

## Modeling of the Growth Kinetics of Occult Breast Tumors: Role in Interpretation of Studies of Prevention and Menopausal Hormone Therapy

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### Abstract

**Background:** Autopsy studies report a reservoir of small, occult, undiagnosed breast cancers in up to 15.6% of women dying from unrelated causes. The effective doubling times (EDT) of these occult neoplasms range from 70 to 350 days and mammographic detection threshold diameters from 0.88 to 1.66 cm. Modeling of the biologic behavior of these occult tumors facilitates interpretation of tamoxifen breast cancer prevention and menopausal hormone therapy studies.

**Methods:** We used iterative and mathematical techniques to develop a model of occult tumor growth (OTG) whose parameters included prevalence, EDT, and detection threshold. The model was validated by comparing predicted with observed incidence of breast cancer in several populations.

**Results:** Iterative analysis identified a 200-day EDT, 7% prevalence and 1.16 cm detection threshold as optimal parameters for an OTG model as judged by comparison with Surveillance Epidemiology and End Results (SEER) population incidence rates in the United States. We validated the model by comparing predicted incidence rates with those observed in five separate population databases, in three long-term contralateral breast cancer detection studies, and with data from a computer-simulated tumor growth (CSTG) model. Our model strongly suggests that breast cancer prevention with anti-estrogens or aromatase inhibitors represents early treatment not prevention. In addition, menopausal hormone therapy does not primarily induce *de novo* tumors but promotes the growth of occult lesions.

**Conclusions:** Our OGTG model suggests that occult, undiagnosed tumors are prevalent, grow slowly, and are the biologic targets of anti-estrogen therapy for prevention and hormone therapy for menopausal women. *Cancer Epidemiol Biomarkers Prev*; 21(7); 1038–48. ©2012 AACR.

### Introduction

Autopsy studies have identified a "reservoir" of small, occult, undiagnosed breast cancers in up to 15.6% of women with an average of 7% (1–8). The growth kinetics of these reservoir tumors have important implications for interpretation of breast cancer prevention trials, the Women's Health Initiative (WHI) studies, and risk-prediction models (9–23). We integrated a large body of data to serve as a basis for iterative modeling of the prevalence and growth kinetics of tumors in this reservoir and used these data to develop a model, which

computed predicted incidence curves. The parameters used for model development included: (i) estimates of occult "reservoir tumor" prevalence from analysis of published autopsy and contralateral breast pathology studies, (ii) tumor doubling times estimated from mammographic data, and (iii) detection thresholds (DTs) based on tumor diameter. The parameters that best corresponded to observed incidence from Surveillance Epidemiology and End Results (SEER) population data were used to construct an occult tumor growth (OTG) model. Validation of the model involved comparison of predicted with observed incidence rates in 4 additional normal populations, in 3 contralateral breast cancer incidence studies, and from a newly designed computer-simulated tumor growth (CSTG) model.

Knowledge of the biologic properties of occult tumors in the population facilitates interpretation of published breast cancer prevention studies. Our OTG model suggests that anti-estrogens and aromatase inhibitors reduce the growth of occult reservoir tumors and thus represent early treatment, not prevention. We used the OTG model to further interpret the WHI studies (15). The initial report indicated that the relative risk of breast cancer increased by 26% after 5.2 years of use of conjugated equine estrogen

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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plus medroxyprogesterone acetate (RR 1.26; 95% CI, 1.00–1.59) (15). The lay public and media have generally interpreted the WHI studies to indicate that menopausal hormone therapy (MHT) causes *de novo* breast cancer and is thus carcinogenic. However, the WHI study design did not allow distinction between *de novo* tumor development or alternatively, a promotional action to stimulate the growth of occult, undiagnosed tumors and cause them to reach the diagnostic threshold earlier. Assessment of the biologic properties of occult tumors indicated the likelihood that MHT primarily influences the growth of occult reservoir tumors rather than initiating new neoplasms and that breast cancer risk prediction models primarily estimate the prevalence of reservoir tumors. We conclude that the majority of the observed effects of anti-estrogens or aromatase inhibitors for prevention and MHT for symptom relief are exerted on preexisting occult tumors commonly present in the population of otherwise healthy postmenopausal women.

## Materials and Methods

### Sources of data utilized for modeling components

**Prevalence of occult tumors.** A series of 8 recently summarized studies (2) reported the prevalence of occult breast cancer at autopsy in women, primarily ages 40 to 80, who died of other causes (1, 3–5, 7, 8). Percentages differed substantially from 0% to 15.6% in individual studies with an average prevalence of 7% (6% *in situ* and 1% invasive). Histopathologic examination of contralateral breast tissue in women with ipsilateral breast cancer provides another means of assessing the prevalence of occult breast cancer. By examining the contralateral breast removed prophylactically or randomly biopsied in women with ipsilateral breast cancer, the prevalence of occult breast cancer in this setting can be estimated. The average prevalence of occult tumors determined from 19 publications and 6,204 women was found to be 12.4%; see Supplementary Table SI (24–41).

**"Effective doubling time."** We reviewed the pertinent literature reporting doubling times of breast cancer as ascertained by serial mammograms; see Supplementary Table SII (42–49). The technique quantitates the diameter of the breast cancer lesion at initial mammographic diagnosis and compares it with the diameters of lesions in the identical area observed before diagnosis in previously obtained serial mammograms (48, 50). The formula,  $V = 4/3\pi r^3$  is used to calculate tumor size, where  $V$  is the tumor volume and  $r$  is the radius. Doubling times are derived from these calculations. Measured tumor growth rates reflect the integrated contributions of cell proliferation; percent resting ( $G_0$ ) cells; and rates of apoptotic, autophagic, senescent, and necrotic cell death. Measured tumor doubling by mammogram then actually reflects the "effective" doubling time (EDT). Reported EDTs ranged from 50 to 400 days and averaged approximately 200 to 300 days; see Supplementary Table S2 (42–49). Bailey and colleagues used mathematical modeling techniques to

construct age-specific cumulative frequency distribution curves from these data (48). We used the EDTs reported in their manuscript as they provide an integration of published data. Mean EDTs increase as a function of advancing age from 233 days for women 50 to 59, to 260 days for those 60 to 69, and 288 days for those 70 or older. Notably, EDT curves are right skewed and median EDTs are therefore considered more informative than means. In 50- to 79-year-old women (the ages of the majority of women in the WHI), the median EDT approximates 200 days with an interquartile range of 70 to 320 days (48).

**Detection threshold.** The sizes of tumors required for mammographic detection at various ages were derived from the modeling studies of Bailey and colleagues (48). These DTs represent an integration of data reported from various mammographic screening programs (48, 51–54). Average mammographic density decreases with age and sensitivity of detection is inversely correlated with density (55). Accordingly, DTs decrease with age (48); specifically, estimated thresholds are 1.63 cm for ages <40; 1.44 cm (ages 40–49); 1.25 cm (ages 50–59); 1.07 cm (ages 60–69); and 0.88 cm (ages >70) with an average of 1.16 cm for those 50 to 69 years of age.

The number of cells required for a tumor to reach the DT and number of tumor doublings can be calculated from the average volume of cancer cells. On the basis of an average tumor cell size of  $10^{-6}$  mm<sup>3</sup> (56), 28 to 32 doublings are required to reach DTs of 0.8, 1.02, 1.27, 1.69, and 2.04 cm, respectively, and the numbers of cells required are  $0.27 \times 10^9$ ,  $0.54 \times 10^9$ ,  $1.07 \times 10^9$ ,  $2.1 \times 10^9$ , and  $4.3 \times 10^9$ , respectively.

### Assumptions used in modeling

For the OTG model, we assumed that each category of doublings and respective tumor sizes appears in equal proportions throughout the population of tumors in the reservoir (57, 58). For example, because approximately 30 tumor doublings are required to reach the limit of detection, 3.3% of the tumors in the reservoir would have undergone 1, 2, 3, 4, 5, . . . , etc. doublings, respectively. Using this assumption, we calculated the time required for tumors at each number of doublings to reach the DT based on the starting number of doublings and their EDTs. The second assumption is that occult tumors in the reservoir exhibit log-linear growth kinetics. Gompertzian, logistic, quadratic, or power growth kinetics were not used for our calculations as occult tumors are small (i.e., <1.16 cm) and likely had not reached the asymptotic phase of tumor growth that occurs when tumors become large (56, 57, 59–61); for example, the asymptotic component of Gompertzian kinetics is reported to occur at approximately 8 cm (62). The gradual reduction of log-linear growth after volumes approach asymptotic values (modeled by the Gompertzian, quadratic, logistic, or power kinetics techniques) is thought to be because of outgrowth of adequate blood supply in large tumors (57, 61).

### Invasive and *in situ* breast cancer incidence data

Healthy population incidence data were obtained from multiple sources. The data specifically bracketed the years 1997 to 2006 to allow time-concordant comparisons with WHI data, which were collected over the same period (15). The various data bases included (i) 1997 to 2006 SEER invasive and *in situ* breast cancer data from 9 large population centers in the United States in women 50 years old and older (63), (ii) multicenter Breast Cancer Surveillance Consortium (BCSC) data from 1997 to 2006 (64), (iii) Manitoba, Canada mammography screening program data (20), (iv) the placebo arm of the WHI conjugated equine estrogen alone (E-alone) trial (16), and (v) the placebo arm of the WHI conjugated equine estrogen/medroxyprogesterone acetate (E+P) trial (11, 12). Contralateral breast cancer incidence data were obtained from (1) a recent large study (65) of 16,500 women followed for 15 years, (2) an earlier study of Robbins and colleagues (66), and (3) another published by Rosen and colleagues (67).

### Modeling

**Iterations.** We varied the prevalence rates of occult tumors, their EDTs and DTs and examined the effects on predicted tumor incidence rates which were then individually plotted. To determine which iteration best conformed to observed data, we compared predicted rates with those observed in the SEER population incidence data. The iterative parameters best fitting the observed data were chosen for the occult tumor growth (OTG) model.

**Model validation—additional population-based incidence.** To validate our model, we compared the predicted incidence rates based on our model with 2 mammographically detected incidence rates in normal populations and with incidence rates derived from the placebo arms of the WHI E+P and E alone studies. Concordance of predicted with observed incidence rates in several populations provided validation of our model. In addition, we calculated the predicted incidence rate of contralateral cancers during prolonged follow-up and compared this with observed incidence rates obtained from 3 large follow-up studies (65–67).

**Model validation—computer-simulated incidence.** As further validation of our OTG model, we developed a new computer simulation tumor growth (CSTG) model to estimate breast cancer incidence, growth, and detection. The model involved 4 phases: (i) simulation of a cohort of women with *de novo* tumor initiation, (ii) use of randomly generated doubling times, (iii) computation of age-related incidence, and (iv) correction for competing deaths. A detailed description of the method is included in the online Supplementary Methods section.

### Estimation of time to diagnosis of occult tumors

The OTG model was used to determine the times needed for *de novo* tumors to reach the mammographic DT. The cumulative distribution curve for 50- to 69-year-old women, published by Bailey and colleagues (48), was

used to determine the percentage of patients in each doubling time window. Assuming that 30 doublings are required to reach the DT, the percentage of *de novo* tumors reaching detection was estimated. The percent of *de novo* tumors was then multiplied by total incidence to calculate the absolute percentages of tumors arising *de novo* or from the occult tumor reservoir. The CSTG model used the age-dependent *de novo* incidence data calibrated from the overall model, the gamma distribution doubling times for these tumors, and age-dependent DTs to estimate these same data.

### Parameters used to model WHI and tamoxifen studies

Both preclinical and clinical data were used to determine the parameters to be included in the modeling of the WHI E+P, WHI E alone, and tamoxifen prevention studies. The precise details of the parameters used and rationale for their selection are described in Supplementary Methods section.

### Results

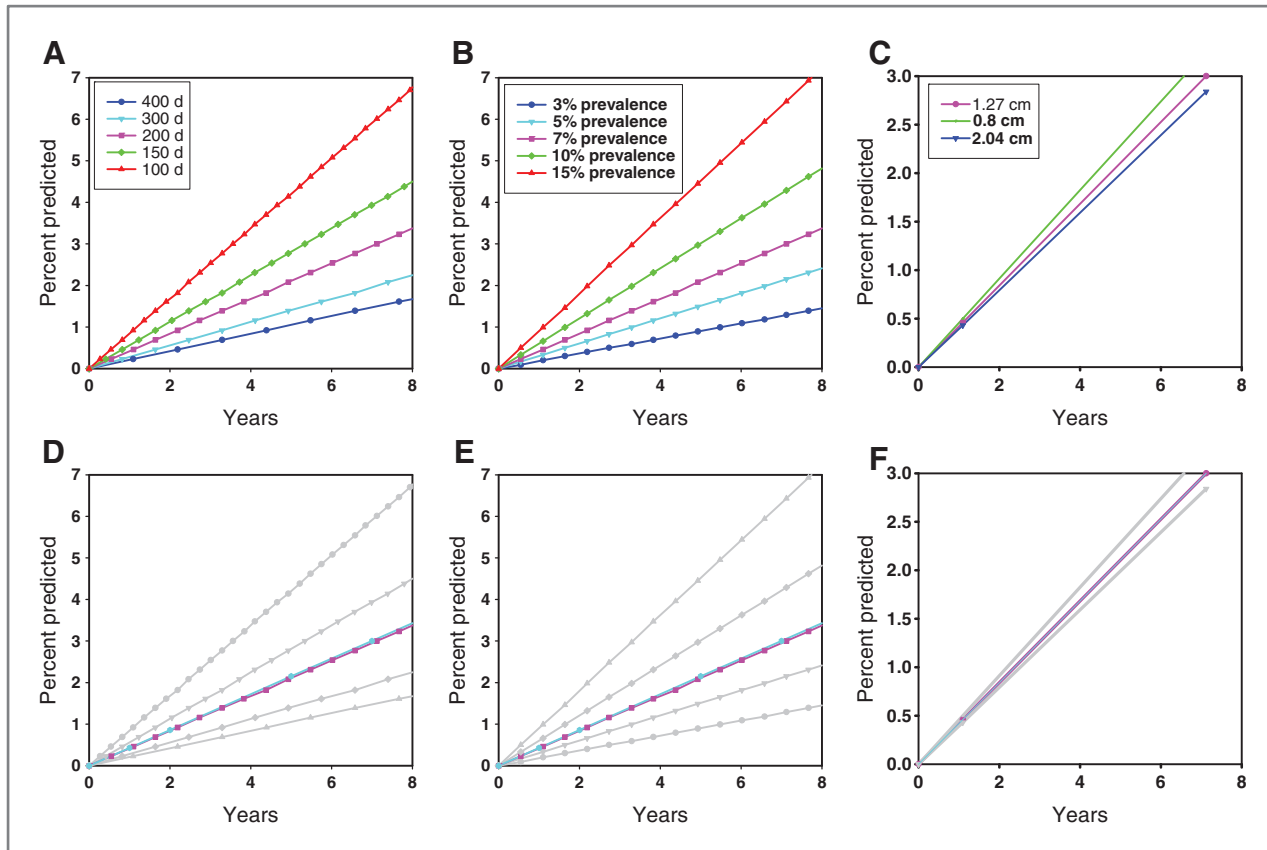
#### Iterative modeling to calculate predicted incidence rates

To estimate the biologic behavior of occult tumors in the reservoir, we used prevalence, doubling time, and DT data to develop a model which predicted observed incidence of tumors in several populations. Close correspondence of model predictions with observed population data provided validation of inferences about the biologic behavior of occult tumors.

**Iterations.** The first set of iterations holds the percent prevalence constant at the published average level of 7% and assesses the effect of varying the EDTs (Fig. 1A). The second set varies prevalence within reported ranges while holding EDT constant at the reported median of 200 days (Fig. 1B). The third set examines the effect of altering the diagnostic threshold from 0.8 to 1.6 cm while holding EDT constant at 200 days and prevalence at 7% (Fig. 1C). The figures (see Fig. 1A–C) show that EDT and underlying prevalence markedly influence the predicted incidence rates, whereas the DTs exert only minimal effects.

**Choosing specific parameters for OTG model.** Our strategy was to select the parameters, which optimally predicted breast cancer incidence in the general population as described by SEER data. Parameters providing the "best fit" included a 200-day EDT (Fig. 1D), 7% prevalence (Fig. 1E), and 1.16 cm DT (Fig. 1F) and the model using these parameters tracked closely with SEER data (Fig. 1D–F). Accordingly, these parameters were chosen for the OTG model.

**Model validation.** The OTG model was validated using additional population incidence data. Predicted incidence as described by our OTG model was compared with that observed in 2 mammographic incidence studies and in 2 populations involved in randomized clinical trials (RCTs) as shown in Fig. 2A. The BCSC and Manitoba incidence rates were derived from mammographic

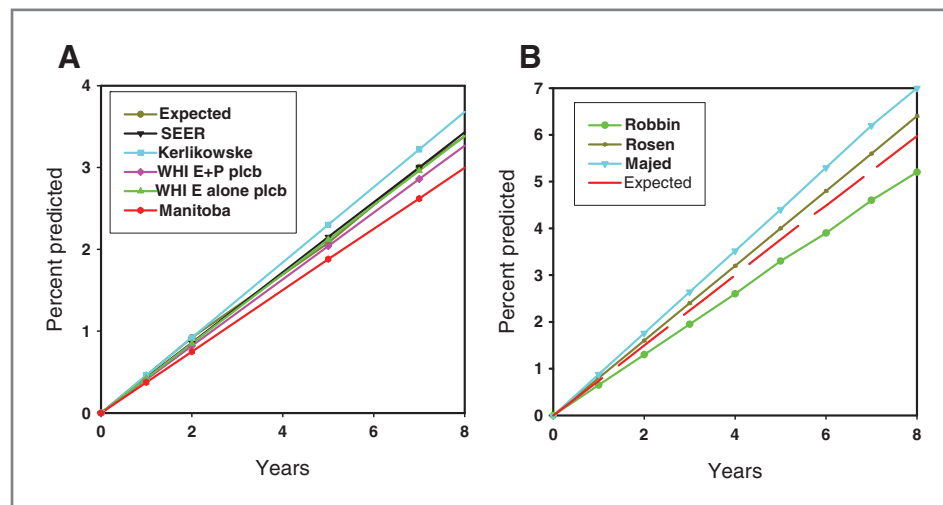


**Figure 1.** A, percentage of predicted incidence of breast cancer over an 8-year period assuming a 7% prevalence of occult, undiagnosed breast cancers in the reservoir and with iterations EDTs of 100 to 400 days. B, percentage of predicted incidence as in (A) with iterations of percentage of prevalence of occult tumors in the reservoir and assuming an EDT of 200 days. C, percentage predicted incidence assuming a 200-day EDT, and 7% prevalence and with iterations of detection thresholds of 0.8, 1.27, and 2.04 cm in diameter (D). The shaded lines represent the EDT iterations and the solid line the observed breast cancer incidence from SEER data. E, the shaded lines represent the percentage of prevalence iterations and the solid line the observed incidence from SEER data. F, the shaded lines represent the detection threshold iterations and the solid line the observed incidence from SEER data.

screening studies, and the placebo arms of the WHI E alone and E+P trials provided incidence data from RCTs (20, 64). These additional incidence curves closely bracketed those predicted by our OTG model (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

**Figure 2.** A, the observed percentage incidence of breast cancer from the SEER, BCSC, Manitoba, WHI E+P placebo (plcb) arm, and WHI E alone placebo arms are compared with the predicted incidence based on the OTG model. B, the observed incidence of breast cancer in the Majed, Robbins, and Rosen studies compared with the expected incidence based on the OTG model (65–67)



a prevalence estimate of 12.4% based on 19 studies of 6,204 breasts; see Supplementary Table SI. Using this 12.4% prevalence figure, an EDT of 200 days and a 1.16-cm DT, we calculated the predicted cumulative incidence of contralateral breast cancer over time (Fig. 2B). The observed incidence was determined from a very large recent study that followed 15,166 patients over a 15-year period (Fig. 2B; ref. 65). Observed and predicted incidence curves closely corresponded. Two additional data-bases from earlier eras were used as a means of reducing the confounding from adjuvant hormonal and chemotherapies (66,67). These observed incidence rates also corresponded closely with predicted, providing additional evidence that the 200-day EDT and 1.16-cm DT parameters were biologically valid for modeling.

**CSTG model.** As described under Materials and Methods, an independent, mathematically based tumor growth model using different assumptions was developed and used to calculate incidence rates in comparison with those determined by the OTG model. Calibration of the CSTG model resulted in a histogram of distributions of tumor doublings, which exhibited a gradual falloff from doublings 1 to 30 (Fig. 3A). It should be noted that this distribution differed from that of the OTG model, which assumed that the percentage of tumors in each doubling category was equal at 3.3%. The CSTG model was then used to calculate age-specific incidence rates (Supplementary Fig.) and average incidence rates for 20- to 85-year-old women (Fig. 3B). The CSTG model incidence predictions slightly underestimated SEER and OTG incidence data (Fig. 4A and B). Specifically, the CSTG model predicts that 2.7% of the 50- to 79-year-old population will develop breast cancer over 8 years (Fig. 4B) and the OTG model, 3.4% (Fig. 4A). The inclusion in the denominator of women dying of other causes probably explains the lower incidence in the CSTG model as removing the deceased women adjusts the CSTG incidence from 2.7% to 3.1%.

#### Time to detection of *de novo* tumors

Analysis of the WHI studies did not address the question whether changes in breast cancer incidence resulted from a promotional effect on the kinetics of preexisting

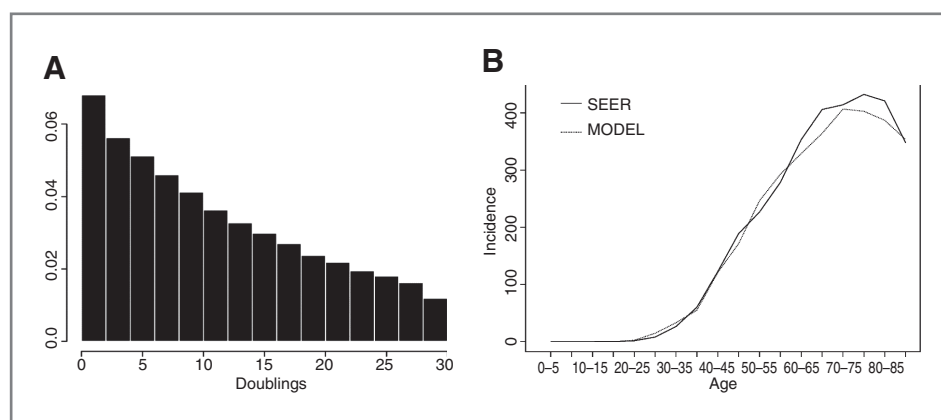
tumors in the reservoir or from an increase in *de novo* tumors. Using published EDT frequency distributions (48), we calculated the percentage of tumors that would have occurred *de novo* during the 7.2-year follow up period of the WHI E alone study. With EDTs of 50, 100, 150, 200, and 250 days, the times required to reach the 1.16-cm diagnostic threshold ranged from 2.05 to 20.5 years (Fig. 5A and B). Only tumors with doubling times of 100 days or less would have had sufficient time to grow to exceed the DT within 7.2 years. Published data estimated the percentages of women from ages 50 to 69 whose tumors are in each doubling time category (49, 50, 56). One percent had an EDT of <25 days and 10% each had doubling times of 26–50, 51–75, and 76–99 days. On the basis of these figures, we calculated that the incidence of *de novo* tumors would be 0.14% at 5 years and 0.34% at 7.2 years (Fig. 4A). In comparison, the CSTG model estimated the incidence of *de novo* tumors in the population of 50- to 79-year-old women to be very similar at 0.21% and 0.44%, respectively (Fig. 4B). By subtracting the *de novo* tumor incidence from the total, the incidence of occult tumors only was calculated (Fig. 4A and B).

#### Application of OTG model to interpretation of clinical studies

##### Percent *de novo* tumor development in WHI studies.

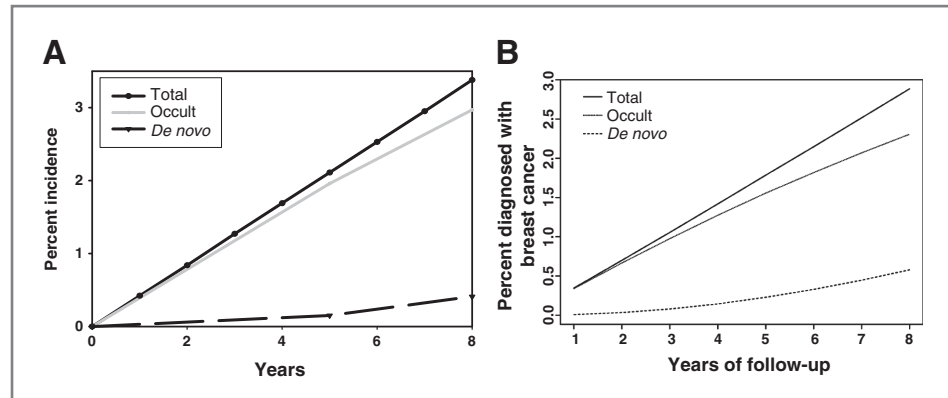
We first determined the incidence of tumors reaching the diagnostic threshold in the WHI study, which would represent *de novo* tumors. Dividing *de novo* incidence (0.14%) by total incidence (2.08%) indicates that only 6.7% of the newly diagnosed tumors at 5 years would reflect *de novo* tumors and 93.3% occult in the WHI E+P placebo arm (12). Similar calculations indicate that 11% of tumors in the E alone arm would have arisen *de novo* at 7.2 years 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 seem to be promotional, causing preexisting occult tumors to grow faster and reach the DT earlier.

**Modeling of effect of E±P on tumor incidence.** We used the OTG model to assess the predicted effects of E+P in the WHI study on the 93.3% of tumors arising from



**Figure 3.** A, the distribution of tumor doublings in a cohort of 50-year-old women bearing occult tumors, as calculated by the CSTG model. The vertical axis represents the fraction of occult tumors in each category. B, the age-related annual incidence of breast cancer (per 100,000 women) calculated with the CSTG model (dotted line) compared with SEER-based incidence (solid line).

**Figure 4.** A, the incidence of total tumors expressed as a percentage of the population, which reached the detection threshold over a period of 8 years compared with the incidence of *de novo* and occult tumors based on the OTG model. B, the incidence of total tumors expressed as a percentage of the population, which reached the detection threshold over a period of 8 years compared with the incidence of *de novo* and occult tumors based on the CSTG model.



occult lesions not taking into account the 6.7% arising *de novo*. Using the parameters described in Materials and Methods, the curves predict an incidence in the placebo group of 2.38% at 5.2 years and 2.99% in the E+P group (relative risk 1.26). The observed data reported 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; ref. Fig. 6A). These data support the conclusion that MHT reduces the EDTs of occult tumors in the reservoir from an average of 200 to 150 days.

We next calculated the effect of stopping E+P therapy in the population after publication of the first WHI report (Fig. 6B). The incidence of breast cancer from the OTG model over the years 1997 to 2001 was predicted to be 2.46% and from 2002 to 2006, 2.29%, a 7% drop. The observed data, taken from the BCSC (64), reported the observed cumulative incidence dropping from 2.56% from 1997 to 2001 to 2.27% from 2002 to 2006 a decline of 11.4%. Similarly, SEER data report a cumulative incidence from 1997 to 2001 of 2.37% and from 2002 to 2006, 2.17%, a decline of 9.1% (Fig. 6B; ref. 63).

**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; ref. 14). Using assumptions described under Materials and Methods, the OTG predicted incidence of breast cancer fell similarly from 2.96% in the placebo group to 2.31% in those taking estrogen, a similar 22% decrement (Fig. 6C).

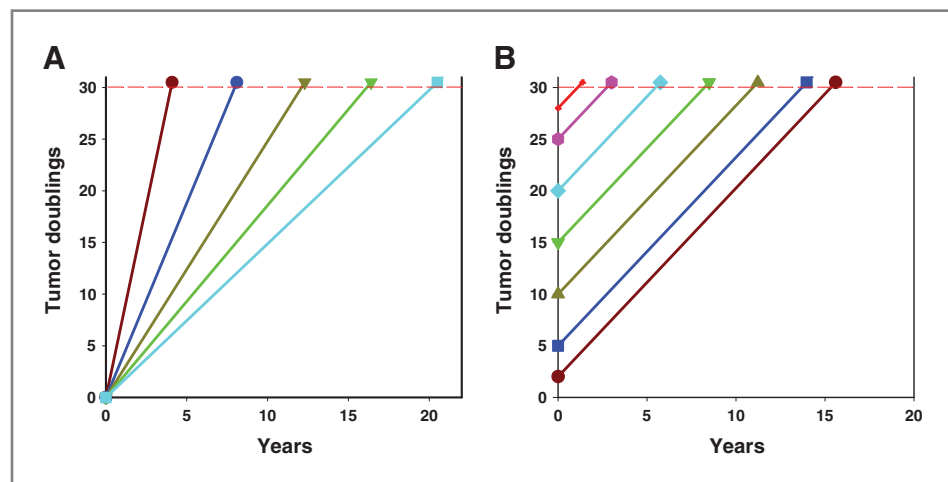
**Modeling of tamoxifen and breast cancer incidence.**

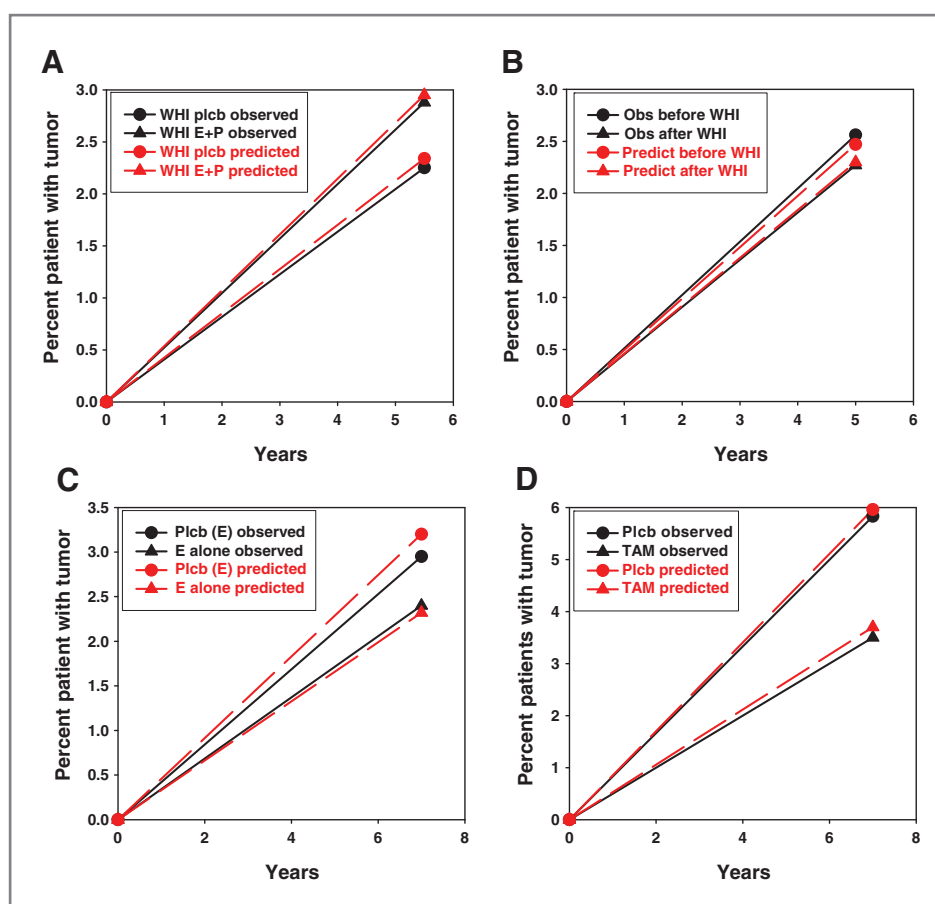
The NSABP-P1 prevention trial included only women at increased risk of breast cancer based on the Gail model. Examination of the occult tumor prevalence iterations (Fig. 1B) in conjunction with actual incidence in the placebo group (6.3% at 7.2 years) allowed us to estimate that the prevalence of preexisting tumors in the placebo arm was 14%. On the basis of data from advanced breast cancer, we assumed that tamoxifen caused regression or stabilization of 50% of tumors. With these assumptions, the model calculated an expected incidence at 7.2 years of 6.0% in the placebo group and 3.7% in the tamoxifen group. As shown in Fig. 6D, this corresponded closely with the observed percentages of 6.3% and 3.6%, respectively.

**Discussion**

This study used iterative techniques to develop a model to characterize the biologic properties of the reservoir of

**Figure 5.** A, the time to reach the detection threshold at 30 tumor doublings (i.e., 1.16 cm) with effective doubling time iterations represented by the various colors: 50-day EDT —, 100-day EDT —, 150-day EDT —, 200-day EDT —, and 250-day EDT —. B, the time to reach the detection threshold of 30 tumor doublings (i.e., 1.16 cm) for tumors with iterations representing the given number of doublings at the beginning of the observation period 2 doublings —, 5 doublings —, 10 doublings —, 15 doublings —, 20 doublings —, 25 doublings —, and 29 doublings —.





**Figure 6.** A, the incidence of breast tumors predicted in the placebo and hormone arms of the WHI E+P trial over a 5.2-year period based on the OTG model. In comparison are shown the observed data in the placebo (plcb) and hormone-treated arms of the WHI E+P trial. B, the incidence of breast tumors predicted in the general population in the years 2002 to 2006 after the first report of the WHI E+P trial. Calculations are based on the OTG model and the numbers describing the reduction of use of E+P in this population are based on the data from the BCSC mammography population. Observed data are derived from the reported incidence of breast cancer from 1997 to 2002 and 2003 to 2006 reported from the BCSC mammographic data. C, the incidence of breast tumors predicted in the placebo and hormone arms of the WHI E-alone trial over a 7.2-year period based on the OTG model. In comparison are shown the observed data in the placebo and hormone-treated arms of the WHI E alone trial. D, the predicted incidence of breast cancer in the NSABP-P1 trial based upon the OTG model and the assumption that tamoxifen (TAM) prevents the growth of 50% of ER+ tumors. In comparison, the observed data from the NSABP-P1 trial are plotted (9, 10, 21–23).

small, undiagnosed breast tumors present in the otherwise healthy population of 50- to 80-year-old women. This OTG model was used to further interpret the results of the NSABP-P1 breast cancer prevention and WHI studies. The model was based on the assumptions of 7% average prevalence of tumors in the occult, undiagnosed tumor reservoir; median 200-day EDT; and an average DT of 1.16 cm. Validity of the model rested on the robust concordance of predicted incidence with observed incidence rates from multiple sources including 5 independently studied healthy populations (12, 16, 20, 64) and 3 contralateral breast cancer studies (65–67). Further validation compared the OTG incidence rates with computer-simulated data (CSTG model) based on assumptions differing from those in the OTG model. Specific differences in the CSTG model included a gamma distribution of doubling times, rates of competing mortality, and incidence rates of

*de novo* cancer as a function of age. On the basis of the concordance of predicted with observed breast cancer incidence, these data provide strong inferential evidence about the biologic properties of occult tumors in the reservoir.

Cognizance of the biology of reservoir tumors implies that only a small fraction (i.e., approximately 6.7%) of tumors diagnosed in the WHI arose *de novo*. The remaining 93.3% likely represented occult tumors in the reservoir at study entry which reached the DT more rapidly in response to the proliferative effects of hormone therapy. This suggests that menopausal hormone therapy primarily promotes the growth of occult tumors but causes initiation of *de novo* tumors less commonly. The best "fit" to match observed data was achieved by an effect of E+P to enhance tumor growth with a reduction of EDT from 200 to 150 days. We also calculated that a

return in doubling time from 150 to 200 days upon cessation of E+P would predict a 7% reduction in breast cancer incidence over the next 5 years. This predicted result conformed closely to the observed 11.4% decrease in incidence in the BCSC study and 9.1% from SEER data (63, 64).

The 10.7-year follow-up of the estrogen alone arm of the WHI study reported a paradoxical, statistically significant, 23% (RR 0.77; CI, 0.62–0.95; ref. 14) reduction in breast cancer diagnosis in the estrogen alone group. Our OTG model data are consistent with the mechanistic hypothesis of a proapoptotic effect of estrogen (68) with a 30% reduction of cell number in ER+ occult tumors. Preclinical data show that estrogens can cause apoptosis through the FAS-ligand/FAS death receptor and mitochondrial pathways in breast tumors but only in those deprived of estrogen long term (68–77). The average age of women in the WHI study was 63 years, a full 12 years beyond the average age of menopause of 51. Accordingly, the majority of these women had been "deprived" of premenopausal levels of estrogen long term. Although these considerations support the plausibility of the estrogen proapoptotic hypothesis, further evidence is required for confirmation, and other explanations are possible.

The concept of a large reservoir of undiagnosed tumors in the general population has major implications about current strategies for prevention of breast cancer. An understanding of the biology of reservoir tumors suggests that the reduction in breast cancer associated with the tamoxifen, raloxifene, or exemestane prevention strategies primarily reflects a diminution in growth of occult, ER+ tumors and represents early treatment, not prevention (9, 10, 21–23, 78). Accordingly, a major research focus should be on developing new, highly sensitive methods to detect these occult cancers and to determine their degree of aggressiveness. Our model also suggests that risk prediction models primarily assess the percent prevalence of preexisting tumors in the undiagnosed reservoir and not *de novo* tumor development. The Gail and other models (79) calculate the risk of breast cancer developing over a 5-year period, a time when only approximately 6.7% of cancers, arise *de novo*.

Several factors could have confounded our OTG model development and application. Non-breast cancer-related death rates reduce the estimated incidence of breast cancer in the general population, particularly in the older subgroups. This was showed by our computer-simulated model, which took this factor into account. Inclusion of non-breast cancer death rates reduced predicted 8-year incidence from 3.4% to 2.7% (80). Another confounding factor is that predicted incidence of breast cancer, calculated from the parameters of autopsy prevalence, doubling time, and DT, is influenced by the increasing appearance of *de novo* tumors over time. Notably, this would not be an important factor over the 5 to 7 years of the WHI and NSABP-P1 studies where only approximately 6.7% to 11% of tumors were calculated to arise *de novo*.

It has not been uniformly accepted that breast cancer incidence over time has decreased as a result of cessation of hormone therapy occurring after publication of the WHI study in 2002. Many factors, including a reduction in the prevalence of mammographic screening, have been raised as alternative explanations (2, 20, 68, 89). The BCSC data are the strongest to support a causal role of cessation of hormone therapy because it obviated the problems resulting from mammographic detection.

Previous investigators have also suggested that the early effects of hormone therapy promote occult tumors in the reservoir and lead to early diagnosis but have not extensively modeled these effects (58, 81). Dietel and colleagues also raised the question whether this earlier diagnosis of occult tumors may be beneficial as supported by the reports of enhanced survival from breast cancer in women diagnosed while receiving MHT (81). This issue is controversial because only observational but not randomized trials have reported improved survival in MHT users (2).

The majority of lesions at autopsy were DCIS and not invasive breast cancer (IBC; ref. 82). One might contend that blockade of progression from DCIS to IBC actually is breast cancer prevention. However, if DCIS is truly breast cancer and not a preneoplastic lesion, then this contention would not be correct. On the other hand, blockade of progression from atypical hyperplasia to DCIS would represent true prevention. Tamoxifen in the NSABP-P1 trial reduced the incidence of ADH and thus "prevented" one of the more advanced stages of premalignant lesions (83). In this sense, hormonal therapy might then ultimately reduce the development of the *de novo* DCIS lesions. The OTG model was not designed to assess such early stages of neoplastic development. These considerations highlight the need to consider strategies to interrupt the development and progression of premalignant, benign breast lesions in the future.

### Summary

Breast cancers too small to be detected at the onset of RCTs have important implications about interpretation of data. On the basis of an analysis of the biology of occult tumors, we suggest that the changes in breast cancer incidence observed in the WHI, NSABP-P1, and Star (tamoxifen versus raloxifene) trials likely represent effects on the reservoir of undiagnosed tumors. Accordingly, breast cancer prevention strategies likely represent early treatment rather than prevention. The biologic properties of occult reservoir tumors also indicate that the Gail, Tyrer-Cuzick, and other risk prediction models seem to assess the prevalence of occult, undiagnosed tumors rather than the onset of *de novo* tumors. Development of more sensitive methods to identify individuals with preexisting occult tumors and to determine their inherent aggressiveness should be a high-priority target for future research.



### Disclosure of Potential Conflicts of Interest

R.J. Santen has received Commercial Research Grant from Pfizer, is a Consultant/Advisory Board member of Pfizer and Teva. No potential conflicts of interest were disclosed by the other authors.

### Authors' Contributions

**Conception and design:** R.J. Santen, D.F. Heitjan  
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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** R.J. Santen  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** R.J. Santen, D.F. Heitjan

**Writing, review, and/or revision of the manuscript:** R.J. Santen, D.F. Heitjan

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** R.J. Santen, W. Yue  
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