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Modeling of the growth kinetics of occult breast tumors: role in interpretation of studies of prevention and menopausal hormone therapy

Richard J. Santen, MD¹, Wei Yue, PhD¹, and Daniel F. Heitjan, PhD³

^{1,2}Department of Internal Medicine, Division of Endocrinology, University of Virginia, Charlottesville, Virginia, 22908

³Department of Biostatistics & Epidemiology, University of Pennsylvania, Philadelphia, PA 19104

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 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, effective doubling time 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 effective doubling time, 7% prevalence and 1.16 cm detection threshold as optimal parameters for an OTG model as judged by comparison with 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.

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 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 utilized for model development included: (1) estimates of occult “reservoir tumor” prevalence from analysis of published autopsy and contralateral breast pathology studies, (2) tumor doubling times estimated from mammographic data, and (3) detection thresholds based on tumor diameter. The parameters that best corresponded to observed incidence from 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 Women's Health Initiative (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 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 pre-existing occult tumors commonly present in the population of otherwise healthy post-menopausal women.

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 40–80, 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 6204 women was found to be 12.4%; see supplemental Table I (24–41).

Effective Doubling Time—We reviewed the pertinent literature reporting doubling times of breast cancer as ascertained by serial mammograms; see supplemental Table II (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 prior to 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 (G0) 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 200–300 days; see supplemental Table II (42–49). Bailey et al. utilized mathematical modeling techniques to construct age-specific cumulative frequency distribution curves from these data (48). We utilized 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 50–59, to 260 days for those 60–69, 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 70–320 days (48).

Detection Threshold—The sizes of tumors required for mammographic detection at various ages were derived from the modeling studies of Bailey et al. (48). These detection thresholds 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, detection thresholds 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 50–69 years of age.

The number of cells required for a tumor to reach the detection threshold and number of tumor doublings can be calculated from the average volume of cancer cells. Based on an average tumor cell size of 10^{-6} mm³ (56), 28 to 32 doublings are required to reach detection thresholds of 0.8 cm, 1.02cm, 1.27cm, 1.69cm and 2.04 cm, respectively, and the numbers of cells required are 0.27×10^9 , 0.54×10^9 , 1.07×10^9 , 2.1×10^9 and 4.3×10^9 , 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, since 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 detection threshold 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 utilized 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 due to 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 1997–2006 to allow time-concordant comparisons with WHI data which were collected over the same period (15). The various data bases included (1) 1997–2006 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) (2) multicenter Breast Cancer Surveillance Consortium (BCSC) data from 1997–2006 (64), (3) Manitoba, Canada mammography screening program data (20), (4) the placebo arm of the WHI conjugated equine estrogen alone (E-alone) trial (16), and (5) 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 et al (66) and (3) another published by Rosen et al (67).

Modeling

Iterations—We varied the prevalence rates of occult tumors, their EDTs and detection thresholds (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 to 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 two 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 three 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 four phases: (1) simulation of a cohort of women with de novo tumor initiation (2) use of randomly generated doubling times (3) computation of age related incidence and (4) correction for

competing deaths. A detailed description of the method is included in the online supplemental 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 detection threshold. The cumulative distribution curve for 50–69 year old women, published by Bailey et al. (48), was used to determine the percentage of patients in each doubling time window. Assuming that 30 doublings are required to reach the detection threshold, 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 utilized the age dependent de novo incidence data calibrated from the overall model, the gamma distribution doubling times for these tumors, and age dependent detection thresholds to estimate these same data.

Parameters used to model WHI and tamoxifen studies—Both pre-clinical 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 the online supplementary methods section.

Results

Iterative modeling to calculate predicted incidence rates—To estimate the biologic behavior of occult tumors in the reservoir, we utilized prevalence, doubling time and detection threshold 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 regarding 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 effective doubling times (EDTs) (Figure 1A). The second set varies prevalence within reported ranges while holding EDT constant at the reported median of 200 days (Figure 1B). The third examines the effect of altering the diagnostic threshold from 0.8 cm to 1.6 cm while holding EDT constant at 200 days and prevalence at 7% (Figure 1C). The figures (see Figures 1A–1C) demonstrate that EDT and underlying prevalence markedly influence the predicted incidence rates, whereas the detection thresholds 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 (figure 1D), 7% prevalence (Figure 1E) and 1.16 cm detection threshold (Figure 1F) and the model using these parameters tracked closely with SEER data (Figures 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 two mammographic incidence studies and in two populations involved in randomized clinical trials (RCTs) as shown in Figure 2A. The Breast Cancer Screening Consortium (BCSC) and Manitoba incidence rates were derived from mammographic 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 a *prevalence* estimate of 12.4% based on 19 studies of 6204 breasts; see supplemental Table I. 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 (Figure 2B). The observed incidence was determined from a very large recent study that followed 15,166 patients over a 15-year period (Figure 2B) (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 detection threshold parameters were biologically valid for modeling.

Computer simulation tumor growth (CSTG) model—As described under 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 (Figure 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 (supplemental figure) and average incidence rates for 50–79 year old women (Figure 3B). The CSTG model incidence predictions slightly underestimated SEER and OTG incidence data (Figures 4A and 4B). Specifically, the CSTG model predicts that 2.7 % of the 50–79 year old population will develop breast cancer over 8 years (Figure 4B) and the OTG model, 3.4% (Figure 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 pre-existing 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 25, 50, 100, 200, and 250 days, the times required to reach the 1.16 cm diagnostic threshold ranged from 2.05 to 20.5 years (Figures 5A and 5B). Only tumors with

doubling times of 100 days or less would have had sufficient time to grow to exceed the detection threshold within 7.2 years. Published data estimated the percentages of women from ages 50–69 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. Based on 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.(Figure 4A). In comparison, the CSTG model estimated the incidence of de novo tumors in the population of 50–79 year old women to be very similar at 0.21 % and 0.44%, respectively (Figure 4B). By subtracting the de novo tumor incidence from the total, the incidence of occult tumors only was calculated (Figures 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 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—We utilized 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 the methods section, 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) (Figure 6A). These data support the conclusion that MHT reduces the EDTs of occult tumors in the reservoir from an average of 200 days to 150 days.

We next calculated the effect of stopping E+P therapy in the population after publication of the first WHI report (Figure 6B). The incidence of breast cancer from the OTG model over the years 1997–2001 was predicted to be 2.46% and from 2002–2006, 2.29%, a **7% drop**. The observed data, taken from the BCSC (64), reported the observed cumulative incidence dropping from 2.56% from 1997–2001 to 2.27% from 2002–2006 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%** (Figure 6B) (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) (14). Using assumptions described under 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 (Figure 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 (Figure 1B) in conjunction with actual incidence in the placebo group (6.3% at 7.2 years) allowed us to estimate that the prevalence of pre-existing tumors in the placebo arm was 14%. Based on 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 Figure 6D, this corresponded closely with the observed percentages of 6.3% and 3.6%, respectively.

Discussion

This study employed 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 50–80 year old women. This occult tumor growth (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 detection threshold 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. Based on the concordance of predicted with observed breast cancer incidence, these data provide strong inferential evidence regarding 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 detection threshold 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 days 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) (14) reduction in breast cancer diagnosis in the estrogen alone group. Our OTG model data are consistent with the

mechanistic hypothesis of a pro-apoptotic effect of estrogen (68) with a 30% reduction of cell number in ER+ occult tumors. Preclinical data demonstrate 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. While these considerations support the plausibility of the estrogen pro-apoptotic 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 regarding 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 pre-existing 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 five 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 demonstrated 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 detection threshold, 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 6.7–11% 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 since 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 et al. 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

since 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) (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 pre-neoplastic 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 pre-malignant 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 pre-malignant, benign breast lesions in the future.

Summary

Breast cancers too small to be detected at the onset of randomized clinical trials have important implications regarding interpretation of data. Based on 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 appear 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 pre-existing occult tumors and to determine their inherent aggressiveness should be a high priority target for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Panel A: percent 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 of Effective Doubling times (EDTs) of 100 to 400 days

Panel B: percent predicted incidence as in panel A with iterations of percent prevalence of occult tumors in the reservoir and assuming an EDT of 200 days

Panel C: percent 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

Panel D. The shaded lines represent the EDT iterations and the solid line the observed breast cancer incidence from SEER data.

Panel E: The shaded lines represent the percent prevalence iterations and the solid line the observed incidence from SEER data.

Panel F. The shaded lines represent the detection threshold iterations and the solid line the observed incidence from SEER data.

Figure 2.

Panel A. The observed percent incidence of breast cancer from the SEER, BCSC, Manitoba, WHI E+P placebo arm and WHI E alone placebo arms are compared with the predicted incidence based on the OTG model.

Panel 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)

Figure 3.

Panel 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.

Panel B. The age related annual incidence of breast cancer (per 100,000 women) calculated with the CSTG model (dotted line) compared to SEER-based incidence (solid line).

Figure 4.

Left Panel: The incidence of total tumors expressed as a percentage of the population which reached the detection threshold over a period of 8 years compared to the incidence of de novo and occult tumors based on the OTG model

Right panel: The incidence of total tumors expressed as a percentage of the population which reached the detection threshold over a period of 8 years compared to the incidence of de novo and occult tumors based on the CSTG model.

Figure 5.

Left panel. 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 effective doubling time _____
- 100 day effective doubling time _____
- 150 day effective doubling time _____
- 200 day effective doubling time _____
- 250 day effective doubling time _____

Right panel. 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 _____
- 29 doublings _____

Figure 6.

Panel 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 and hormone treated arms of the WHI E+P trial.

Panel 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.

Panel 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.

Panel D. The predicted incidence of breast cancer in the NSABP-P1 trial based upon the OTG model and the assumption that tamoxifen prevents the growth of 50% of ER+ tumors. In comparison, the observed data from the NSABP-P1 trial are plotted (9;10;21–23).

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