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Review

Effects of menopausal hormonal therapy on occult breast tumors

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ABSTRACT

An estimated 7% of 40–80 year old women dying of unrelated causes harbor occult breast tumors at autopsy. These lesions are too small to be detected by mammography, a method which requires tumors to be approximately 1 cm in diameter to be diagnosed. Tumor growth rates, as assessed by "effective doubling times" on serial mammography range from 10 to >700 days with a median of approximately 200 days. We previously reported two models, based on iterative analysis of these parameters, to describe the biologic behavior of undiagnosed, occult breast tumors. One of our models is biologically based and includes parameters of a 200 day effective doubling time, 7% prevalence of occult tumors in the 40-80 aged female population and a detection threshold of 1.16 cm and the other involves computer based projections based on age related breast cancer incidence. Our models facilitate interpretation of the Women's Health Initiative (WHI) and anti-estrogen prevention studies.

The biologically based model suggests that menopausal hormone therapy with conjugated equine estrogens plus medroxyprogesterone acetate (MPA) in the WHI trial primarily promoted the growth of pre-existing, occult lesions and minimally initiated de novo tumors. The paradoxical reduction of breast cancer incidence in women receiving estrogen alone is consistent with a model that this hormone causes apoptosis in women deprived of estrogen long term as a result of the cessation of estrogen production after the menopause. Understanding of the kinetics of occult tumors suggests that breast cancer "prevention" with anti-estrogens or aromatase inhibitors represents early treatment rather than a reduction in de novo tumor formation.

Our in vivo data suggest that the combination of a SERM, bazedoxifene (BZA), with conjugated equine estrogen (CEE) acts to block maturation of the mammary gland in oophorectomized, immature mice. This hormonal combination is defined by the generic term, tissue selective estrogen complex or TSEC. Xenograft studies with the BZA/CEE combination show that it blocks the growth of occult, hormone dependent tumors in nude mice. These pre-clinical data suggest that the BZA/CEE TSEC combination may prevent the growth of occult breast tumors in women. Based on the beneficial effects of this TSEC combination on symptoms and fracture prevention in menopausal women, the combination of BZA/CEE might be used as a means both to treat menopausal symptoms and to prevent breast cancer.

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1. Introduction

An estimated 7% of 40–80 year old women are found to have undiagnosed breast cancer at autopsy [1–8]. We have developed both a biologically based and a computer-derived model to assess the growth of these occult tumors during the period in which they are too small to be detected by mammography. The biologic properties of the undiagnosed tumors provide insight into interpretation of the Women's Health Initiative (WHI) studies, breast cancer prevention trials, and risk prediction methods [9–23]. From these models, we conclude that the majority of the observed breast cancer effects of menopausal hormone therapy are exerted on pre-existing occult tumors commonly present in the population of otherwise healthy post-menopausal women. Additionally, use of anti-estrogens or aromatase inhibitors for breast cancer prevention actually represents early treatment of occult lesions.

The substantial prevalence of occult breast tumors in women has important implications. Recent data have indicated that most symptomatic women just entering menopause experience more benefit than risk from menopausal hormone therapy [2]. Current recommendations suggest use of hormone therapy in these women provided that they are not at enhanced risk for heart disease or breast cancer. However, a strategy that would both relieve symptoms and prevent breast cancer would add another dimension to this approach. Accumulating clinical data suggest that the combination of an estrogen with a SERM might relieve symptoms and at the same time provide early treatment for occult breast cancers. The SERM/estrogen combination has been termed a TSEC or tissue selective estrogen complex. This review will provide an overview of the biologic data indicating the importance of occult breast tumors and detail the studies suggesting that a TSEC might serve as early treatment of occult lesions. In this manuscript, we will cite our own data predominantly but also refer to studies that confirm and extend the concepts underlying the kinetics of occult tumor growth.

2. Methodology used to develop tumor growth kinetic models

Our two models have been previously published [24] and are described here only briefly. For the occult tumor growth (OTG) model, we used iterative analyses to construct a series of breast cancer incidence curves utilizing the following parameters: effective[2] tumor doubling times of 100–400 days, occult tumor prevalence in the normal population of 3–15%, and mammographic detection thresholds of 0.8 cm to 2.0 cm [24]. Published data indicate that one billion cells are required for a tumor to reach the threshold required for mammographic detection [25]. Thirty tumor doublings are needed to reach one billion cells, based on an average tumor cell size of 10^{-6} mm^3 [25]. Individual incidence curves were constructed with iterations involving each of these parameters. We compared the incidence curves predicted by the iterative parameters with actual population incidence data to determine which parameters fit best with incidence data. On this basis a model utilizing a 200-day effective doubling time, 7% prevalence of occult undiagnosed tumors, and 1.16 cm detection threshold was developed and validated.

[2] The term "effective doubling time" is used since certain populations of tumor cells are undergoing apoptosis; others have entered a G^0 resting phase; and non-cancerous stromal cells may contribute to tumor volume. The apoptosis and G^0 populations would cause underestimation of the actual doubling time of populations of proliferating tumor cells. The term "effective doubling time" integrates these four components (i.e. proliferating tumor cells, apoptotic cells, G0 cells and non-tumor stromal cells) and represents the time required for a tumor to double in size even though some cells in the tumor are dying and others resting.

Assumptions underlying the OTG model: We assumed that each category of tumor doublings (i.e. tumors that have undergone 1, 2, 3, 4, 5, . . . 30 doublings, etc.) appears in equal proportions throughout the population of tumors in the reservoir [26,27]. For example, since approximately 30 tumor doublings are required to reach the limit of detection, 3.3% of the tumors in the reservoir would have undergone 2 doublings, 3 doublings, 4 doublings . . ., respectively. We also assumed that occult tumors in the reservoir exhibit log-linear growth kinetics and validated this by examining the growth kinetics of small breast tumors in mouse xenografts [28]. The computer based model was developed using four steps: (1) simulation of a cohort of women with de novo tumors initiated at randomly generated ages; (2) simulation of doubling times for the generated tumors; (3) computation of age of incidence; and (4) correction for deaths from competing causes. [24]. There was a major difference between the OTG and computer based tumor growth (SCTG) models. Specifically, the OTG model assumes an equal distribution of tumors in each doubling time category whereas the CSTG model allows this distribution to be generated by the model, finding a positive skew with a greater proportion of occult tumors residing in the lower doubling categories [24].

Model validation: Based on iterative analyses, the parameters which best fit the population incidence data included a 200-day doubling time, 1.16 cm detection threshold and 7% occult tumor prevalence (Fig. 1A) since they tracked closely with SEER data [12,16]. Occult contralateral breast cancer prevalence and observed incidence data provided another means of validating the OTG model. Histologic examination of excised or biopsied contralateral breast tissue provided a *prevalence* estimate of 12.4% based on 19 studies of 6204 breasts [24]. Using this 12.4% prevalence figure, an EDT of 200 days, and a 1.16 cm detection threshold, we calculated the predicted cumulative incidence of contralateral breast cancer over time (Fig. 1B). The observed incidence was determined from three studies that followed patients long term (Fig. 2B) [29].

De novo versus occult tumors: As described previously, our models calculated that only tumors with a doubling time of 50 days or less would be detected during the five years of the WHI estrogen plus a progestogen study. This allowed us to calculate the percentage of tumors detected during the WHI study which were de novo rather than occult. Both the OTG (Fig. 2A) and computer models (Fig. 2B) suggested that 6% of tumors arose de novo and 94% were occult. Similar calculations indicate that 11% of tumors in the E alone arm would have arisen de novo at 7.2 years (the duration of estrogen alone use in the WHI) and the remaining 89% would be in the occult undiagnosed reservoir. As the fraction of de novo tumors is small, the primary effects of MHT (menopausal hormonal therapy) appear to be promotional, causing pre-existing occult tumors to grow faster and reach the detection threshold earlier.

Modeling of effect of E ± P on tumor incidence: Utilizing the OTG model, we then predicted the effects of E + P in the WHI study on the 94% of tumors arising from occult lesions. We assumed that 80% of tumors detected were ER^+ as reported in the WHI E + P trial. Iterative modeling indicated that the best fit of observed with predicted data was achieved by assuming that E + P increased growth rates, reducing effective doubling time from 200 to 150 days (Fig. 3). The OTG model estimates predicted an incidence of diagnosed breast cancer in the placebo group of 2.38% at 5.2 years and 2.99% in the E + P group (relative risk 1.26). These predicted incidence rates closely paralleled the observed data that 2.28% of women developed breast cancer in the placebo group and 2.88% in the E + P group, representing a RR of 1.26 (95% CI 1.00-1.59).

Modeling of effect of estrogen alone on incidence: Observed data from the 10.7-year follow-up report of the WHI E-alone trial indicated a statistically significant 23% decline in breast cancer incidence (RR 0.77 95% CI 0.62–0.95) [14] in the estrogen arm (Fig. 4). In our previously published analysis, we assumed that 30% of the 80%