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

Richard J. Santen1, Wei Yue1, and Daniel F. Heitjan2

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 OTG 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.

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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
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, $V = \frac{4}{3}\pi r^3$ 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).

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 data 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
screening studies, and the placebo arms of the WHI E alone and EþP 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 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.

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 differed from those determined by the OTG model, 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 closely matched with predicted, providing additional evidence that the 200-day EDT and 1.16-cm DT parameters were biologically valid for modeling.

**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...
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
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
over a 5-year period, a time when only approximately 6.7% to 11% of tumors were calculated to 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 shown 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
Development of methodology: R.J. Santen, D.F. Heitjan
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

Study supervision: R.J. Santen

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