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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Effect of Genomics on Venous Thrombosis: Relation to Sex Steroids

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SUMMARY

Venous thromboembolism (VTE) is a multicausal disease with a significant component of combinations of rare and common genetic variations. For young women, a major environmental factor is the use of hormonal preparations for contraception. For postmenopausal women, a history of VTE is an additional risk factor if estrogen treatment is given.

Hormonal preparations can increase VTE risk in some existing high-risk groups causing clinical expression or shifting expression to an earlier age. The specific effects of hormones can also theoretically put other groups at high risk, and these risks are probably specific to combinations of genetic variations.

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The challenge is to find as many relevant high-risk combinations as possible and devise genetic methods to detect them. The main difficulty will be the identification of the combinations, which are rare to very rare. The study on women using oral contraceptives provides relevant information in this respect for postmenopausal women. The higher absolute VTE risk for postmenopausal women renders the clinical significance for this group higher.

INTRODUCTION

The risk of venous thrombosis is, to a significant extent, determined by genetic deviations in one or more of the multiple factors in haemostasis. The risk of venous thrombosis is increased for women using estrogen with oral contraceptives and hormone replacement. Pregnancy is also associated with an increased risk. The risk associated with estrogen is expected to essentially follow similar mechanisms in these different situations. Both the use of oral contraceptives and HRT show the so-called "starter effect".^{1,2} This effect represents the

FROM THE EDITOR

David F. Archer, M.D.

This edition of *Menopausal Medicine* addresses the association of Estrogen with Thrombosis and Breast Cancer, two issues that repetitively arise in discussions of hormone therapy. Both are relatively common problems that are seen by Practitioners, and neither has definitive answers regarding causality.

Dr. Cornelius Kluff and colleagues address the issue of thrombosis in an effort to identify genetic causes. Thrombosis is a disease with several well-recognized causes such as deficiency of Protein C and Protein S, or increased Factor VII in blood. The genetic aspects of thrombophilia are obvious from those families who have multiple individuals with clinical thrombosis. Factor V Leiden is a well-known inherited factor as is the prothrombin mutation G to A 20210. Estrogens have been linked to thrombosis although the precise mechanism(s) are unknown. Dr. Kluff makes the point that screening for risk factors using molecular or biochemical techniques is not appropriate based on the low incidence of occurrence of many genetic diseases. The use of estrogen appears to identify a group of women at risk for thrombosis. Only some women have clearly identified causes to account for the thrombosis while others are associated with estrogen use or considered idiopathic. The future is to determine the risk factor(s) that is activated or associated with estrogen, in order to allow us to identify these women.

Dr. David F. Archer returns as an essayist to present his interpretation of the role of estrogen in the breast cancer debate. The issue regarding the use of estrogen in postmenopausal women is: do estrogens cause or promote the growth of breast cancer? Breast cancer is a disease that has multiple confounding factors such as a family history, environmental exposures, life style (obesity), and hormone use. Assigning a specific cause to estrogen in any individual case is difficult, if not impossible. Using population demographics only identifies the incidence and not the individual(s) at risk. A percentage of breast cancers are identified between yearly mammography evaluations indicating that even sensitive detection methods are not foolproof, and suggesting that the size or growth of the cancer allows us to identify it.

Many women perceive estrogen as causing breast cancer. This is due to the publicity relating an increased incidence or risk of breast cancer with estrogen or estrogen plus progestin use. We are potentially identifying a group of women whose breast cancer is responsive to hormonal stimulation. We may be demonstrating a similar occurrence as described with thrombosis: identifying after the fact those individuals where the hormonal intervention increases susceptibility for a disease. If this hypothesis of selecting at-risk women were to be proven true, then estrogen is really not causal, but is a promoter of breast cancer growth.

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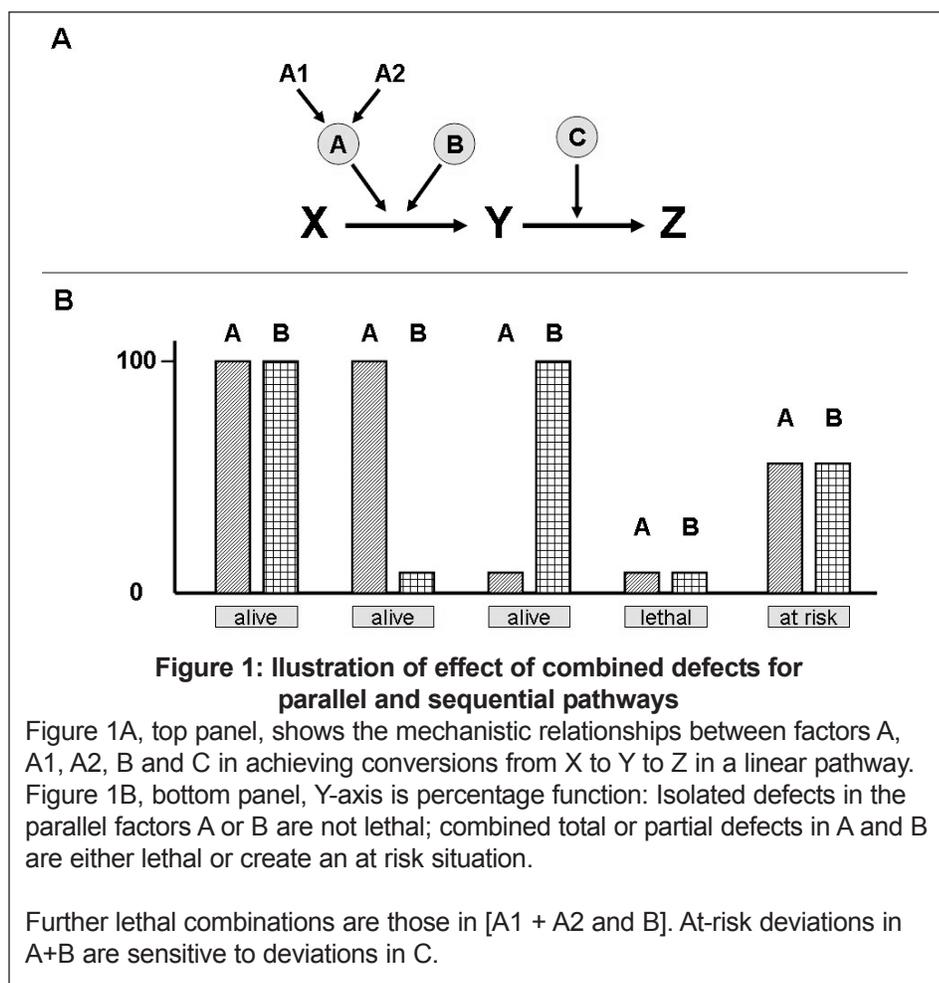
situation that, in a group of women beginning to use estrogen, the initial two years show a strongly increased number that develop venous thromboembolism, while later a plateau of increased risk is established. This phenomenon may be explained (at least partially) by the occurrence of a subgroup of women with increased susceptibility to estrogen-induced thrombosis. The total risk in the first two years for oral contraceptives is estimated to be of the magnitude of 1:1,000, compared to ~ 0.4:1,000 in later years.

Although it is a challenge to identify

GENOMIC VARIABILITY: WHAT MAKES SENSE?

It is wellknown that genomic variability exists in the human population and that it contributes to differences among individuals in disease risk and responses to the environment, including medication. The challenge is to translate the genetic variability of around 1 in 200 base pairs to functional consequences of one, or most likely, many combinations of multiple variations.

A first criterium for the importance of genetic variability is that the genetic variation shows a functional conse-



all causes of increased risk of thrombosis associated with estrogen increase, the number of women involved who are affected by the starter effect suggests that this effect should receive ample attention as well. The question addressed here is how and whether genetic deviations might help us to identify individuals at future risk.

quence in protein production or function and is not merely a silent variation/mutation for function. Examples of the latter are many genetic mutations in introns, silent mutations for coding amino acids and permissive variability in non-essential areas of the proteins.

A second criterium at a higher level

of organization of the organism is that the functional protein variability shows clinical expression. Here it is essential that most proteins function in pathways and in cooperation with various types of organizations. Typically, the organization can be in linear pathways in a sequential manner or in a parallel manner.

The consequences of a protein abnormality for parallel pathways are illustrated in figure 1 and follow the so-called principle of synthetic lethality.³ In the example of Figure 1, only deviations in both parallel pathways (A and B) will lead to serious abnormalities. It has been shown in micro-organisms that many parallel or redundant pathways exist and that frequently also more than two parallel mechanisms exist.³ A similar reasoning for cooperating abnormalities can be given for steps in a linear pathway (see legend to Figure 1).

There are genetic variations in single proteins that are critical in basic mechanisms (redundancy is absent), and subsequently these functional variants have a large impact on health, e.g. the well-known heritable diseases of Huntington and Duchenne. Here the abnormality in one gene product is a direct and dominant cause of clinical expression. This type of nearly monogenetic disease is very rare (mutation frequency well below 1% in the population) and only severity and age at onset are variables determined by additional genetic factors.

Most other genetic variations concern proteins with a less essential role, and the variation results in a partial or quantitative change of function. In this case, only combinations of variants become a serious health threat (see figure 1). This phenomenon is frequently covered by the term “multifactorial disease,” in which environmental factors also play a role.

For environmental factors and medication, a special aspect of genetic variability concerns the regulation of genes. It is possible that genetic variation determines the degree of response

of a gene and defines low non- and hyper-responders to the environmental factor or medication.⁴ An example for estrogens is the response of factor VII, which is dependent upon the genotype of factor VII.⁵

The consequence of the above principles of genomics and physiology is that combinations of deviations are of specific importance in determining risk. In the case of estrogen-induced venous thrombosis, the combinations may be specifically due to the selective participation of factors sensitive to estrogen and genetic variations regulating the response to estrogen. The group of women developing estrogen-induced venous thrombosis may be partially different from those not receiving estrogen (or being pregnant) and from males with venous thrombosis. The latter may conform to the low predictive value of family history of those at specific risk of the effects of oral contraceptives.⁶

VENOUS THROMBOSIS AND COMBINED RISK FACTORS: SPECIFICITY OF COMBINATIONS TO ORAL CONTRACEPTIVES

Venous thrombosis runs in families, suggesting the dominance of a single risk factor. However, on a broader scale, it was found that the single factor deficiency is clinically dominant in some families and is asymptomatic in others. The family specificity may be explained by the co-segregation of other deviations/variations, together making up the familial risk.

The increased risk of combinations of defects has been documented in various case reports, small studies and in meta-analysis.⁷ These show an increasing risk when the number of risk factors rises.⁸

It is difficult to document the effect of combinations of risk factors since the prevalence of individual risk factors is often low and combinations are even lower. In this respect, the increased risk of combinations of the more common deviations such as of

factor V Leiden (~5%) and the prothrombin mutation G to A 20210 (~2%) could be best documented. The combination (heterozygotes) of both mutations is expected to occur in the population at a frequency of 1:1,000. The increased risk is illustrated by the fact that the occurrence of this combination is 20-50 times more frequent in patients with venous thrombosis.^{7,9}

In addition to the expected increase in occurrence of combinations, the type of combinations that show an increased risk is also likely to be relevant. This specificity of combinations is related to the fact that the mechanisms or pathways involved are relevant for determining the impact of the combinations (see Figure 1).

Indeed, we can find indications for such specificity of combinations. Thus, it has been reported that deviations in factor V (factor V Leiden plus the HR2 mutation, and factor V Leiden plus factor V antigen) show in combination an increased risk, while the combinations of the HR2 mutation with the prothrombin mutation G to A 20210 do not show this.^{9,10} Also, high factor VIII levels contribute apparently specifically to the thrombotic risk in families with factor V Leiden.¹² A dedicated, aggregated analysis is warranted.

Since the documentation of the increased risk of usually quite rare combinations requires very large studies, using mechanistic considerations to add plausibility may help in deciding about relevant combinations.

ESTROGEN EFFECTS

Estrogen effects on haemostasis variables as observed during the use of oral contraceptives, HRT and pregnancy are abundant (> 25 variables are involved).¹³ Many changes are plausibly linked to an increased risk of VTE, but some counteract this, thus complicating the interpretation. This indicates that many candidates exist for evaluating significance. A status of surrogate end-point has not been established for any of these vari-

ables.¹⁴ Experts have made a consensus list, adopted by EMEA for oral contraceptives, of variables that should at least be considered and may be a basis for hormonal treatment as well.

INDIVIDUALS WITH GENETIC VARIATIONS THAT RESPOND STRONGLY TO ESTROGEN TREATMENT SHOWING A HIGH RISK OF VTE ARE OF SPECIAL SIGNIFICANCE.

This has been documented for factor V Leiden carriers (both COC and HRT) and the prothrombin mutation G to A 20210.^{15,16} Here the risk of venous thrombosis is more than additive (close to multiplicative) when estrogens are used. This implies that some of the estrogen effects are closely related to the change in haemostasis associated with these genetic variations (see Figure 1). It is not a priori established that the same estrogen-induced changes are relevant for both genetic deviations.

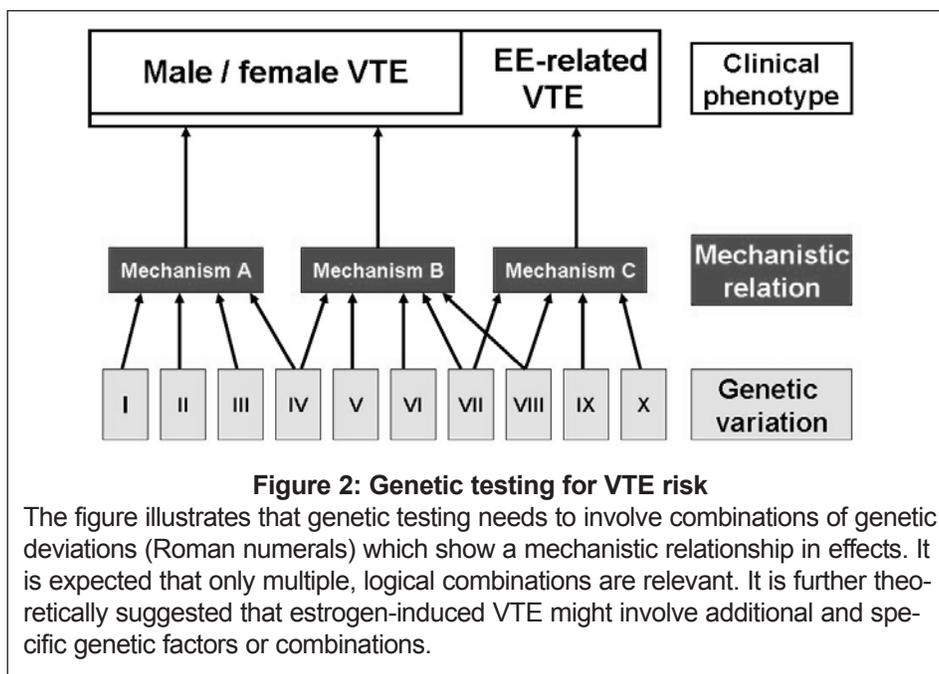
It is of importance to know whether a strong impact of estrogens exists for more genetic defects and for which combinations. It is, however, difficult to establish this in view of the low prevalence of most genetic haemostasis variations.

An additional genetic factor to consider is the polymorphic nature of the estrogen receptor-alpha.^{17,16} The polymorphisms and haplotypes have been implicated in modulating quantitatively the effects of estrogens. It shows us the phenotypes sensitive to estrogen quantity. In population studies involving mainly the endogenous estrogen exposure, numerous associations with disease have been identified, but those

for venous thrombosis have not yet been reported.

It would be of interest to know whether or not this genetic variation in ER-alpha is also involved in the magnitude of response of haemostatic factors to estrogen use. Thus far only such an effect has been demonstrated for the response of HDL, SHBG and E-selectin to estrogen use in post-menopausal women.^{17,18} In a preliminary analysis of the effects of the polymorphisms in the ER-alpha gene on multiple haemostasis factors we did not observe any strong effect (in preparation).

DIAGNOSTIC PROGRESS



With regard to estrogen use, we may be interested in identifying women with an increased baseline risk of VTE who might have an increase in risk due to estrogen use, that becomes unacceptable by criteria as yet to be decided. In addition, we might wish to identify subgroups with a susceptibility to an extra increased risk due to estrogens, putatively leading to the starter effect.

Previous VTE creates a risk by itself.¹⁹ When we restrict ourselves to genetic testing of asymptomatic cases, it can be stated that technology will not be a major hurdle and cheap and easy methods with a multitude of tests

can be expected to become available. In view of the risk of VTE in the order of 1:1,000 women for oral contraceptives, the number needed to diagnose one case will be minimally 1,000.

At present, familial thrombophilia (risk of developing VTE = 1:10) is the only reason to consider exclusion from estrogen use. This concerns 0.033% of the women. In an ideal situation, with the above-mentioned tests, we would consider exclusion for 0.1% of women. This would be influenced by the specificity of the test and drop below 0.1% when not all genetic combinations are known. It would increase above 0.1% when the tests show diagnostic specificity below 1. Recently, factor V Leiden alone as an exclusion criterium was considered unacceptable since it involved 5% of women with a risk of developing VTE.

The major hurdle is the evidence-based development of the test and the question of whether this will show acceptable efficiency at some point. First of all, we can expect a large number of combinations of defects with a low prevalence and demonstration of the baseline risk and extra risk with estrogen use requires large studies or meta-analysis. It at least requires a systematic collection of cases that have developed VTE with and without estrogen use to increase the basis for evidence-based diagnostics.

Most likely the test will not contain all possible genetic risk combinations in the near future or ever, and will cover < 100% of possible at-risk individuals. When the percentage of coverage becomes acceptable will require economic and ethical consensus.

Further, progress in mechanistic studies is of paramount importance. This is illustrated by the recent unexpected finding of a new factor and in particular its Marburg I mutation. This factor, Factor Seven Activating Protease, FSAP, shows in the population a prevalent mutation (~3%) which seems associated with VTE risk of a similar magnitude to factor V Leiden.²⁰ This would increase significantly the possibility of combinations of mutations. This observation requires confirmation.²¹ It is not known yet whether or not this Marburg I mutation shows an extra increased risk during estrogen use as demonstrated for factor V Leiden and the Prothrombin mutation.

DISCUSSION

The data summarized above of the increased risk of venous thromboembolism with estrogen use (COC, HRT) can result in the identification of susceptible women. The principles and feasibility of such an approach are discussed.

Identification of unacceptable risk can lead to reduced application of the current preparations. An alternative is the development of further modification of the preparations. For COC, the past development has been to reduce the estrogen dose and, more recently, it became clear that the type of progestogen is also of importance. Further developments for HRT are in tissue-specificity and route of administration. Thus, adjustments to the treatment are also an option for reducing VTE risks. The diagnostic approach to identifying high-risk individuals for VTE is also of significance for pregnancy.

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Hormone Therapy and Breast Cancer: Issues in Counseling Women

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INTRODUCTION

Breast cancer is a major concern of women. The impact of breast cancer on women is due to the association of the female breast with femininity, reproduction, and sexuality. Breast cancer is almost 99% confined to women, rarely occurring in men. The breast tissue undergoes changes at the time of puberty and menopause and alters its growth characteristics during the menstrual cycle and pregnancy. Multiple hormones interact to allow for lactation to occur after delivery of an infant. All of these reasons have made for the compelling case that hormones influence the female breast. This concept is extended to conclude that exogenous hormones, since they are not endogenous and do not reflect normal physiology, could be bad for the breast and cause cancer to occur.

These issues have resulted in a large volume of both clinical and basic research into the role of hormones and breast cancer. The implication derived from the mass media is that hormones increase the risk (cause) of breast cancer. To some extent this reflects the medical debate over the role of exogenous estrogens and/or progestins and breast cancer. The media have a tendency to only report the bad news and ignore the good news regarding estrogen and breast cancer. Since there is a debate, it is important to objectively evaluate the data from both sides. A comprehensive review of the material is diffi-

cult, but this essay points out the weak association between hormones and breast cancer and tries to place hormones into perspective with other breast cancer risks such as family history and obesity. The cause of breast cancer is multifactorial, yet cellular changes are influenced by both genetics and other local and peripheral molecular processes which we are just now beginning to comprehend.

Women who were provided a scenario based on the attributable risk of breast cancer and the use of hormonal medication experience a significant change in attitude and potentially behavior.¹ This often results in the individual rejecting appropriate hormonal therapy (estrogen or estrogen plus a progestogen, HT), even though they are experiencing moderate to severe menopausal symptoms. Many women feel that a diagnosis of breast cancer is a death sentence. This is because the public believes the death rate associated with breast cancer to be high, although breast cancer is not the principal cause of death in women in the United States. The United States had 215,000 new cases of breast cancer and 40,000 deaths attributed to breast cancer in 2004 (<http://www.cancer.org>). The survival rate of breast cancer is high because of several factors, not the least of which is improved early diagnosis from the use of screening mammography (see Table 2).²

COUNSELING AND OBESITY

Obesity or a high Body Mass Index (BMI) is associated with an increase in the risk of breast cancer.³⁻⁵ Diet and weight gain have been linked to an increase in breast cancer risk while exercise is associated with a decrease in the risk.^{3,6} Other modifiable factors have included alcohol intake and smoking as associations with an increased risk of breast cancer.⁷⁻¹⁰ Obviously the role of genetics

(family history) and environmental factors have been implicated with an increased risk of breast cancer (See Table 1).¹¹

**Table 1
Etiology of Breast Cancer**

**Genetics
Diet
Environment
Hormonal
Lifestyle**

Source: www.cancer.org

COUNSELING

AGE-RELATED RISKS

No age is spared from the possibility of developing breast cancer, but advancing age is a significant risk factor (see Table 3). The incidence of breast cancer increases dramatically after age 50.¹² Over 80% of breast cancers in postmenopausal women occur in women who have never received hormone therapy. Age is pos-

**Table 2
Survival Rate of Breast Cancer**

**87% at 5 years after diagnosis
77% 10 years after diagnosis
63% after 15 years
52% after 20 years**

Source: www.cancer.org

itively correlated with the occurrence of breast cancer.¹² That is to say that as an individual ages, the incidence of breast cancer increases.¹² It is obvious that postmenopausal women have low endogenous estrogen levels. An association has been reported between elevated (but still postmenopausal) estrogen levels and the occurrence of breast cancer.^{13,14}

ASSOCIATION WITH HORMONE THERAPY

The major problem with Hormone Therapy (HT) and breast cancer is that both physicians and consumers infer that the increased relative risk (RR) of breast cancer associated with the use of HT indicates causality. It is important to stress that the associations found in epidemiologic studies for breast cancer are only associations and do not imply that they cause cancer. An example of this is the finding of an elevated relative risk for breast cancer in women who have used long-term antibiotics

for upper respiratory infections.¹⁵ Support for this statement is the Relative Risks for certain factors associated with breast cancer shown in Table 4 and Figure 1. Each of these factors has some relevancy or biologic plausibility to account for the potential relationship to breast cancer. Knowing this does not indicate that the assumptions made of altered estrogen levels or estrogenicity is the cause of the breast cancer.

FAMILY HISTORY AND GENETIC ISSUES

Several hypotheses could be evoked to explain the development of breast cancer. Perhaps the most compelling is the association of genes and breast cancer, especially since the strongest association is with a family history of breast cancer.^{7,16-18} The family history is a surrogate for genetic analysis. At present it is estimated that

only 5% to 10% of breast cancers are genetically determined. It is possible that as we accumulate more information we will find an increased incidence of genetic causes of neoplasia.¹⁷

EPIDEMIOLOGIC STUDIES

The medical literature is replete with a variety of observational studies that have shown an increase, a decrease,

and no significant change in the relative risk of breast cancer in postmenopausal women receiving estrogen (ET) or estrogen plus progestin therapy (EPT).¹⁹ The evidence from observational studies is not consistent for an association of HT and breast cancer.¹⁹ A more compelling aspect of these findings is that

estrogen or estrogen plus progestin could increase the growth of an existing breast neoplasm in postmenopausal women. This could result in early diagnosis, and thus be associated with an increased incidence in the population under study. This hypothesis implies that the

use of exogenous estrogen or estrogen plus progestin does not cause breast cancer, rather it increases the growth rate of an existing breast cancer, resulting in an increase in the size of the tumor that allows for its clinical detection.²⁰⁻²²

Estrogens and progestins can stimulate the growth of breast cancer cells in animal models and in vitro.²¹ There is no direct evidence that Hormone Therapy (HT consisting of either ET or EPT) can cause neoplasia.²¹ One of the most compelling observations is that after stopping HT, the risk of breast cancer rapidly returns to that observed in never users of HT.^{12,23} These data would suggest a lack of stimulation rather than an induction of neoplasia.

NEOPLASIA WITHOUT CLINICAL DISEASE

A current hypothesis is that all individuals, both men and women, harbor nests of neoplastic cells that do not progress to a clinically detectable

tumor.²⁴ This hypothesis is partly based on the findings of microscopic breast cancer cells in 39% of women aged 40-50 years from an autopsy series.^{25,26} The actual incidence of breast cancer is 1.0% in women of comparable age (40-50 years).^{25,26} The proponent of this hypothesis believes

The stem cell has the potential for pleomorphic changes that could result in the multiple histologic patterns seen in breast neoplasia. These data suggest that neoplastic changes may not be related to a hormonal induction mechanism, but another mechanism not well understood at the present time.

Table 3
Age Specific Probabilities of Developing Breast Cancer

Current age	Probability of Breast Cancer in next 10 years	Incidence 1 in
20	0.05%	2,152
30	0.40%	251
40	1.45%	69
50	2.78%	36
60	3.81%	26
70	4.31%	23

Source: www.cancer.org

DETECTION BIAS

Epidemiologic studies that have shown an increase in the incidence of breast cancer could be interpreted as reflecting an overall increase in breast cancer detection in a population of women who are using HT. This is certainly possible in the Women's

Health Initiative (WHI) HT arm, where, for the first four years of the study, the occurrence of breast cancers was the same in both the placebo and HT-treated women.³⁰ A significant finding in this study was the larger tumor size at diagnosis and the increased incidence of positive lymph nodes in the HT users.³⁰ These findings could be attributable to the proposed growth-promoting activities of HT as discussed below.

RANDOMIZED CLINICAL TRIALS

The two randomized clinical trials of conjugated estrogen and MPA in older women show different outcomes. The Heart and Estrogen/progestin Replacement Study (HERS) evaluated a group of women using EPT whose average age was 67. The breast cancer hazard ratio (HR) was 1.30 (95% CI 0.77-2.19), not statistically significant, and remained the same in the additional 2.7 years of follow up, HR 1.39 (95% CI 0.84-2.28).^{31,32} It should be

BREAST STEM CELL DYSFUNCTION

Recent reports have implicated a dysfunction in endogenous stem cells or progenitor cells in the breast as the potential etiology of the neoplasia.²⁷⁻²⁹

noted that breast cancer was not a primary or secondary outcome measure for the HERS trial.

The Women's Health Initiative, the second randomized clinical trial of EPT, initially did not find a statistically significant increase in the occurrence of invasive breast cancer with a HR 1.26 (95% CI 1.00-1.5).³³ The HR for breast cancer was 1.06 (0.81-1.38) for women who had never before used HT33. This finding is in agreement with the Collaborative Group report of a relative risk of 1.05 (95% CI 0.99-1.12) in women who used HT for less than five years.¹² The overall risk of breast cancer in

the WHI trial was elevated in previous users of HT.³³ These data would argue that it takes five-plus years before the effects of the hormone therapy are apparent in terms of the detection of breast cancers. The data would also support the contention that estrogens or progestins stimulate the growth of a pre-existing breast cancer.²² The final unweighted relative risk for invasive breast cancer was 1.24 in EPT users (nominal 95% CI 1.01-1.54).³⁰

It is important to understand that none of the women, upon entry into the EPT arm of the Women's Health Initiative, had evidence of breast cancer. During the first four years of the

Table 4 Relative Risks for Breast cancer	
Relative Risk >4.0 strong association	Factor Breast Cancer in two or more first degree relatives Personal History of breast cancer Postmenopausal Breast Density (radiographic) Genetic mutations (BRCA -1; BRCA-2)
2-4 moderate association	Breast Cancer in one first degree relative Biopsy confirmed atypical hyperplasia High Bone Mineral Density (postmenopausal)
1.1- 2.0 weak association	First full term pregnancy >30 years Early menarche <12 years Late menopause >55 years No full term pregnancy Never Breast fed a child Obesity Long term use of hormone therapy High alcohol intake Tall (height)
Source: http://www.cancer.org	

study, breast cancers were detected both in the placebo as well as the EPT group. These cancers must have existed prior to the study but were undetected by mammography and clinical evaluation. The subsequent increase in the incidence of invasive breast cancer in the EPT arm of the WHI could be related to the fact that they grew to a detectable size faster compared to the placebo group. Therefore, the Women's Health Initiative has a hazard ratio for the detection of breast cancer rather than a hazard ratio that is increased due to EPT causing breast cancer.

Support of this latter hypothesis is the fact that the tumor size in the EPT

alone, as well as estrogen plus progestin users have an increase in the relative risk for breast cancer in current users. The most important aspect of the Million Women study is the fact that upon stopping hormone therapy, the increased incidence of breast cancer dissipates rapidly. The relative risk for breast cancer is 1.03 (95% CI 0.92-1.12) within one year of stopping HT.²³ The reduction in the risk of breast cancer with stopping HT was also present in the Collaborative Group reanalysis.¹² These data would support the hypothesis that the neoplastic change in the breast cancer cell may not be caused by estrogen, but

group was slightly larger compared to placebo 1.7 versus 1.5 cm (p=0.4).³⁰ The EPT arm had a higher incidence of positive lymph nodes 25.9 versus 15.8%. There were no differences in the histology or SEER grade of the tumors between the two groups,³⁰ further evidence that these differences may be attributable to a growth promoting effect of hormones.

OBSERVATIONAL STUDY

The Million Women Study, has reported that duration of hormone therapy is related to the incidence or occurrence of breast cancer.²³ Both estrogen

that existing breast cancer is grown to a detectable size secondary to increased mitotic activity by the use of either ET or EPT.

ROLE OF PROGESTIN

There is concern over the fact that the progestogen may be a more significant factor than estrogen in the risk of breast cancer. This hypothesis is based on the biologic finding that there is a stimulation of mitotic activity in female breast tissue by progestins.^{34, 35} Continued use of a progestin or increase in the concentration of the progestin often result in an increase in apoptosis and cessation of cell growth.^{36,37} Progestins also have been found to increase the mitotic activity in normal human breast tissue from postmenopausal women.^{35,38}

Supporting the contention that the progestin is significant in development of breast cancer comes from the estrogen-only arm of the WHI. Invasive breast cancer was decreased with a relative risk 0.77 (nominal 95% CI 0.59-1.01), which was not statistically significant.³⁹ There are differences in the demographics of the participants in the EPT and ET arms of the WHI. Despite this, the diametrically oppo-

site findings of the relative risk of breast cancer with EPT increased and ET reduced underscores the fact that even randomized controlled clinical trials can have divergent results.⁴⁰

Observational studies, case controlled trials, and even prospective randomized trials, have generally shown a relatively small and borderline statistically significant increase in the occurrence of breast cancer in postmenopausal women using HT. The relative risk or hazard has usually been about 1.2, a point estimate found in the Women's Health Initiative.^{19,30} The absolute increase in the WHI EPT arm was approximately seven more cases of breast cancer per 10,000 women per year or 0.7 per 1,000. The overall incidence of breast cancer in a 50-year-old woman not on EPT is 20 per 1,000 based on data from never users in the Collaborative Group analysis. The incidence rises to approximately 40 cases per 1,000 at age 60.¹² Using the WHI data, one could see that the increase in incidence of breast cancer is low, 0.7 per 1,000 women per year using EPT. The Million Women Study estimate that after 10 years there are five additional cases of breast cancer per 1,000

women in ET users, and 19 additional cases per 1,000 women in EPT users.²³ The Canadian Gynecologic and Obstetrical Society has listed the extra cases of breast cancer associated with various risk factors (see Table 5). These attributable risks should be used in counseling patients since it is a more accurate representation of their individual risk than the relative risk estimate.

The basic and clinical research literature is very mixed as to whether or not there is causality, that is the ability of estrogen to induce or cause neoplasia in the breast.^{19,21} This author's opinion is that mitotic activity or growth in an existing breast cancer is stimulated by both estrogen and progestin, but there is no compelling evidence that either estrogen or progestin is a carcinogen causing breast cancer.²¹

Neither the Gail model used to estimate the risk of breast cancer, nor a family history of breast cancer was found to correlate with the occurrence of breast cancer in the WHI study.³³ The Gail model, although useful for clinical trial work, is not particularly suited to the individual patient because a major factor in the model is the age of the individual. As a woman

**Table 5
Extra Cases of Breast Cancer Based on Risk Factor**

TABLE 2
BREAST CANCER RISK AND HRT: RESULTS FROM THE REANALYSIS OF EPIDEMIOLOGICAL STUDIES BY THE COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER (1997) AND THE CANADIAN CONSENSUS ON MENOPAUSE AND OSTEOPOROSIS^{21,22*}

Risk Factor	Breast Cancers Diagnosed Over the 20 Years from Ages 50 to 70	Extra Breast Cancers
Never used HRT	45/1000	—
>5 years' HRT use	47/1000	2/1000
>10 years' HRT use	51/1000	6/1000
>15 years' HRT use	57/1000	12/1000
Late menopause (age 60)	59/1000	14/1000
Alcohol (2 drinks/day)	72/1000	27/1000
No daily exercise	72/1000	27/1000
Weight gain (>20 kg)	90/1000	45/1000

*Data from V. Beral and the Collaborative Group on Hormonal Factors in Breast Cancer;²¹ Table was adapted from Table 1, Belisle and Derzko, *Hormone Replacement Therapy and Cancer*,²² and appears by permission of the Society of Obstetricians and Gynaecologists of Canada.

Source: Canadian Obstetrical and Gynecologic Society web site: <http://sogc.medical.org>

ages, she has an increasing incidence of breast cancer that results in a significant risk factor for breast cancer in women over the age of 60. The Gail model, therefore, is not useful for counseling individual patients, since most women over the age of 60 have a sufficient risk to qualify them for an anti-estrogen [Selective Estrogen Receptor Modulator (SERM) such as Tamoxifen].

RADIOGRAPHIC BREAST DENSITY

Data from both the Postmenopausal Estrogen and Progestin Intervention (PEPI) and WHI indicate that women using HT have an increase in breast density on their mammograms.^{30,33,41} Published studies have reported an association between increased mam-

mographic density and breast cancer.⁴¹⁻⁴³ There is no evidence of a link between increased mammographic density due to HT and breast cancer at this time, rather it is a hypothesis.⁴⁴ The WHI investigators have pointed out that increased mammographic density may impede the detection of breast cancers in women on HT.³⁰ It is of interest that new breast cancers can develop (be detected) between routine mammographic screenings, arguing again for growth of an existing tumor rather than a new tumor in the interval between screenings.^{45,46}

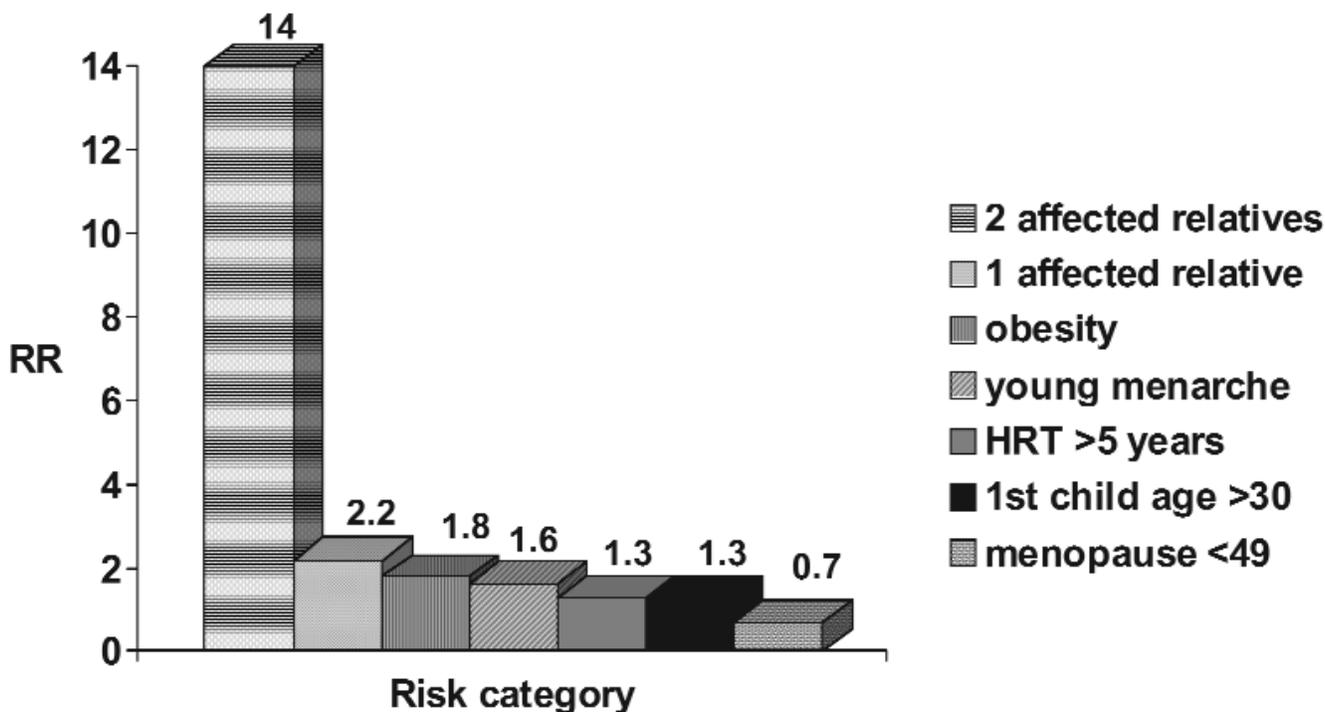
SUMMARY

The relationship between HT and breast cancer is weaker than other modifiable risks such as obesity and alcohol intake, based on epidemiolog-

ic studies. A direct neoplastic effect of estrogen or progestin on the conversion of normal breast tissue to neoplasia is not apparent. These two statements continue to result in the inference that there is a relationship between HT and breast cancer. A plausible explanation for the discrepancies is that breast cancer is multifactorial and HT may be involved more as a promoter than an inducer of cellular neoplasia.

The physician is faced with the difficulty in condensing this information into a viable counseling strategy for his or her patient. The aim of the consultation is to evaluate the individual risk benefit ratio for the menopausal woman and provide her with the most appropriate intervention based on her symptoms and clinical findings. The

Figure 1
Relative Risks of Breast Cancer



incidence of breast cancer per 1,000 women per year may be a more useful counseling tool than the relative risk. Using this incidence, it is apparent that 997 out of 1,000 women aged 50 to 60 will not develop breast cancer even if they use HT.

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