OSTEOPOROSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic factors:</td>
</tr>
<tr>
<td>female sex</td>
</tr>
<tr>
<td>Caucasian or Asian race</td>
</tr>
<tr>
<td>positive family history</td>
</tr>
<tr>
<td>small build</td>
</tr>
<tr>
<td>Endocrine factors:</td>
</tr>
<tr>
<td>female sex</td>
</tr>
<tr>
<td>early menopause (or oophorectomy)</td>
</tr>
<tr>
<td>nulliparity</td>
</tr>
<tr>
<td>Environmental factors:</td>
</tr>
<tr>
<td>lifelong low calcium intake</td>
</tr>
<tr>
<td>sedentary lifestyle</td>
</tr>
<tr>
<td>alcohol abuse</td>
</tr>
<tr>
<td>cigarette smoking</td>
</tr>
<tr>
<td>high caffeine or proteins or sodium or phosphate intake</td>
</tr>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>cortisone</td>
</tr>
<tr>
<td>heparin</td>
</tr>
<tr>
<td>anti-epileptics</td>
</tr>
<tr>
<td>high dose thyroid medication</td>
</tr>
</tbody>
</table>

Adapted from Lindsay, R.*

The diet of women taking hormone replacement should be evaluated to provide a minimum of 800 to 1,200 mg of elemental calcium per day. In the absence of estrogen treatment, dietary calcium supplementation should be considered as part of the therapeutic regimen to provide 1,000 to 1,500 mg per day. Long-term studies of calcium intake, even at high doses, have not been shown to be protective against the development of osteoporosis!

A programme of exercise should be discussed with each patient and adapted to their needs. Weight bearing and aerobic exercise are important to maintain bone strength and muscle tone, and at the same time to maintain a good equilibrium, and prevent falls and fractures. For most women in that age group, walking for half an hour a day, at a fast rate, is sufficient.

For established osteoporosis, estrogen remains the first choice but other therapies are also being used (etidronate, calcitonin, fluoride, progestogens, 1.25-dihydroxy vitamin D, and others). These are beyond the scope of this document.
TABLE 2

TABLE 2
MINIMUM EFFECTIVE DOSAGES FOR PROPHYLAXIS AND TREATMENT OF OSTEOPOROSIS

| Conjugated Equine Estrogen (Premarin) | 0.625 mg |
| Estrone Sulfate (Ogen)               | 0.625 mg |
| Estradiol 17β (Estrace)              | 2 mg    |
| Estradiol Transdermal (Estraderm)    | 50-100 mcg |

EXECUTIVE SUMMARY

1. The medical and social implications of fractures in the postmenopausal woman are significant.
2. Estrogen deficiency plays a major role in the postmenopausal loss of bone density.
3. Hormone replacement therapy (HRT) prevents this loss of bone density, reduces the incidence of fractures, and should be offered to all women as soon as they become menopausal.
4. Clinical risk factors are not sufficiently sensitive to identify women at the highest risk.
5. Bone densitometry is the gold standard for identifying osteoporosis.
6. In Canada, bone densitometry can only be used selectively.
7. Lifestyle factors such as diet and exercise are extremely important for maintaining good bone health, but should be used in conjunction with HRT for optimal results.

REFERENCES

In recent years, a 50 percent reduction of myocardial infarction in postmenopausal women receiving hormone replacement therapy (HRT) has been reported. This dramatic decrease in cardiovascular disease, combined with the previously well-established protective effects against osteoporosis and urogenital atrophy have prompted the philosophy that virtually all postmenopausal women should consider reaping the benefits of HRT. However, most Canadian women are reluctant to proceed in this direction, largely because of information in the media warning that HRT increases the risk of cancer. It is important to put these perceived risks in perspective and to examine the relative risk for any postmenopausal woman developing cancer at any sites. This information is provided in Table 1. The lifetime risk to a 50+ year old Caucasian woman of developing endometrial cancer is 2.6 percent and the probability of her dying from this carcinoma is 0.3 to 0.7 percent. The relationship between estrogen, progesterone, and endometrial, ovarian, and breast neoplasia will now be discussed in detail.

### Table 1

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of new cases</th>
<th>Percentage of new cases</th>
<th>Number of deaths</th>
<th>Percentage of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>520,000</td>
<td>(100%)</td>
<td>240,000</td>
<td>(100%)</td>
</tr>
<tr>
<td>Lung</td>
<td>55,000</td>
<td>(11%)</td>
<td>50,000</td>
<td>(21%)</td>
</tr>
<tr>
<td>Breast</td>
<td>150,000</td>
<td>(29%)</td>
<td>44,000</td>
<td>(18%)</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>79,000</td>
<td>(15%)</td>
<td>30,900</td>
<td>(13%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>20,500</td>
<td>(4%)</td>
<td>12,400</td>
<td>(5%)</td>
</tr>
<tr>
<td>Uterus and cervix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>22,000</td>
<td>(4%)</td>
<td>7,400</td>
<td>(3%)</td>
</tr>
<tr>
<td>Skin</td>
<td>12,800</td>
<td>(3%)</td>
<td>3,100</td>
<td>(1%)</td>
</tr>
<tr>
<td>Oral</td>
<td>10,100</td>
<td>(2%)</td>
<td>2,775</td>
<td>(1%)</td>
</tr>
<tr>
<td>All other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Source: Silverberg, 1990)


### Endometrial Carcinoma

In the early 1960s, estrogen became a popular treatment for postmenopausal hypo-estrogenic changes. However, by the mid-70s many investigations began reporting an approximately threefold increase in the risk of endometrial carcinoma in women who were given estrogen replacement therapy. Although this estrogen-induced carcinoma was curable in the majority of cases, and indeed a study by Collins and colleagues showed no excess deaths due to endometrial carcinoma, the risks versus benefits of estrogen replacement therapy was appropriately questioned.
Most postmenopausal women who develop endometrial carcinoma are not receiving HRT.\textsuperscript{12,25} Obese women (defined as 50 pounds above their ideal weight) have 10 times increased relative risk of this malignancy\textsuperscript{11} which is more than three times the risk of women using estrogen-only replacement therapy.

This high rate of development of endometrial neoplasia in overweight, postmenopausal women is related to the endogenous production of estrogen through the peripheral conversion of androstenedione to estrone,\textsuperscript{13} combined with the fact that the levels of sex hormone-binding globulin (SHBG), the specific serum-binding protein for estradiol, are markedly reduced in obese women.\textsuperscript{14} This allows increased estrogen production and high free estradiol levels to stimulate such target tissues as the endometrium.\textsuperscript{15} Women with liver disease\textsuperscript{18} and a history of polycystic ovarian syndrome\textsuperscript{14} are similarly at increased risk of developing endometrial carcinoma due to low SHBG concentrations resulting in increased serum-free estradiol levels.\textsuperscript{13}

Progesterone theoretically functions in the uterus as an anti-estrogen by decreasing cytoplasmic estrogen receptors\textsuperscript{14} and inducing 17-beta-hydroxysteroid dehydrogenase,\textsuperscript{16} promoting the metabolism of the potent estrogen, estradiol, to the less potent estrone. In human cohort studies, Gambrell\textsuperscript{22} and Varma\textsuperscript{21} and others\textsuperscript{22} have shown that women given progestin-containing HRT regimens are less likely to develop endometrial carcinoma than women not receiving HRT. This is most likely because women at high risk of developing endometrial carcinoma, for example obese women, are protected by the inclusion of a progestin in their regimen. Thus, progestin-containing HRT regimens do not increase the risk of endometrial carcinoma, rather they protect against the development of this neoplasm.

Confusion exists for treatment of women with previous endometrial cancer. The use of HRT in women with stage I grade I endometrial neoplasia was first demonstrated to be safe in studies by Creasman and Associates.\textsuperscript{23} The over 90 percent expected long-term survival of women following surgical treatment for early stage endometrial carcinoma\textsuperscript{12} and only a five percent recurrence risk, make the benefits of HRT outweigh the risks. It is, therefore, recommended, after stage I grade I endometrial carcinoma has been treated, that these patients be given HRT.\textsuperscript{22,23} With higher grade or higher stage endometrial cancers, or in those incompletely treated due to unsuitability for surgery, HRT treatment must be individualized since recurrence risks may be as high as 50 percent even without treatment. There is no consensus on HRT use in this group.

Furthermore, epidemiology studies overall have revealed a reduction in endometrial cancer risk of 11.7 percent per year with oral contraceptive (OC) use. Also epidemiologic studies have confirmed that this protection lasts for up to 15 years after cessation of OC use.\textsuperscript{55,56}

<table>
<thead>
<tr>
<th>EXECUTIVE SUMMARY • ENDOMETRIAL CARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On the basis of currently available data, the benefits of HRT outweigh the risks of this treatment causing endometrial carcinoma.</td>
</tr>
<tr>
<td>2. The addition of a progestin decreases the risk of endometrial carcinoma.</td>
</tr>
<tr>
<td>3. For specific women at increased risk, addition of a progestin reduces the risk and is protective at any age.</td>
</tr>
<tr>
<td>4. Hormone replacement therapy should not be withheld from women with treated stage 1 grade I carcinoma of the endometrium.</td>
</tr>
<tr>
<td>5. The oral contraceptive given during the reproductive years is protective against uterine cancer.</td>
</tr>
</tbody>
</table>
OVARIAN CANCER

Some physicians have been reluctant to give hormonal replacement therapy to patients with ovarian cancer, their concern relating to decreased survival or increased chances of cancer recurrence.

To clarify our thinking, we must consider risk factors for cancer and the effects of hormones on ovarian cancer growth. Approximately 21,000 cases of ovarian cancer are diagnosed each year and about 13,000 women die annually of the disease. It is a leading cause of cancer deaths among American and Canadian women. One point four to two percent of women develop ovarian cancer during their lifetime (one out of 70).

Some risk factors are well known in ovarian cancer. The woman who has a history of hereditary ovarian cancer has a 50 percent lifetime probability of developing ovarian cancer. There are three cancer syndromes associated with this increased risk.

1. Specific site ovarian cancer syndrome.
2. Breast-ovarian cancer syndrome.
3. Hereditary non-polyposis colorectal cancer (Lynch syndrome II).

Incessant ovulation, because of repeated injury to the ovarian epithelium, would explain most of the following factors: nulliparity and late first pregnancy, infertility, early menarche. Another explanation could be the effects of elevated levels of gonadotrophin in the blood. The latter observation could explain the increased incidence in women over 45 years of age, the association apparently being related to the use of gonadotrophin hormones, and late menopause. There might be other factors not yet studied including the effects of viruses and environmental influences.

Early menarche, nulliparity, late first pregnancy, and infertility, all permit women to ovulate without respite. It is postulated that this incessant injury to the ovarian epithelium may increase the risk of developing ovarian carcinoma.

Incessantly ovulating women are exposed to elevated levels of gonadotrophin on a monthly basis. If these levels are carcinogenic, the phenomenon might also explain the observed increased incidence in women over the age of 45.

There is a great deal of confusion surrounding the role of hormone receptors. Estrogens, progesterone, androgen and LH RH receptor concentration have been found in ovarian neoplasms. Contrary to the breast and endometrium where they have prognostic and therapeutic implications, they are not correlated with treatment or survival in cases of ovarian neoplasia.

Some factors reduce the incidence of ovarian cancer and include multiparity and oral contraceptive use. The oral contraceptive will reduce the risk after five years of use by approximately 50 percent.

Because it has been proven that the oral contraceptive decreases the incidence of ovarian cancer, it would be logical to offer it as a prophylactic measure for all women but particularly to those in the reproductive age group at risk for ovarian cancer. The patient with a family history of ovarian cancer, that is not an hereditary ovarian cancer syndrome, should have the choice of using the oral contraceptive.
The patient with a hereditary ovarian cancer syndrome should have both ovaries removed once child bearing has been completed. Epidemiologic studies are unclear about the risk of ovarian cancer in women using estrogen replacement therapy (ERT). These studies show a relative risk of 0.6 to 1.6 but there was only a small number of cases in these reports.

It is reassuring to know that one of the biggest studies from the Gynaecological Oncology Unit of Royal Marsden Hospital in London dealt with 373 ovarian cancer patients, age 50 or younger, of whom 78 had received HRT starting a median of four months after diagnosis. Some were treated for more than 49 months and showed no significant difference in survival or recurrence of the disease from those who did not receive HRT.

We conclude, because of the benefits of ERT on cardiovascular disease, on osteoporosis, on alleviation of vasomotor symptoms and urogenital atrophy, that patients with treated ovarian cancer should be offered HRT. This is particularly true of those who have had their ovaries removed prophylactically at an early age. Based on current evidence there seems to be no advantage in adding progestins after hysterectomy and bilateral salpingo-oophorectomy.

Whether there is a beneficial effect of HRT on ovarian cancer survivors must be investigated in large randomized controlled trials. On the basis of the current literature, the link between estrogen and epithelial ovarian malignancy remains unproven.

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**EXECUTIVE SUMMARY - OVARIAN CANCER**

1. The oral contraceptive given in the reproductive years is protective against ovarian cancer.
2. The use of HRT does not increase the risk of development of ovarian cancer.
3. Following treatment of ovarian cancer, estrogen replacement therapy should be offered, and not withheld.
4. The effect of hormone administration upon rare non-epithelial ovarian cancers is not known.

**BREASTCANCER**

Many women choose not to accept the multiple benefits of hormone replacement therapy (HRT) for fear that it may increase their risk of breast cancer. Indeed, in one study, seven out of ten women stated that their greatest concern with taking HRT, was fear of developing cancer of the breast.

The lifetime risk of breast cancer has increased from one in 13 in 1973 to one in eight in 1993. The incidence would be better described as one in eight women at age 85 will develop breast cancer, while at age 40 it is one in 217, at age 50 one in 50, and at age 60 the incidence is one in 2444 (see Table 2).

Thirty-four percent of the cases of breast cancer occur in women under the age of 50 and only 20 percent of cases occur in women with a positive family history. Factors possibly related to cancer risk include diet, exogenous hormones (oral contraceptives or hormone replacement therapy), alcohol consumption, breast trauma, viral infection, higher socio-economic status, and obesity. The 1993 projection from the USA is that there will be 46,000 deaths from breast cancer and 350,000 deaths from cardiovascular disease during the same year.
Estrogen replacement therapy and now HRT, have been investigated in many studies as possible causes of the increased relative risk of breast cancer. There has been much confusion in developing a consensus and, therefore, we are presenting a summary of the five meta-analysis studies which have been published in the last five years. These data are shown in Table 3.

It is evident from these figures that the relative risks are basically 1.1 to one except for the Steinberg study in which the relative risk is increased to 1.3. What has to be added is that this relative risk appeared after 15 years of estrogen use. In the DuPont study, there was no significant increase with the use of 0.625 mg of conjugated equine estrogens (CEE) but with an increased dosage of 1.25 mg CEE there was a possible twofold increase. They also determined that the history of benign breast disease was not a contraindication to the use of the 0.625 mg CEE.

The role of progestin is still unclear. It cannot be stated with any authority that the addition of a progestin to HRT has a beneficial or detrimental effect on the risk for developing breast cancer. However, this lack of clarity with respect to breast cancer should not allow us to forget the important role of progestin in protecting women from endometrial cancer. When a woman is diagnosed as suffering from breast cancer, a prior history of HRT use does not appear to prejudice her likelihood of surviving her cancer?

While these issues are perhaps the most important with respect to the relationship between HRT and breast cancer, other questions remain unresolved and are sources of confusion to patients and physicians alike. The Committee is unable to give firm recommendations but offers the following suggestions:
1. Benign breast disease is not a contraindication to HRT.

2. If a biopsy of a breast lesion shows atypical changes but no frank malignancy, the patient is already at risk of developing breast cancer, whether or not she receives HRT. Under these circumstances, the Committee cannot recommend routine administration of HRT. If the individual is prepared to accept a possible detrimental effect of HRT, she should be given the opportunity to have it.

3. This same advice alludes to the situation of a woman with one first degree relative who suffers from premenopausal breast cancer. If two or more first degree relatives had breast cancer, HRT is contraindicated.

4. The Committee cannot support the use of HRT in the woman who suffers from breast cancer. In rare individualized cases, HRT could be given provided the patient has given informed consent.

| TABLE 3 |
| ESTROGEN THERAPY AND BREAST CANCER |
| Meta-analysis | Number of studies | R.R. | 95% CI |
| Armstrong BK | 23 | 1.01 | 0.95-1.08 |
| Bates SK | 11 | 1.03 | 0.87-1.17 |
| Du Pont WD et al. | 28 | 1.08 | 0.96-1.2 |
| Sillero-Arenas M et al. | 47 | 1.06 | 1.00-1.18 |
| Steinberg KK, et al. | 16 | 1.3 | 1.20-1.6 |

EXECUTIVE SUMMARY

1. The use of estrogen for HRT does not appear to increase significantly the risk of breast cancer.

2. Progestin added to ERT for its recognized protective effect on endometrial carcinoma has yet to be shown to exert either beneficial or detrimental effect on the development of breast cancer.

3. A history of benign breast disease is not a contraindication to HRT.

4. Many other issues remain unanswered.

REFERENCES


44. ACOG Technical Bulletin. 1991;158.

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