COMMENTARY

Relative Versus Attributable Risk of Breast Cancer from Estrogen Replacement Therapy

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Estrogen deficiency causes vasomotor instability and urogenital atrophy in a large fraction of menopausal women. Short term use of estrogen replacement therapy (ERT) can effectively relieve symptoms related to these conditions (1, 2). ERT may also relieve neurocognitive symptoms of mood changes, irritability, and depression resulting from acute estrogen deprivation (3). When given long term, estrogens prevent the development of osteopenia, osteoporosis, and bony fractures (4, 5) and may be effective for primary prevention and reduction of mortality from cardiovascular disease (6, 7). Observational studies suggest that the incidence of colon cancer and Alzheimer’s disease may be reduced by hormone replacement therapy (8–12). The Nurses Health Study, a large prospective cohort study, reported that all causes of mortality among nurses who use postmenopausal hormones are lower than those among nonusers (13).

The overall benefits of estrogen therapy to relieve symptoms and to prevent osteoporosis and cardiovascular disease have led to recommendations that the majority of women should consider taking ERT. However, surveys in the United States indicate that an average of only 20% of postmenopausal women take ERT (14–16). Even among nurses, only 50% report ever using ERT, and those choosing to take ERT generally discontinue it after a period of 1–3 yr (6).

With substantial evidence supporting the use of ERT, why do most women choose not to start or to discontinue estrogen replacement? One reason is the concern about breast and uterine cancer. Although these risks may be real, the lay public and physicians generally do not fully understand the implications of studies reporting the risks of estrogen causing cancer. One reason for this misunderstanding is the widespread use of relative risk (RR) statistics that are often interpreted as attributable risk. This treatise will clarify the meaning of relative and attributable risk, review data regarding the effects of ERT on these two parameters, and provide a practical approach to aid women in the decision making process.

Concepts underlying calculation of RR

The incremental risks of breast and endometrial cancer attributable to estrogen are small, and the absolute number of women adversely affected is minimal. For this reason, epidemiological methods are required to detect small differences in incidence rates of these diseases among groups of ERT users. These techniques often use RR as the summary measure of disease frequency and involve both case-control and cohort methodologies. The initial studies of ERT and breast cancer risk used case-control methodology (17, 18). In a case-control study, a group of women with breast cancer and a comparable group of women without breast cancer are compared with respect to various characteristics, such as ERT use. In a matched case-control study, one or more controls may be matched to each patient to reduce potential confounding factors affecting the control group. The next step is to determine how many of the breast cancer patients and controls are currently receiving (or ever used) ERT. For example, it may be found that 100 of the breast cancer cases of a total of 1000 are using ERT (10%) at time of diagnosis and 200 of the 4000 controls are using ERT (5%). In case-control studies, the RR is estimated by the odds ratio, the ratio of the odds of exposure among the cases to that among controls. This ratio is expressed by dividing the percentage in the case group (10%) using ERT by the percentage in the control group (5%) using ERT. In this instance the RR is estimated as 2.0. Ninety-five percent confidence intervals (CI) around the RR estimates are calculated and statistical significance affirmed if the CI does not include 1.0 (e.g. 2.0 with CI of 1.01–3.50). This methodology actually examines the differential prevalence of taking estrogen in the 2 groups rather than the relative increase in disease incidence.

A cohort study involves observation over time (19). A group of individuals without the disease of interest is identified, classified by ERT use, and monitored for subsequent development of breast cancer. The incidence of breast cancer in the groups of women taking or not taking estrogen is compared. As an example, if 10 of 1000 women taking estrogen over a 10-yr period develop breast cancer (1%) vs. 20 of 4000 women not taking this hormone (0.5%), the RR is estimated as 2.0 (1% divided by 0.5%). Confidence limits are again determined, and results are considered significant if limits do not include 1.0.
Confusion of relative with attributable risk

Both case-control and cohort studies provide powerful means to estimate RR, but give no information about how many women are affected. For clinical decision-making, it is important to know the absolute risk attributable to estrogens and the number of individuals that may be adversely affected. An excellent example of the importance of distinguishing RR from absolute number affected is provided by the example of diethylstilbestrol use and adenocarcinoma of the vagina (20–22). The RR of this cancer was found to exceed 32 in daughters of diethylstilbestrol users, and this finding was highly statistically significant (P < 0.001). However, the absolute number of daughters developing vaginal adenocarcinoma approximated only 1 in 1000. This study demonstrated the statistical power of the case-control method in demonstrating association even when the number of patients affected represented only 0.1% of users.

Although an important epidemiologic statistic, the term RR causes confusion for patients and is not interpreted clearly by members of the mass communications media. Commonly, these groups interpret RR in absolute terms. Media sources, for example, report that the increased risk of breast cancer from ERT is 30%. This is conveyed in such a way that a woman interprets this as a one-third chance that she will get breast cancer if she takes ERT. In actuality, the 30% figure represents relative and not attributable risk.

Definitions of relative and attributable risk

RR refers to the likelihood of disease in exposed patients relative to those who are not exposed (23). The term RR is independent of and does not require knowledge of the overall incidence of disease in the population. Attributable risk provides information about the excess risk of disease in patients taking ERT compared with that in patients not taking ERT. In cohort studies, attributable risk is calculated as the difference in incidence rates. In case-control studies, incidence rates are usually not available. Most studies summarizing ERT report only relative, not attributable, risk. It is possible, however, to make inferences about attributable risk by using other sources of information. The incidence of breast cancer in large populations and by age groups is summarized in the Surveillance and End Results (SEER) reported by the NCI (24). Using the SEER estimate of the total incidence of breast cancer and an estimate of the proportion of women using ERT, one can estimate the incidence. Attributable risk can be estimated as the difference between user and nonuser incidence rates (see tables for formulas).

Problems with RR data

In the absence of randomized, placebo-controlled, prospective studies, RR data are required to calculate attributable risk. Several problems have been inherent in studies that determine RR. To provide a rationale for the arbitrary choice of RR figures to be used in subsequent calculations, we will first review known problems and then chose a method for estimating attributable risk.

Although over 50 studies report the RR of breast cancer from ERT, results are widely conflicting (17, 25). Several factors confounding interpretation of these studies have been identified. One problem is the use of hospital-based controls in case-control studies. Hospitalized women do not represent an otherwise healthy group and may not be comparable to the cases with breast cancer. A second problem is that information regarding the duration of use of estrogen was not available in early case-control studies; consequently, the generic terms “ever use” and “never use” were used as descriptors. Recent studies suggest that the duration of estrogen usage is related to the rate of development of breast cancer. Probably as a result of these two problems, most earlier studies (before 1980) reported no increased risk of breast cancer with “ever use” of ERT (17). More recent studies (after 1985) using community-based controls and considering the duration of use have found statistically significant increases in RR in the range of 1.3–1.5. (17). A third problem is the lapse of time between the onset of menopause and the initiation of ERT use. Recent studies identify this as an important factor that can confound interpretation of data (25). As a fourth problem, obesity influences the effect of ERT on breast cancer risk. The aromatase enzyme increases proportionately with obesity and results in increasing extraglandular estrogen production (26). Consequently, thin women produce smaller amounts of endogenous estrogen than obese women and experience a greater risk of breast cancer from ERT (25).

The recently published meta-analysis of 51 studies involving 52,705 women with breast cancer and 108,411 without provides a rigorous analysis of the RR of breast cancer from ERT (25). Both case-control and cohort studies were included in this analysis. Duration of use, lapse of time since menopause, nature of the control population, and obesity were all considered in the analysis. Overall, there was a significant increase in the RR of breast cancer in ever users compared with that in never users of ERT (RR = 1.14; P < 0.001). The RR was 1.35 for women who used ERT for 5 yr or more. Analysis of the duration of use showed a linear increase in the RR of breast cancer of 2.3%/yr for current users of ERT.

Prospective cohort studies are preferable to those involving retrospective case-control methodology. Cohort studies involve concurrent follow-up of groups of women taking or not taking ERT. Although prospective, these studies do not involve randomization of women into no therapy and ERT groups. Consequently, biases may be introduced by possible differences in underlying breast cancer risk in those choosing to take estrogens. For example, women with a greater degree of obesity or later menopause are less likely to take ERT. These factors could result in an underestimation of underlying breast cancer risk attributable to ERT. Nonetheless, cohort studies provide the ability to characterize the underlying characteristics of both groups, to mathematically correct for these differences, and to determine rates of development with longer duration of ERT.

The Nurses Health Study provides the largest single cohort study of ERT and breast cancer RR; 78,000 nurses have been followed over a period of 15 yr with over 700,000 patient yr of follow-up (19). In this study, RR is defined as “the incidence of breast cancer among women who had taken hormones after menopause divided by the incidence among women who had never used such therapy.” This study reported significant in-
creases in RR of breast cancer from ERT. Among current users of conjugated estrogen, the RR was 1.32 (95% CI, 1.14–1.54). RR increased in those using ERT for a period longer than 5 years. Older women had greater RR for use of estrogen than did younger women. The use of ERT for more than 5 years starting at age 50–54 yr resulted in a RR of 1.46; at age 55–59 yr, it was 1.54, and at age 60–64 yr, it was 1.71.

**Calculations of attributable risk of breast cancer from use of ERT**

Based upon the above analysis of RR data, we concluded that duration of estrogen use may be the most important parameter. Conservatively, we chose RR to represent an increase in 2.3% for each year of estrogen use, as substantiated by the most recent and largest meta-analysis (25). These RR data were then used to calculate risk of breast cancer attributable to ERT. An example is cited to illustrate the methods used. Calculations involve multiplication of RR by incidence rates in the population. Age-related incidence rates are available from the large population-based SEER database (24). SEER data indicate that 2.52 of 100 women 50 yr of age develop breast cancer over a 10-yr period. Multiplication of a RR of 1.23 (2.3%/yr times 10 yr) times the absolute incidence of 2.52 yields an absolute risk of 3.10 women/100 who would develop breast cancer if taking ERT. The difference between 2.52 and 3.10 would be the increased risk attributable to estrogens or 0.58 in 100 women over 10 yr. Stated simply, 0.58 in 100 women would be expected to get a breast cancer that she would not otherwise get if she took estrogens for 10 yr. Another meaningful statistic is the attributable increase in death from breast cancer in an estrogen user. Only 1 in 5 women diagnosed with breast cancer die of this disease. Assuming 0.58 additional cases of breast cancers/100 women over 10 yr, only 0.12 in 100 (0.6 divided by 5) will die from a cancer occurring because of use of ERT (27).

**Risks and benefits of ERT**

Clinical decision-making involves a trade off between the risks and benefits of the treatment proposed. The relevant comparisons relate to the frequency of events, which is best assessed by attributable risk and benefit data (28). To aid the clinician in decision-making, we have calculated attributable risks and benefits relating to breast cancer and cardiovascular events attributable to ERT.

**Attributable risk and benefit calculations**

**Age 50–59 yr.** Table 1 contains the data presented above regarding 50-yr-old women and the risk of breast cancer attributable to ERT. Additional data from the Nurses’ Health Study indicate an absolute benefit of preventing a new cardiovascular event in 0.37 of 100 women taking ERT for 10 yr and prevention of cardiovascular death in 0.14, assuming a RR of 0.63 for death from cardiovascular disease as determined by Grady et al. (29).

**Age 60–69 yr.** Similar calculations for women starting estrogens at age 60 yr and taking them for 10 yr indicate an attributable risk of breast cancer from ERT of 0.80 and a risk of death of 0.19. Attributable cardiovascular benefit would be 0.66, and reduction of death would be 0.24.

**Lifetime risks and benefits.** Women starting ERT at age 50 yr and continuing long term would expect a lifetime estrogen attributable risk of breast cancer of 2.8/100 women and deaths from breast cancer of 0.67/100 women. With respect to cardiovascular disease, 11.9/100 women would benefit from prevention of a new event, and 4.4 of these would not die from cardiovascular disease (29).

**Short term use of 2 yr or less.** Nearly 100% of women benefit from relief of symptoms of vasomotor instability and urogenital atrophy in response to estrogen. The breast cancer risks from ERT taken for 2 yr or less are minimal, 0.02/100 women. The benefits from prevention of cardiovascular risk are somewhat higher at 0.04/100 women because the benefits are experienced very quickly after beginning estrogen therapy.

**Other risks and benefits.** With concomitant use of progestins, women should not expect a substantial increased risk of developing endometrial cancer (30). RR’s of venous thrombosis and pulmonary emboli increase by 2- to 3-fold, and absolute risks approximate 0.47/100 women over a 2-yr period based upon data in women taking placebo in the National Surgical Adjuvant Breast and Bowel Project breast cancer prevention trial (31, 32). Benefits in preventing bone fractures from osteoporosis from lifetime use approximate 4.8/100 women at risk for hip fracture (29).

**Months of prolongation of life and ERT**

Absolute risk calculations, stratified for underlying risk of breast cancer and cardiovascular disease, can be used to estimate months of prolongation of life. For women at lowest risk of breast cancer and highest risk of cardiovascular disease, ERT prolongs life by approximately 40 months. Only in those with a high risk of breast cancer and a low risk of heart disease is ERT use associated with a reduction in life by approximately 3–5 months (Fig. 1) (33).

**Presentation of data to patients**

Our approach is to inform patients that recommendations regarding ERT are based upon a worst case analysis.

**TABLE 1. Risk or Benefit from ERT**

<table>
<thead>
<tr>
<th>Age ERT use initiated</th>
<th>Duration of use</th>
<th>Attributable risk of breast cancer per 100 women</th>
<th>Attributable risk of death from breast cancer per 100 women</th>
<th>Cardiovascular event avoided per 100 women</th>
<th>Death from cardiovascular event avoided per 100 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 yr old</td>
<td>&lt;2 yr</td>
<td>0.02</td>
<td>0.004</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>50 yr old</td>
<td>10 yr</td>
<td>0.58</td>
<td>0.12</td>
<td>0.37</td>
<td>0.14</td>
</tr>
<tr>
<td>50 yr old</td>
<td>Lifetime</td>
<td>2.8</td>
<td>0.67</td>
<td>11.9</td>
<td>4.40</td>
</tr>
<tr>
<td>60 yr old</td>
<td>10 yr</td>
<td>0.80</td>
<td>0.19</td>
<td>0.66</td>
<td>0.24</td>
</tr>
</tbody>
</table>
We assume the worst case that current data regarding estrogen and breast cancer are correct. We convey the concept that until the Women’s Health Initiative Study is completed in 2007, no randomized, controlled, prospective data will be available to correctly estimate breast cancer risk and cardiovascular benefit attributable to estrogen. As the relationship between breast cancer and ERT use is highly plausible based upon basic, animal, and human data, it is prudent to accept the worst case that ERT does cause breast cancer. We explain that even with this worst case analysis, the overall benefits of estrogen generally outweigh the risks. To provide concise explanations to the patient, our approach considers two patient groups: one considering short term use to control symptoms, and the other considering long term therapy to prevent cardiovascular disease or osteoporosis.

Breast cancer attributable to short term ERT occurs in approximately 2 in 10,000 women starting therapy at age 50 yr and continuing for 2 yr or less. Nearly 100% of these patients are benefited by relief of symptoms. Clearly the benefits outweigh the risks under these circumstances. Long term use to prevent osteoporosis or heart disease involves continued therapy for at least 10 yr. For a 50-yr-old woman facing a choice of ERT for this reason, the chance of an estrogen-attributable breast cancer over this 10-yr period approximates 0.58 in 100 women. This figure in absolute attributable risk is much less frightening to a patient than the 30% increased RR conveyed by newspaper articles and other media sources. The risk can be stated in yet another way, which appears to be even less alarming: 96.8% of 50-yr-old women taking ERT for a 10-yr period will not get breast cancer. This can be compared to the group not taking estrogen, in whom 97.5% will not develop breast cancer. This risk is counterbalanced by a 0.37 in 100 chance of having a new cardiovascular event prevented. For lifetime use of ERT to prevent heart disease or osteoporosis, the chances of experiencing an estrogen-induced breast cancer are 2.8 in 100. On the other hand, 11.9/100 women will have prevention of a new cardiovascular event.

Women are informed that risks and benefits differ depending upon the age at which therapy is started. A 60-yr-old woman has a 0.80 in 100 chance of experiencing an estrogen-induced breast cancer over a 10-yr period vs. a 0.58 in 100 chance in a 50-yr-old woman. For both groups, this is less than a 1 in 100 chance of being harmed and is counterbalanced by a 0.37–0.66 in 100 chance of not having a new cardiovascular event.

The worst case analysis concept serves to reassure patients that a physician is cautious about the published risks of ERT and breast cancer. However, even when one accepts the worst case, the benefits of ERT nearly always outweigh the risks for short term relief of symptoms. For long term prevention of osteoporosis and cardiovascular disease, the benefits generally outweigh the risks, particularly in those with risk factors for heart disease or preexisting osteopenia or osteoporosis.

Caveats and cautionary notes

Patients frequently ask whether estrogen use adds to or acts synergistically with other factors to increase the risk of breast cancer beyond that imparted by estrogen use. Available data have demonstrated neither an additive nor a synergistic effect between estrogen use and family history of breast cancer, presence of atypical ductal hyperplasia, or other proliferative breast lesions (13, 25). Surprisingly, one study suggested that estrogen
use decreased the RR of breast cancer associated with atypical ductal hyperplasia from a RR of 4.5 to 3.0 (34). Both the Nurses’ Health Study and the recent large meta-analysis detected no additive or synergistic interactions between estrogen use and family history of breast cancer. As these studies may not have had sufficient power to detect such interactions, a conservative approach is to assume additive linear interactions between any risk factor and estrogen use. To calculate the magnitude of this effect, one can multiply relative by attributable risk. For example, a 50-yr-old woman taking estrogens for 10 yr has an attributable risk of breast cancer of 0.58 in 100. With atypical ductal hyperplasia, her RR without estrogen use would be 4.5 (34), and her attributable risk would be 4.5 times 0.58, or 2.61/100. According to the NCI computer risk model (Breast Cancer Risk Assessment, an interactive tool to measure a woman’s isk of invasive breast cancer, NCI, 1998), a 50-yr-old woman with an average age of menarche, menopause, and child bearing but with one first degree relative with breast cancer has a RR of 2.9. Multiplied by 0.58, this would result in an attributable risk of 1.68/100 women taking estrogens for 10 yr. Similar calculations can be made for typical ductal hyperplasia or breast papillomatosis, which have RR of approximately 2. The attributable risk would then approximate 1.16/100 women over a 10-yr period. It should be recognized that these calculations are based only upon assumptions and are not backed by supporting data.

Various ranges of attributable risk of breast cancer can be calculated depending upon which database is chosen (see Appendix, Table A). For example, the Nurses’ Health Study reported a RR of breast cancer of 1.46 for a 50-yr-old using ERT for greater than 5 yr. Using this factor, a 50-yr-old taking estrogen for 10 yr would have an estrogen-attributable risk of 1.06 vs. 0.58 in our calculations. The Nurses’ Health Study RR for a 60-yr-old was 1.71. This factor would translate into an attributable risk of 2.15 vs. 0.80 in our calculations.

The attributable risk also depends upon the data used to calculate incidence of breast cancer among the general population. The SEER database provides the best assessment of this incidence. However, an unknown fraction of these women had taken estrogens at the time of or shortly before the diagnosis of breast cancer. This fact would result in an overestimation of breast cancer incidence in women not taking estrogen. To assess the impact of differing prevalence of use data, we calculated attributable risk using average estimates of use of 21% (14–16) or an extreme of 40% (Appendix, Tables B and C). With these figures, the calculated risk of breast cancer attributable to estrogen decreased as the prevalence of use increased. For example, the attributable risk from the Nurses’ Health Study in a 50-yr-old would decrease from 0.106/100 women/yr (21% prevalence of estrogen use) to 0.098/100 women/yr (40% prevalence of use). It can be seen from these various calculations that attributable risk is influenced by the databases used, but not to a clinically meaningful degree.

Calculations of lifetime risk also involve a number of assumptions. If the linear 2.3%/yr increase in RR assumption is used, a 50-yr-old woman taking estrogen for 40 yr would have a RR of breast cancer of 1.92. With an average rate of breast cancer incidence of 335/100,000 women/yr (i.e., 252/100,000/yr at age 50 yr and 419/yr/100,000 at age 85 + yr, the increased risk attributable to estrogen would be 12/100 women. This much exceeds the calculations of Grady et al. (29), which estimate an attributable lifetime risk of 2.8/100 women. However, the vast majority of women do not take estrogen for more than 20 yr. The attributable risk for a woman using estrogen for 20 yr would be 2.76/100 women.

It should be understood that the methodological data used in this analysis are exclusively observational. Derivative data on disease incidence are from populations different from those in the observational studies. Consequently, the estimates of absolute risk must be considered in this perspective.

Several factors qualify interpretation of data regarding the cardiovascular benefits of ERT. In a recent published discussion of this issue, Dr. Elizabeth Barrett-Conner (35) pointed out many confounding biases regarding studies of ERT and cardiovascular risk that could make the benefits of estrogen appear to be better than they really are. These included selection biases relating to health, wealth, education regarding prevention, compliance, and preexisting disease. These critiques are difficult to reconcile with the more than 30 studies reporting a positive effect of estrogen on primary and secondary prevention of heart disease. However, Barrett-Conner’s cautions were supported by the recently reported HERs study (36), a large placebo-controlled, randomized trial of hormone replacement therapy (Premarin plus Provera-or Prem-pro) for the secondary prevention of new cardiovascular events. This study demonstrated an increase in new cardiovascular events during the first year of hormone replacement with a reduction during yr 2–5. Overall, there was no benefit at the 5 yr interval. This study strongly contradicts data available from observational studies (37).

On the other hand, the researchers suggest an initial prothrombotic effect of estrogen that would be particularly harmful in a group with preexisting vascular disease. The apparent reduction of cardiovascular events during yr 2–5 might represent cardioprotective effects from lipid-lowering and direct vascular effects that could be delayed.

Longer term studies are needed before issues raised by the HERs trial can be clarified. While awaiting such data, it is probably prudent to conclude that the effects of secondary prevention with estrogens may not be as substantial as previously reported or may not occur at all. Primary prevention of cardiovascular events with estrogen would appear to be more likely and less affected by potential prothrombotic actions. For this reason, the risk benefit analysis in this manuscript assumes that reported observational studies regarding cardiovascular benefits of estrogen for primary prevention are correct.

The frequency of dying from breast cancer is calculated from 1996 statistics that estimated 184,300 new cases of breast cancer in the United States in 1996 but only 44,300 deaths, a factor of 1 in 5 (27). Similar proportions of patients dying from breast cancer can be calculated from SEER data (i.e., 24% of 50-yr-old women die of their breast cancer) (24). Our analysis assumes that the death rate from breast cancer is similar in women in whom breast cancer results from the use of ERT. The assumption is probably too conservative, as several studies have now shown that the death rate from breast cancer is at least 10% lower in women taking ERT at the time of diagnosis (38–40). This conclusion, if correct, would further increase the ratio of benefit to risk in women receiving ERT, as excess risk attributable to ERT is probably overestimated to some extent.
Basic biological and clinical studies suggest that progestins may be mitogenic to normal breast tissue and could theoretically increase the risk of breast cancer (41). One widely quoted study suggested that this may be the case, but the number of women taking both estrogen and progestin were small (42). Other existing data do not support an increased risk from combined estrogen and progestrone. Based on these data, our analysis combines data from studies using estrogen alone and those from studies using estrogen plus progestrone.

References

### Appendix

#### TABLE A. Effect of database used on calculations

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Duration of ERT use</th>
<th>Risk</th>
<th>Excess breast cancer/100 women</th>
<th>Excess death from breast cancer/100 women</th>
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<tbody>
<tr>
<td>50</td>
<td>&lt;2 yr</td>
<td>Linear&lt;sup&gt;a&lt;/sup&gt; increase, 2.3%/yr</td>
<td>0.02/2 yr</td>
<td>0.004/2 yr</td>
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<td>50</td>
<td>10 yr</td>
<td>Linear increase, 2.3%/yr</td>
<td>0.58/10 yr</td>
<td>0.12/10 yr</td>
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<td>50</td>
<td>20 yr</td>
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<td>2.76/20 yr</td>
<td>0.54/20 yr</td>
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<tr>
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<td>40 yr</td>
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<td>RR 1.46&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>10 yr</td>
<td>Linear increase, 2.3%/yr</td>
<td>0.80/10 yr</td>
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<td>RR 1.71&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.15/10 yr</td>
<td>0.44/10 yr</td>
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<sup>a</sup>, (24); <sup>b</sup>, (19).

#### TABLE B. Effect of prevalence of ERT use on calculations

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<tr>
<th>P&lt;sub&gt;e&lt;/sub&gt;</th>
<th>Age (yr)</th>
<th>Use (yr)</th>
<th>I&lt;sub&gt;T&lt;/sub&gt;</th>
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<td>0.21</td>
<td>50</td>
<td>≥5</td>
<td>251.9/100,000</td>
<td>1.46</td>
<td>0.106/100/yr</td>
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<tr>
<td></td>
<td>60</td>
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<td>347.4/100,000</td>
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<tr>
<td>0.40</td>
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<td>≥5</td>
<td>251.9/100,000</td>
<td>1.46</td>
<td>0.098/100/yr</td>
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<tr>
<td></td>
<td>60</td>
<td>≥5</td>
<td>347.4/100,000</td>
<td>1.71</td>
<td>0.192/100/yr</td>
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<sup>a</sup>, (24); <sup>b</sup>, (19). P<sub>e</sub>, Proportion in total population who use ERT; RR, relative risk.

#### TABLE C. Formulas used in calculations

<table>
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<th>Cohort</th>
<th>Case control</th>
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<td>Relative risk (RR)</td>
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<td>≡ OR</td>
</tr>
<tr>
<td>Attributable risk (AR)</td>
<td>I&lt;sub&gt;e&lt;/sub&gt; - I&lt;sub&gt;n&lt;/sub&gt;</td>
<td>I&lt;sub&gt;e&lt;/sub&gt; - I&lt;sub&gt;c&lt;/sub&gt;, where I&lt;sub&gt;e&lt;/sub&gt; = I&lt;sub&gt;T&lt;/sub&gt; / (RR(P&lt;sub&gt;e&lt;/sub&gt; + P&lt;sub&gt;c&lt;/sub&gt;), I&lt;sub&gt;c&lt;/sub&gt; = (RR)(I&lt;sub&gt;n&lt;/sub&gt;)</td>
</tr>
</tbody>
</table>

I<sub>e</sub>, Incidence of disease in ERT group; I<sub>n</sub>, incidence of disease in non ERT group; OR, odds ratio; P<sub>e</sub>, proportion in total population who use ERT; P<sub>n</sub> = 1-P<sub>e</sub>; I<sub>T</sub>, overall incidence rate of disease in the population, I<sub>T</sub> = I<sub>e</sub>P<sub>e</sub> + I<sub>n</sub>P<sub>n</sub>.