Supplementary methods:

Computer simulated tumor growth model: 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 involves four phases. First, for a simulated cohort of women, de novo tumors are deemed to be initiated at randomly selected ages according to a designated hazard function. Second, each initiated tumor is assigned a randomly generated doubling time. Third, an age at tumor detection is computed by assuming that 30 doublings are required to achieve a detection diameter of 1 cm. Fourth, a time of death from causes other than breast cancer is generated for each woman. With this model, we generated large numbers of sample women and identified vital status, presence of a diagnosis of breast cancer if alive, presence of occult breast cancer if no diagnosis has occurred, and number of doublings occurring if an occult tumor exists. The primary use of the model is to generate curves of the predicted incidence of occult or diagnosed breast cancer in simulated cohorts of women comparable to the other observed cohorts studied in this paper.

Non-breast cancer annual death hazards were computed by subtracting breast cancer death hazards from total death hazards using data from recent national incidence reports. Data on breast cancer death rates and data on overall mortality are from Xu et al(1). Data on breast cancer incidence are from the SEER web site: **http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=4&page=sect_04_table.12.Html**. The simulations assume that doubling times of tumors have a gamma distribution with mean 200 days, 25th centile 70 days, and 75th centile 320 days. The gamma parameters that best fit this distribution are $\alpha=1.187$ and $\beta=\alpha/200=0.005935$.

We selected the annual hazard rates for incident occult tumors by assuming an underlying linear spline model for the incidence rates, generating data from this model, generating doubling times for each simulated tumor, and matching diagnosis rates to those occurring in the SEER data cited above. We assumed a model with continuous hazard equal to 0 prior to age 18, and with knots at ages 35, 50 and 70. Our final model used slopes that gave the best fit to the SEER data.

We assumed that tumors would be detected at diameters that depend on the age of the woman and with 30 doublings corresponding to a diameter of 1 cm. We assumed a linear regression of detection diameter on age, with diameters ranging from 1.63 cm at age 30 to 0.88 cm at age 70 (2). Simulations were conducted in TIBCO Spotfire S+ Version 8.1.1 for Sun SPARC, SunOS Version 5.8 (TIBCO Software, Inc.; Palo Alto, CA). Code is available from the third author.

Parameters used to model WHI E+P study: 77% of diagnosed tumors in the WHI E+P study were estrogen receptor positive (ER+) (3). Pre-clinical and clinical data were utilized to model the effects of E+P on proliferation. Although previously controversial (4), the weight of preclinical data demonstrate that estrogen alone and to greater extent, estrogen plus a progestogen increase the rate of proliferation of ER+ breast cancer cell lines, xenografts, and normal breast tissue (5-14). Studies uniformly demonstrate an effect of estrogen alone. Progestogens when added to estrogens stimulate the growth of breast cancer xenografts further(9;10) .This appears to be a class effect since several synthetic progestogens together with E stimulate xenograft growth (9) . In women, estrogen alone stimulates terminal duct lobular unit proliferation and estrogen plus a progestin to a greater extent(15). Based on these data, we concluded that E+P reduces doubling time as a consequence of increased proliferation.

Iterative modeling (data not shown) examined the effects of reducing doubling time to 100, 125, 150, 160 and 175 days on tumor incidence rates. The “best fit” involved a reduction in EDT from 200 days to 150 days. Predicted curves were then calculated from our OTG model assuming 7% prevalence of occult tumors and 1.16 cm detection threshold. EDTs were set at 200 days in the placebo group and (based upon iterative modeling) at 150 days in the 77% of ER+ tumors in the E+P group and 200 days in the 23% in the E+P group that were ER−.

Parameters used to model cessation of E+P: Similar assumptions were used to calculate the effect of stopping E+P therapy. The doubling time was assumed to increase from 150 days to 200 days in the 77% of ER+ tumors and to remain at 200 days in the ER− tumors. Breast Cancer Surveillance Consortium (BCSC) data were used to

determine the percent of women who stopped E+P in the general population after publication of the initial WHI study in 2002. The reported data indicated that MHT use was stable at 48% of women from 1997 to 2001, falling to 39% in 2002, 30% in 2003, and 13% in 2006 (16). Accordingly, prior to the WHI publication in 2002, 48% (4800/10,000) were taking MHT and after the WHI 24%, the mean percentage taking MHT over that 5-year period. The percentage drop in usage of MHT was utilized to determine the number of women who stopped using E+P in the population.

Parameters used to model E alone in the WHI Study: Preclinical data provide evidence that estrogens in doses reflecting post-menopausal hormone therapy cause programmed cell death (apoptosis) in breast cancer cells deprived of estrogen long term (17-26). Post-menopausal patients treated with estradiol, ethynyl estradiol or DES experience tumor regressions, likely due to apoptosis (27;28). In the WHI study, the average age of patients was 63, twelve years after the average age of onset of menopause in non-smokers. It should be noted that smokers undergo menopause at age 49 on average and non-smokers, age 51. Based on pre-clinical data, estrogens would be expected to induce apoptosis in small occult tumors. This would decrease the size or completely exterminate occult tumors in the reservoir and result in a reduced incidence of diagnosis. The assumptions used in the modeling were that 30% of the cells in ER+ tumors would undergo apoptosis and 77% of tumors were ER+ in the WHI E alone arm.

Assumptions to model effect of tamoxifen: A 50% reduction in the size of advanced ER+ tumors occurs in 30% of patients with ER+ breast cancer and a <50% reduction or stabilization in another 30% 68. If this effect occurred similarly in the reservoir of occult tumors, one would expect to see a reduction of breast cancer incidence over time. We modeled this effect to determine predicted rates of breast cancer reduction in comparison with observed data in the NSABP-P1 prevention trial (29;30). The women eligible for the NSAPB-P1 trial had an increased risk of breast cancer and presumably a higher prevalence of occult tumors. Over the 7.2 years of the study, 6.3% of women in the placebo arm developed breast cancer. Extrapolating from our iterative figures on prevalence and assuming doubling times of 200 days, this would correspond to a prevalence

of 14% of occult breast cancer in this high-risk population. Accordingly, to calculate predicted rates, we assumed a 14% prevalence of occult tumors and a 200-day doubling time.

Supplementary discussion:

Estimates of the prevalence of occult tumors as reported by autopsy and contralateral breast cancer studies are subject to critical questioning. Autopsy data were obtained decades before the wide application of mammography or MRI screening and early detection of cancer (31). Based on this confounding factor, the current prevalence of undiagnosed cancer may be lower than previously reported since more sensitive imaging techniques now are capable of detecting smaller lesions. However, mammography and MRI are only sufficiently sensitive to detect tumors which have undergone one fewer tumor doubling than tumors clinically detected. Data from five trials (32-35) reported a mean tumor diameter of 1.6 cm in patients undergoing mammographic screening and 2.1 cm in those with clinically detected lesions. This 0.5 cm difference would represent less than one tumor doubling. These data suggest that autopsy data would not be influenced substantially by mammographic screening.

Another confounding factor with the autopsy studies is that the prevalence reported is positively related to the intensity of ascertainment and the number of histologic sections examined. On this basis, averaging of all studies (as in the current analysis) would likely underestimate the actual prevalence since the majority of studies did not examine serial sections of the entire breast. Notably, the autopsy study reporting the highest prevalence, 15.6%, intensively examined serial sections. The issue of intensive sampling also confounds interpretation of the actual prevalence of occult tumors in contralateral breast tissue. The estimate of 12.4% contralateral breast prevalence, reported in this study, might also be underestimated on this basis.

If the autopsy and contralateral breast data were to have underestimated prevalence, why then did 7% prevalence coupled with a 200-day EDT appear to fit well with observed incidence data? The answer could be related to the fact that certain tumors are dormant and grow slowly if at all. This concept has been raised in recent discussions of breast tumor “over-diagnosis” (36;37). The “over-diagnosis” concept is based on the difference between the number of women diagnosed with breast cancer during mammographic screening and

those diagnosed clinically. By follow-up over time, one can demonstrate a persistent difference between the incidence in the screened group and that in the clinically detected group. The logical conclusion from this concept is that some screen-detected cancers do not grow or might even regress. Authors espousing this thesis have estimated that the rate of over-diagnosis may be as high as 40% (36;38).

On initial analysis, our model does not appear to support the "over-diagnosis" concept as the number of expected tumors, based on a 7% average prevalence, parallels that observed. However, if we did underestimate the prevalence of undiagnosed tumors in the reservoir, the difference between our estimates and actual prevalence could represent over-diagnosed tumors. For example, if the actual prevalence of tumors in the reservoir was 10% (rather than 7%) and the doubling time was 200 days, we would expect 6.2% of the population to have diagnosed tumors at 10 years. The observed percent in the SEER data was 4.2 %, a 33% difference. From these data, it is possible that the other 33% have a very slow doubling time or cease growing at some point and would be considered the "over-diagnosed" tumors. These considerations could reconcile the "over-diagnosis" concept with our modeling studies, but experimental confirmation of this possibility is required in the future.

Our data on EDTs can also be questioned. Only the tumors that have grown sufficiently to reach the detection threshold are included in the effective doubling time analysis. If there were a population of tumors in the reservoir with very long EDTs, these might never reach the detection threshold and therefore not contribute to the doubling time estimates. Under these circumstances we would be underestimating the median EDT. On the other hand, with very rapidly growing tumors, measureable lesions would not be seen on antecedent mammograms and EDTs would be overestimated. These two factors, influencing doubling times in opposite directions, might cancel each other out and result in an accurate estimate of doubling times. No direct data are available to test these possibilities.

It should be noted from our iterative analysis that the detection threshold, while important, influences the time required for detection only marginally. For example, if the detection threshold were set at 1.6 cm rather than 1.1 cm, the times to detection would then increase by only 50, 100, 150, 200 or 250 days (i.e. one doubling time) for tumors ranging from doubling times of 50 to 250 days. This concept has important implications

regarding breast cancer screening. It is estimated that tumors having undergone 29 doublings (i.e. 0.88 cm in diameter) are associated with 14% nodal metastasis, whereas those having undergone 30 doublings (i.e. 1.16 cm diameter) are associated with 18.7% nodal metastases (39). Mammographic screening can only detect tumors which have undergone one less doubling time than required for clinical detection. As mortality increases with the number of involved nodes, detection earlier would only reduce the number of women with negative nodes by 4.7% and mortality would be reduced only marginally. A recent analysis reviewed multiple studies and found only a small reduction in advanced cancers with mammography (38). These concepts, taken together, have led some investigators to suggest that mammography screening may have less impact on survival than is generally believed (40;41), but this issue is highly controversial.

Prior studies have also modeled the growth of occult breast cancer, but with the goal of determining the optimal frequency of breast cancer screening (2;42-53). These models support the concept that a population of small, occult tumors are slow growing (42;51) or that some even regress (51). The incidence of breast cancer in 50–69 year old women approximates 0.45% per year whereas the reservoir of occult, undiagnosed tumors is 7%. Accordingly, the ratio of undiagnosed to diagnosed tumors from our calculations would be 16. While these various models provided evidence of the biologic properties of occult tumors in the reservoir, our study is the first to apply these concepts to data from the WHI and the tamoxifen, raloxifene and exemestane prevention studies.

Several publications have addressed whether breast cancer incidence declined following publication of the WHI studies and the resultant sharp drop in use of MHT among women. The weight of evidence supports a decline, but controversy still exists (54). Critical reviews suggest that the decrease in breast cancer incidence began several years before the publication of the WHI and that a decrease in incidence might reflect a reduction in adherence to mammography screening. It has been pointed out that introduction of mammographic screening initially increases the incidence of breast cancer, but this increase is usually followed by a decline. In some countries, the decline in breast cancer during the years of 2002 to 2006 might reflect this decline after initial mammographic screening (54). Other factors might also be involved such as an increase in exercise, reduction in alcohol consumption, use of tamoxifen for prevention, or alteration in adherence to mammographic

screening. Not all countries reported a drop in breast cancer incidence from 2002–2006, after the WHI report. For example, declines were not reported in studies from the UK (55;56), Norway (57;58) or the Netherlands (59).

One of the issues suggested as a factor confounding the interpretation of the fall in breast cancer incidence after the publication of the WHI data has now been addressed. The BCSC data ruled out the possibility that the decline represented a decrease in mammographic screening (16). The data in this study are exclusively from mammographic screening and a decline of 9% was observed. The Scientific Statement of the Endocrine Society has concluded that the totality of data suggest the likelihood that the incidence has decreased in most countries (31). This conclusion was based on the number of publications reporting a decline. Studies in the USA and in other countries reported declines in breast cancer incidence in women over age 50 after the first WHI report. Examples include the studies of Ravdin et al. (7%) (60), Clarke et al. (61), Marshal et al. (26%)(62), Robbins et al. (8.8-22.6%) (63), Hausauer 13.2% (64), Glass et al. (4.9%) (65), Keegan et al. (66) (3.6%) and Ereman et al. (67) (33.4%). Declines have also been reported in Australia (8.8%) (68), France (2.1–4.3%) (69), and Germany (11%) (70). The average of these studies suggests a mean reduction of 8.9%, very similar to the predictions from our OTG model.

We concluded that the majority of effects of MHT are on the growth rate of pre-existing occult tumors. This conclusion was based on the small fraction of de novo tumors, the known effect of hormone therapy on proliferation, and the concordance of our OTG model (which omits de novo tumors) with observed data. However, it might be argued that all of the MHT effects represented initiation of de novo tumors. If this were the case, EDTs of de novo tumors would have to have been less than 50 days. In the 10.7-year follow-up of the WHI, the doubling times in the E+P arm best matched 150 days. A subgroup with a marked enhanced growth rate was not apparent. Only 13 excess deaths (0.15% of the 8506 in MHT arm) were observed in the women randomized to the E+P arm at the 11-year time period (71). While it is not possible to rule out the presence of a subgroup with very fast growth rates, the overall analysis suggests that this is not the case.

It should be noted that the fraction of de novo tumors in the total tumor population was higher in the CSTG model than the OTG model. This resulted from the fact that the total incidence was lower in the CSTG

model. We believe that that the OTG data are more relevant since these data only relate to tumors detected in patients still alive. When interpreting the NSABP-P1 and WHI studies, only a very small fraction of participants (1.8%) died during the study. Accordingly, the OTG data are deemed more pertinent.

Our study focused on the effects of tamoxifen as a prevention strategy. Similar studies indicate that raloxifene and exemestane also reduce the incidence of breast cancer by effects on occult, undiagnosed cancer and not reduction of de novo tumors (72-74). It should be noted that the 65% reduction of primary breast cancer with the aromatase inhibitor exemestane occurred after only 3.9 years (72). At this time period, approximately 5% of de novo tumors would have had time to grow to a size exceeding the detection threshold

The fundamental weakness of any modeling study is the use of assumptions; the larger the number of assumptions, the less reliable are the conclusions. The major assumptions utilized in developing our OTG model involved the type of growth kinetics (i.e. log-linear vs. Gompertzian etc.) and the distribution of tumors having undergone each number of tumor doublings (i.e. volume or doubling time distributions.). Our assumptions are plausible but not experimentally verifiable. It should be emphasized, however, that our computer simulation (CSTG) model involves three separate assumptions and yet yields similar data. In this way, the two models reinforce of the validity of each other. Nonetheless, it must be recognized that our conclusions are based on a model and models have intrinsic limitations.

Pre-clinical data suggest that only breast tumors deprived of estrogen long-term adapt such that estrogen causes apoptosis (23). Analysis of the WHI estrogen-alone study supports this hypothesis. Only women never previously receiving hormone therapy (i.e. long term estrogen-deprived) experienced a reduction in breast cancer incidence. Women who had received estrogen prior to the WHI study and then were randomized to receive this therapy after a wash-out period did not have a reduction of breast cancer risk (RR 1.02; CI 0.70-1.50). Those given estrogen shortly after menopause also did not have a reduction in breast cancer incidence (RR 1.12; CI0.39-3.21) (31). It is of interest that only the women in the WHI E+P study who had previously received MHT experienced an increase in breast cancer incidence. It is possible, but without supportive data, that estrogen could have induced apoptosis in the “hormone naïve” group, protecting them from an enhanced detection rate.

An assumption in this manuscript is that occult tumors respond to tamoxifen or to hormonal therapy similarly to tumors which are clinically detectable. Xenograft data in nude mice would appear to support this assumption. Tumors present before they are palpable appear to respond in a manner similar to that of large tumors. Nonetheless, there is no way at present to test this assumption directly.

The conclusions in this manuscript do not rule out a direct carcinogenic effect of estrogens to cause de novo breast cancer. Epidemiologic and experimental evidence suggest that high estrogen exposure increases the lifetime risk of breast cancer and that this effect is likely explained at least partially by initiation of mutations. However, this process evolves over a period of decades and would not be evident over a period of 5 to 7 years of exposure, based on estimated tumor doubling times (Mechanisms Relating Estrogens to Breast Cancer Yager, JD, Santen RJ, Translational Endocrinology and Metabolism, in press, 2012).

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