Hormones and breast cancer

ESHRE Capri Workshop Group*

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The incidence of breast cancer in women varies with age, mammary gland mass and exposure to endogenous and exogenous hormones. Age is the single most important factor and if, as projected, 32% of women will be aged >60 years by 2050, world breast cancer incidence will exceed the current $10^6$ per year. Hormonal influences that affect growth of the mammary gland increase the risk of breast cancer; for example earlier menarche and later meno-pause. Childbearing protects against later development of breast cancer, and breastfeeding further decreases the risk. The breast cancer risk declines more with increasing total duration of breastfeeding. Exposure to hormonal contraceptives has been evaluated in a combined reanalysis of data from 51 epidemiological studies. There is a small transient increase in the relative risk of breast cancer among users of oral contraceptives but, since use typically occurs at young ages when breast cancer is relatively rare, such an increase would have little effect on overall incidence rates. In contrast, exposure to menopause hormone treatment occurs when the baseline risk of breast cancer is higher, and epidemiological studies and randomized controlled trials consistently find an increase in breast cancer risk with exposure to combined estrogen and progestogen. Women with a family history of breast cancer in first degree relatives have an increased risk of breast cancer but there is no evidence to suggest that this differs according to a woman’s use of oral contraceptives or menopause hormone treatment. Selective estrogen receptor modulators are useful in the treatment and/or prevention of breast cancer depending on the specific agonist or antagonist effects on estrogen target tissues.

Key words: breast cancer/contraception/epidemiology/estrogen receptor/menopause hormone treatment

Introduction

An association between female hormones and breast cancer is important because breast cancer is diagnosed in $1 \times 10^6$ women in the world each year, and female hormones are used for contraception or menopause treatment by >10% of reproductive age and post-menopausal women respectively. Risks of hormone use among post-menopausal women will be particularly important in the future, given the worldwide trend to an increase in the number of older women in the population.

Population and incidence

The world population reached $6.3 \times 10^9$ people at the beginning of 2003, of which $5.1 \times 10^9$ live in the less developed regions and $1.2 \times 10^9$ in more developed countries (United Nations, 2003). The Population Division of the United Nations projects that by 2045–2050 the global population will be $8.9 \times 10^9$ people and that $1.6 \times 10^9$ (18%) of these will be women aged ≥50 years. These women who will be aged ≥50 years in 2050 are being born now and they have a life expectancy at birth of 73.1 years in the less developed regions and 81.6 years in the more developed countries (United Nations, 2003). By the time these $1.6 \times 10^9$ women reach the menopause, they can still look forward to living for a further 30 years or more. Their future quality of life requires up-to-date, scientifically valid information and appropriate advice and any menopause hormone treatment should have an established long-term record of safety.

With respect to incidence of disease, the most recent estimates of mortality and morbidity are from the year 2000. There were $55.7 \times 10^6$ deaths worldwide and malignant tumours accounted for 12% of these deaths (World Health Organization, 2001; International Agency for Research on Cancer, 2003); $5.3 \times 10^6$ men and $4.7 \times 10^6$ women developed a malignant tumour and there were $6.2 \times 10^6$ cancer deaths (Table I).

The major difference in cancer incidence between the sexes is the predominance in males of non-reproductive tract cancers of the lung, liver and stomach. Breast and cervical cancer are the most common cancers in women (Table II).
Table I. World incidence of new malignant tumours

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Annual incidence (000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1200</td>
</tr>
<tr>
<td>Breast</td>
<td>1050</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>940</td>
</tr>
<tr>
<td>Stomach</td>
<td>870</td>
</tr>
<tr>
<td>Liver</td>
<td>560</td>
</tr>
<tr>
<td>Cervix</td>
<td>470</td>
</tr>
<tr>
<td>Esophagus</td>
<td>410</td>
</tr>
<tr>
<td>Prostate and testicle</td>
<td>250</td>
</tr>
<tr>
<td>Ovary</td>
<td>190</td>
</tr>
<tr>
<td>Endometrium</td>
<td>188</td>
</tr>
</tbody>
</table>


Table II. Cancer in women: world

<table>
<thead>
<tr>
<th>Site</th>
<th>New cases (per annum, 000s)</th>
<th>Deaths (per annum, 000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1050</td>
<td>373</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>471</td>
<td>233</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>446</td>
<td>238</td>
</tr>
<tr>
<td>Stomach</td>
<td>319</td>
<td>241</td>
</tr>
<tr>
<td>Ovary</td>
<td>192</td>
<td>114</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>189</td>
<td>45</td>
</tr>
<tr>
<td>Liver</td>
<td>166</td>
<td>165</td>
</tr>
</tbody>
</table>


In the year 2000, there were more new breast cancer cases in the developed world (579 000) than in all developing regions together (471 000) and also more breast cancer deaths (189 000 and 184 000, respectively). Due to improved methods of early detection and treatment, 5 year survival rates are > 75% in most developed countries today (International Agency for Research on Cancer, 2003).

Industrial nations with the highest overall cancer rates include the USA, Italy, Australia, Germany, The Netherlands, Canada and France. Countries with the highest age-standardized breast cancer rates (ASR) per 100 000 persons at risk include The Netherlands (91.6), USA (91.4), Denmark (86.1), France (83.2), Australia (82.7), New Zealand (83.6), Belgium (82.2) and Canada (81.8). The average ASR is 63.2 for more developed countries and 23.1 for the less developed regions (International Agency for Research on Cancer, 2003) (Table III).

Countries with the highest age-standardized breast cancer death rates include Iceland (36.8), Denmark (29.2), Malta (28.4), The Netherlands (27.8), UK (26.8), Belgium (26.4), Uruguay (26.3) and Israel (26.2). The mean death rates are 18.6 for developed countries and 9.1 for all developing regions (International Agency for Research on Cancer, 2003) (Table III).

Since breast cancer is the most important malignancy affecting women, the assessment of its possible association with widely used hormonal steroids is of paramount importance, whether the estrogens and/or progestogens are used as contraceptives or for menopause hormone treatment. Studies of this association are part of a larger group of long-term follow-up studies, some of which have demonstrated a well-established protective effect of such hormonal steroids against endometrial, ovarian and colorectal cancer (World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives, 1988, 1989; Thomas, 1991; Grodstein et al., 1999; Burkman, 2002; Writing Group for the Women’s Health Initiative Investigators, 2002; Vessey et al., 2003).

Prevalence of hormonal steroid use

Ever use of contraception among women of reproductive age reached 62% worldwide and 70% in the more developed regions in the year 2001 among those who live in a marital or consensual union. Current use of steroidal contraception including oral, injectable and implantable methods exceeded 8% worldwide and 17% in the more developed countries. Current usage rates for steroidal contraception were as high as 48% in The Netherlands, 46% (Belgium), 36% (France), 26% (Denmark), 24% (Australia), 20% (New Zealand) and 16% (USA) (United Nations, 2002).

Use of hormone preparations among menopausal and postmenopausal women is less well documented and more uncertain. In 1997 the worldwide acceptance of menopause hormone treatment among women aged 45–64 years was estimated to be ~12% (Schneider, 2000).

Heterogeneity

There are several sources of heterogeneity in exposures and effects. With respect to exposures, hormone types are numerous. Estrogens can be made bioavailable by sulphurylation in position 3, the conversion of 17d estradiol into 17d ethinyl-estradiol and micronization. They may be delivered through oral, injection, transdermal and transvaginal routes. Progestogen preparations involve a similar variety of administration routes as well as 21 and 19 carbon root molecules that may have different receptor-binding, pharmacokinetic and pharmacodynamic properties. Thus, the various progestogens used in formulations for contraception or menopause hormone treatment may exhibit markedly different effects. Indeed, the conclusion of a recent review that ‘a progestin is not a progestin’ cannot be disregarded (Oettel et al., 2002). The complexity of the issue is further accentuated by evidence that estrogen–progestogen combinations are associated with greater risk of breast cancer than estrogen alone (Collins et al., 1995; Magnusson et al., 1999; Schairer et al., 2000; Ross et al., 2000; Million Women Study Collaborators, 2003).

With respect to heterogeneity of effects, breast cancer involves different cell types and degrees of cell differentiation, as well as a range of tumour size and clinical extent (Stalsberg et al., 1989). Hence investigations into a possible...
association between hormonal steroids and breast cancer entail extraordinary complexities and require consideration of many variables as well as interactive effects.

Breast cancer in an ageing population

After gender, age is the single most important factor in breast cancer development and the foregoing United Nations projections indicate that many more women will be in the vulnerable age group of >50 years where the breast cancer incidence steeply increases (Diczfalusy, 2002). By the year 2050 there will be $1.9 \times 10^9$ elderly persons aged >60 years, and this increase is unavoidable as these people are already among us as teenagers or young persons (United Nations, 2003). The population composition will be even more different because the increasing number of elderly persons will be associated with a sharply declining number of children, resulting in a population structure never seen before in history. Estimates and projections of the population structure of the more developed countries are shown in Table IV.

In 1950 there were more than twice as many children as elderly persons in developed countries, but by 2050 projections indicate the reverse, with 2-fold more elderly persons than children. The maintenance of the functional capacity and humanitarian integrity of the necessary social services in such a society will pose major challenges, and might perhaps even result in immigration from less developed regions in numbers never imagined before. The greater number of elderly women means that breast cancer incidence will rise to $>1 \times 10^6$ breast cancers per year.

Hormones and breast cancer development

Cancer is generally believed to arise when dividing cells undergo mutations and these genetically damaged cells become susceptible to unrestrained division. Thus, female hormones and other hormones that affect growth of the mammary gland are potential risk factors for breast cancer. In contrast, factors that induce differentiation in the mammary gland, such as pregnancy and lactation, are likely to reduce the risk of breast cancer. The baseline risk is influenced, however, by higher mammary gland mass and several observations provide indirect evidence of the association between mammary gland mass and breast cancer risk (Bernstein and Ross, 1993; Adami et al., 1998): (i) first pregnancy induces terminal differentiation of the breast epithelium and reduces breast cancer risk; (ii) dense mammographic patterns reflecting the dominance of epithelial tissue over fatty tissue are associated with higher risk of breast cancer; (iii) adult height and the attendant higher mammary gland mass is a significant risk factor; (iv) women have more mammary gland mass than men and they experience a 100-fold higher breast cancer risk; (v) Caucasian women have more mammary gland mass than oriental women, who have a lower breast cancer risk; (vi) the left breast is slightly larger on average than the right breast, and more likely to sustain breast cancer.

The studies on hormones in relation to breast cancer are consistent in indicating that virtually every mammotrophic hormone examined is positively associated with breast cancer risk (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). The list includes total and free estradiol, estrone and estrone sulphate, androstenedione, dehydroepiandrosterone and dehydroepiandrosterone sulphate, testosterone and prolactin. Hormonal factors that influence breast cancer risk may act during adult and/or fetal life.

Factors during adult life

Four lines of evidence point to hormones, and particularly sex hormones, as playing a role in the development of breast cancer in the adult woman (Adami et al., 1998; Hankinson and Hunter, 2002). The first springs from the powerful role that female reproductive factors and, indeed, gender itself, play on breast cancer occurrence. Breast cancer risk is increased, for example, in women with earlier menarche and later menopause. The second line of evidence relies on experimental animal data indicating that estrogen and progesterone promote some types of mammary tumours. The third line of evidence derives from studies indicating that exogenous estrogens and progesterone in hormonal contraceptives and menopause hormone treatment regimens increase breast cancer risk, whereas tamoxifen reduces this risk. The fourth line of evidence involves analytic epidemiological studies, particularly cohort investigations, that implicate various hormones and expression of hormone receptors in the risk of breast cancer (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). Studies of endogenous hormones may be more directly relevant to the pathogenesis of breast cancer than studies of exogenous hormones.

Nevertheless, hormonal exposure evidence is stronger for post-menopausal women, possibly because in pre-menopausal women, cyclic variation of hormones during the menstrual cycle increases exposure misclassification (Bernstein and Ross, 1993; Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Hankinson and Hunter, 2002). The pattern of positive associations could, of course, simply reflect powerful mutual confounding that is difficult to disentangle through statistical procedures. An alternative explanation, however, is that all these hormones have growth promoting potential on mammary tumours through inherent anabolic/mammotrophic properties, although the effect may vary among tumour types and stages. The reported, though not yet established, positive association of insulin-like growth factor I with breast cancer risk among pre-menopausal women is compatible with such a hypothesis, except that the possible association is manifested at an earlier stage in life.

Table IV. Population structure of the more developed regions

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>1950</th>
<th>2000</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–14 (%)</td>
<td>27.3</td>
<td>18.3</td>
<td>15.6</td>
</tr>
<tr>
<td>15–59 (%)</td>
<td>60.0</td>
<td>59.2</td>
<td>52.4</td>
</tr>
<tr>
<td>≥60 (%)</td>
<td>12.7</td>
<td>22.5</td>
<td>32.0</td>
</tr>
<tr>
<td>Population ($\times 10^6$)</td>
<td>813</td>
<td>1194</td>
<td>1230</td>
</tr>
</tbody>
</table>

Factors acting during intrauterine life

The hypothesis that breast cancer development may have intrauterine component causes is based on a number of generally accepted assumptions. Mammary gland cells in utero are not terminally differentiated; factors that increase the risk of cancer during adult life, as exogenous and endogenous estrogens do for breast cancer, may have similar effects when they act in utero; estrogens and other hormones with growth-enhancing properties are abundant during pregnancy; and adult life exposures do not fully explain the substantial variability of breast cancer occurrence between and within populations. Potschman and Troisi (1999) concluded that the collective evidence is consistent with the hypothesis that prenatal exposures, notably pregnancy estrogens, are associated with adult life breast cancer risk. More consistent is the evidence concerning the positive association between birthweight and breast cancer risk in the offspring (Ahlgren et al., 2003). It should be noted that a link between perinatal factors and breast cancer risk in the offspring does not necessarily or exclusively incriminate pregnancy estrogens, despite the role of the latter as an important determinant of several of these factors, including birthweight.

The effects of hormonal influences in fetal and adult life are consistent with the hypothesis that breast cancer develops when cells undergo a series of mutations that cause damage to genes involved in the control of cell division (El-Ashry and Lippman, 1994). The genetic damage may inactivate repressor genes or activate proto-oncogenes, leading to structural changes and excessive proliferation. Also, estrogen may be associated with the initiation of breast cancer through oncogenic actions of the aromatase gene (Clemon and Goss, 2001). Both estrogen and progesterone accelerate the rate of breast epithelial cell division, thereby increasing the risk of critical mutational changes (Anderson et al., 1989; Foidart et al., 1998; Hofseth et al., 1999). Increasing cell synthesis also may enhance the survival of genetically damaged cells, leading to promotion of breast cancer, or increase the growth of pre-clinical tumours, leading to earlier diagnosis. Hormones may have an influence at any time during the 15–19 years from mutation to clinical diagnosis of breast cancer (Cutuli et al., 2001).

Thus female hormones may increase breast cancer risk by increasing the number of cell divisions and the likelihood of mutational damage, or after the genetic damage has occurred by promoting the survival and growth of the pre-clinical cancer.

Breast cancer risk in relation to childbearing and breastfeeding

Although childbearing protects against later development of breast cancer, it has been difficult to isolate the impact, if any, of breastfeeding because it is closely related to other aspects of childbearing. For example, women breastfeed only after they have had a livebirth, and the earlier they commence childbearing, the more children they tend to have and the longer their lifetime duration of breastfeeding. Also, patterns of childbearing and duration of breastfeeding vary and few of >40 studies to date had sufficient power to detect small or moderate effects.

The Collaborative Group on Hormonal Factors in Breast Cancer published findings from a collaborative reanalysis of data from 47 epidemiological studies conducted in 30 countries which examined the role of both childbearing and breastfeeding on breast cancer risk. This summary of the current evidence on the relative contributions of childbearing and breastfeeding on breast cancer risk is based on the collaborative report (The Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

The relative contributions of childbearing and breastfeeding to breast cancer risk

Although parity has long been known to protect against breast cancer risk, at least in the long term, the interdependence of key indices of childbearing, such as parity, timing of births and breastfeeding, make it difficult to disentangle which factors have an independent effect on breast cancer risk. For this reason, it is sensible to estimate first the effect of childbearing in the absence of breastfeeding, and then the additional effect of breastfeeding among parous women by adjusting for childbearing history.

Among women who have never breastfed, the risk of breast cancer increases in linear fashion with the age at first birth. Overall, the relative risk (RR) of breast cancer increases by 3% (SEM 0.3%) for each additional year by which the first birth is delayed. With childbearing the RR of breast cancer decreases with increasing parity; after stratifying by age at first birth, each birth reduces the risk by 7% (SEM 1.0%) (Figure 1).

The effect of breastfeeding on breast cancer risk does not fully explain the substantial variability of breast cancer occurrence between and within populations. Potschman and Troisi (1999) concluded that the collective evidence is consistent with the hypothesis that breastfeeding and number of births reported (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). FCI = Floated confidence interval.
that the decline in risk with total duration of breastfeeding differs according to a range of other characteristics including age, family history, menopausal status and ethnic origin.

Impact on different populations
Worldwide epidemiological evidence suggests that breastfeeding has an additional protective effect on breast cancer risk over and above that afforded by childbearing. These associations are significant and are seen consistently in data from developed and developing countries, in women of different ages and ethnic origins having various childbearing and other characteristics.

It is estimated that the cumulative incidence of breast cancer observed in developed countries around 1990 would be more than halved (2.7 per 100 women rather than 6.3 per 100 women by the age of 70) if women had the average number of births and total duration of breastfeeding typical of developing countries until recently (Figure 2). Moreover, breastfeeding could account for almost two-thirds of this reduction in incidence.

Clearly, women in more developed countries are unlikely to return to the patterns of childbearing and breastfeeding that were typical of a century ago in order to reduce breast cancer rates. If the mechanism by which breastfeeding protected against breast cancer were understood, however, it might be possible to mimic the effect of breastfeeding therapeutically or in some other way. In the meantime, important reductions in breast cancer rates could be achieved if women considered breastfeeding for longer than they do now. For example, if women in developed countries were to carry on having 2.5 children, on average, but breastfed each child for 12 months longer than they currently do, there could be potentially 50 000 (11%) fewer breast cancers per annum in these countries.

![Figure 2. Estimated cumulative incidence of breast cancer in developed countries if women had family sizes and breastfeeding patterns typical for developing countries (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).](image)

Hormonal contraception and breast cancer risk
Even a small association between use of hormonal contraception and breast cancer would be clinically relevant because hormonal contraceptives are among the most frequently prescribed drugs in the world (ESHRE Capri Workshop Group, 2002). The most common hormonal contraception is combined estrogen–progestogen oral contraception. A reanalysis of epidemiological data published in 1996 addressed many of the common questions about breast cancer risk associated with oral contraceptive use (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a,b). The findings were based on a total of 53 297 women with breast cancer and 100 239 controls, the majority from North America or Europe. The main finding was a small increase in breast cancer risk during use of oral contraception, which began to decline shortly after stopping and which disappeared 10 years after discontinuation. The RR of breast cancer was estimated at 1.24 [95% confidence interval (CI) 1.15–1.33] for current users compared with non-users. Within 10 years after discontinuing use of oral contraception the RR declined to 1.01 (95% CI 0.96–1.05). Cancers in oral contraceptive users were 12% less likely (95% CI 5–19) than those in non-users to have spread beyond the breast.

The small elevation in breast cancer risk among women who are taking oral contraceptives or have recently stopped reflects a higher RR at age <35 years when breast cancer incidence is low. In the Collaborative reanalysis the RR of breast cancer for recent users who first began oral contraception prior to 20 years of age, as compared with non-users, was 1.95 for women aged <30 years at the time of diagnosis. The corresponding estimates of RR for women aged 30–34 and 35–39 years at diagnosis were 1.54 and 1.27 respectively. For recent users who had initiated oral contraception after the age of 20 years, the RR of breast cancer was estimated to be 1.22 and 1.11 respectively for women aged 40–44 years and 45–49 years at diagnosis (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a).

A large case–control study has evaluated breast cancer risk associated with hormonal contraception among women who were 35–64 years old. The study involved 4575 women with breast cancer and 4682 controls and indicates that the RR of breast cancer was 1.0 (95% CI 0.8–1.3) for women who were currently using oral contraceptives and 0.9 (0.8–1.0) for previous users. The RR did not increase consistently with longer periods of use or with higher doses of estrogen (Marchbanks et al., 2002). The RR of breast cancer associated with oral contraceptive use was not increased among women with a family history, or among women who initiated oral contraceptive use at a relatively young age. Thus, among women aged 35–64 years, current or past use of oral contraception was not associated with a significantly increased risk of breast cancer.

The absolute number of breast cancers attributable to oral contraceptive use by young women would be 1.5 cases (95% CI 0.7–2.3) and 4.7 cases (95% CI 2.7–6.7) per 10 000 women using oral contraceptives from ages 20 to 24 years and from 25 to 29 years respectively during and 10 years after use ceased (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a).

Epidemiological studies published since the Collaborative reanalysis are generally consistent with the findings in...
the Collaborative study. Breast cancer risk appears to be higher with daily dosage of ethinylestradiol greater than 35 μg and with higher daily and cumulative exposure to progestogens (Althuis et al., 2002; Dumeaux et al., 2003). Breast cancer risk was increased with longer duration of oral contraceptive use (Kumle et al., 2002; Dumeaux et al., 2003) and risk was higher among women diagnosed before 35 years of age (Althuis et al., 2002).

The trend to lower breast cancer risk after discontinuing oral contraceptive noted in the Collaborative study was found, however, in only one (Althuis et al., 2002) of four subsequent studies that evaluated breast cancer risk by recent use of oral contraceptive (Althuis et al., 2002; Kumle et al., 2002; Dumeaux et al., 2003; Newcomer et al., 2003). One case–control study found that oral contraceptive use was more likely to be associated with the less common lobular histology than ductal carcinoma (Newcomer et al., 2003). In a further study where both breast cancer cases and controls were BRCA1 or BRCA2 mutation carriers, the RR of increased breast cancer associated with oral contraceptive use was 1.20 (95% CI 1.02, 1.40) among BRCA1 carriers and 0.94 (95% CI 0.72, 1.24) among BRCA2 carriers (Narod et al., 2002).

A relatively small proportion of the expected lifetime incidence of breast cancer occurs before the age of 50 years. The use of oral contraceptives does not appear to increase the risk of breast cancer later in life, when the incidence of breast cancer is higher.

Menopause hormone therapy and breast cancer risk

Epidemiological studies

The risk of breast cancer in women receiving menopause hormone treatment was reported in a reanalysis of individual data from 51 epidemiological studies including >52 000 women with breast cancer and 108 000 without breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Menopause hormone therapy increased breast cancer risk by ~2.3% per year of use. The increased breast cancer risk associated with menopause hormone therapy declines within a few years after stopping use (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Beral et al., 1999; La Vecchia and Franceschi, 2003). These estimates mainly reflect use of unopposed estrogen, which accounted for 80% of hormone use in the 51 studies.

Combined estrogen–progestogen use, which reduces the excess endometrial cancer risk induced by unopposed estrogen (La Vecchia et al., 2001) is associated with a higher breast cancer risk. In an American cohort study involving 1935 new invasive breast cancer cases during 725 550 person-years of follow-up, the RR of breast cancer were 1.3 for estrogens alone, and 1.4 (95% CI 1.2–1.7) for estrogens–progestins (Colditz et al., 1995). In a Swedish case–control study involving 3345 women with breast cancer, RR increased with duration of different types of combined estrogen–progestin use, up to 2.4 for women treated for ≥10 years (Magnusson et al., 1999). In the Breast Cancer Detection and Demonstration Project, among 46 355 participants followed for a mean of 10.2 years, the RR of breast cancer among women who had used combined estrogen and progestins was 1.4 (95% CI 1.1, 1.8) compared with never users (Schairer et al., 2000). The risk from combined therapy was non-significantly greater than that observed with unopposed estrogens (RR 1.2, 95% CI 1.0–1.4). Women who had used HRT in the past but stopped also did not have an increased risk.

In a Los Angeles County population-based case–control study involving 1897 post-menopausal cases and 1637 post-menopausal population controls, the RR for breast cancer was 1.06 (95% CI 0.97–1.15) for each 5 years of estrogen therapy, but 1.24 (95% CI 1.07–1.45) for combined estrogen–progestogen treatment (Ross et al., 2000). In a further American multicentre case–control study involving 1870 cases and 1953 controls, breast cancer risk was 1.5-fold higher with continuous combined estrogen–progestogen among users of ≥3 years (Weiss et al., 2002). The Women’s Health Study involved 17 835 women who gave information on menopause hormone therapy use (Porch et al., 2002). The RR for breast cancer were 1.0 with ever use of estrogens only, 1.4 with estrogen–progestin and 1.8 with continuous progestin pattern.

In a Washington case–control study of 975 cases and 1007 controls, unopposed estrogen therapy had no appreciable excess risk of breast cancer, even with use for ≥25 years (Li et al., 2003). Users of combined menopause hormone therapy, however, had an overall 1.7-fold higher (95% CI 1.3–2.2) increased risk of breast cancer, which increased with longer duration of use. The RR were 2.7-fold for invasive lobular carcinoma, 1.5-fold for ductal carcinoma, and 2.0-fold for estrogen receptor and progesterone receptor positive breast cancers. This higher risk of the lobular type of breast cancer reflects the observation of a substantial rise in the incidence of lobular cancers in population-based series (Levi et al., 2003; Verkooijen et al., 2003).

The above epidemiological studies generally lacked sufficient power to evaluate breast cancer risk with specific types of menopause hormone treatment. The Million Women Study enrolled 1 084 110 women aged 50–64 years between 1996 and 2001 who returned a questionnaire before an appointment for mammography screening (Million Women Study Collaborators, 2003). Table V summarizes the main analysis in 828 923 post-menopausal women, showing a small but significant increased risk with use of unopposed estrogen and a 2-fold increase in risk with use of estrogen–progestin during an average 2.6 years of follow-up.

Table V. Menopause hormone use and breast cancer risk

<table>
<thead>
<tr>
<th>Hormone use</th>
<th>Cases</th>
<th>Population</th>
<th>Cases/10 000</th>
<th>Relative risk</th>
<th>95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>2894</td>
<td>392 757</td>
<td>73.7</td>
<td>1.00</td>
<td>0.96–1.04</td>
</tr>
<tr>
<td>Past</td>
<td>1044</td>
<td>150 179</td>
<td>69.5</td>
<td>1.01</td>
<td>0.95–1.08</td>
</tr>
<tr>
<td>Current</td>
<td>991</td>
<td>115 383</td>
<td>85.9</td>
<td>1.30</td>
<td>1.22–1.38</td>
</tr>
<tr>
<td>Estrogen only</td>
<td>1934</td>
<td>142 870</td>
<td>135.4</td>
<td>2.00</td>
<td>1.91–2.09</td>
</tr>
<tr>
<td>Estrogen–progestogen</td>
<td>184</td>
<td>18 186</td>
<td>101.2</td>
<td>1.45</td>
<td>1.25–1.67</td>
</tr>
<tr>
<td>Tibolone</td>
<td>93</td>
<td>95 484</td>
<td>97.4</td>
<td>1.44</td>
<td>1.17–1.76</td>
</tr>
</tbody>
</table>

<sup>a</sup>Relative to never use: stratified by age, time since menopause, parity, age at first birth, family history of breast cancer, body mass index and deprivation index.

<sup>b</sup>Floated confidence interval.
With use of unopposed estrogen there were no important differences between equine estrogen and estradiol preparations or by dosage of either type of estrogen. With use of estrogen–progestogen there were no important differences between preparations containing medroxyprogesterone acetate, norethisterone and levonorgestrel and no detectable differences between sequential and continuous combined regimens, although there were only 23,708 users of the continuous regimen and 243 breast cancer cases (Million Women Study Collaborators, 2003).

With respect to duration of use, the RR with estrogen only for <5 years and ≥5 years were 1.21 (95% CI 1.07–1.37) and 1.34 (95% CI 1.23–1.40) respectively. With estrogen–progestogen use the RR for <5 years and ≥5 years were 1.70 (95% CI 1.56–1.85) and 2.21 (95% CI 2.06–2.37) respectively. Breast cancer risk declined (RR 0.94, 95% CI 0.84–1.05) within 1 year of discontinuing use (Million Women Study Collaborators, 2003).

The cumulative incidence of breast cancer during the 20 years from age 50 to 65 years is ~32 cases in 1000 women. Use of estrogen only for 5 years may add two cases to this number and for 10 years six cases (Table VI). Use of estrogen–progestogen for <5 years may add six cases and for 10 years 19 cases (Million Women Study Collaborators, 2003).

**Randomized controlled trials**

Among randomized controlled trials that were set up to study cancer and cardiovascular endpoints, two small and one large trial have addressed the issue of menopause hormone treatment and breast cancer risk. The overall pooled RR and breast cancer was 1.27 (95% CI 1.03–1.56; Beral et al., 2002).

In the HERS trial, there were 34 breast cancer cases among users of combined estrogen–progestogen therapy and 25 among controls, and the RR was 1.38 (95% CI 0.82–2.31) (Hulley et al., 2002). The WEST trial found five cases in the estrogen-only users and five cases in controls, a RR of 1.00 (95% CI 0.30–3.50) (Viscoli et al., 2001).

Breast cancer risk also was analysed in The Women’s Health Initiative study (Chlebowski et al., 2003). The trial involved 8506 women aged 50–70 years treated with combined estrogen–progestogen and 8102 in the placebo group. After an average 5.6 years of follow-up the relative hazard was 1.24 (95% CI 1.01–1.54), which is within the range of the above epidemiological study estimates of breast cancer risk with current use of estrogen–progestin (Figure 3). The absolute risk was eight breast cancer cases for every 10,000 women per annum in addition to the 31 cases per 10,000 in the placebo group.

**Tumour characteristics**

The frequency of in situ breast cancers was not significantly different in the estrogen–progestogen and placebo groups (relative hazard 1.18, 95% CI 0.77–1.82). Among the invasive cancers, there was no specific association with ductal or lobular types, degree of differentiation and estrogen or progesterone receptor status. Tumours in the estrogen–progestogen group, however, were 2 mm larger (P = 0.04), more likely to be regional or metastatic than localized (25.4 versus 16.0%, P = 0.04) and more likely to involve lymph nodes (25.9 versus 15.8%, P = 0.03).

Thus, the evidence from randomized controlled trials is consistent with the findings in epidemiological studies. The absolute risk of breast cancer associated with use of oestrogen–progestogen is estimated to be eight cases per 10,000 women per annum.

### Table VI. Absolute risk of breast cancer with estrogen-only menopause treatment: epidemiological studies

<table>
<thead>
<tr>
<th>Duration of use (years)</th>
<th>Excess breast cancer cases/1000 women aged 50–65 years</th>
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<td>Collaborative analysisa</td>
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<td>2</td>
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<td>10</td>
<td>6</td>
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</table>

bMillion Women Study Collaborators (2003).

**Figure 3.** Estrogen and estrogen–progestin risk estimates. Point estimates: 49 epidemiological studies; diamonds and 95% confidence intervals: three randomized controlled trials. (See text for references.).

**Figure 4.** Relative hazards according to use of menopausal hormones before enrolment in the Women’s Health Initiative study in the estrogen–progestogen (E/P) and placebo groups (drawn from data of Chlebowski et al., 2003).
**Breast cancer mortality**

Although menopause hormone treatment has been associated with an increased incidence of breast cancer, use appeared to lead to improved prognosis in some observational studies (Willis et al., 1996; Schairer et al., 1999). Thus, in the American Cancer Society Cancer Prevention Study II, breast cancer mortality did not increase with estrogen use overall, and no excess risk was observed for thin or heavy women (Rodriquez et al., 2001). This effect may be due to increased breast cancer surveillance among users of menopause hormone treatment. In the Million Women Study Collaborators (2003), however, breast cancer mortality was 1.2-fold higher in current versus never HRT users ($P < 0.05$) (Million Women Study Collaborators, 2003). Likewise, in the Women’s Health Initiative results above, invasive breast cancers diagnosed in the estrogen–progesterone group were larger and at a more advanced stage.

**Family history, breast cancer and hormone use**

To study the relationship between breast cancer, family history and external hormones, a lifetime history of drug use, medical conditions, socio-economic status and lifestyle factors is required, because of multiple associations. It is not adequate to study only small sections of past history, such as in database studies.

Epidemiological studies have established a set of relatively convincing risk factors for breast cancer such as: family history of breast cancer, possibly due to inherited genetic abnormalities; rapid growth early in life, greater height, higher socio-economic status, and older age. In addition, some probable risk factors are: diet low in fruit and vegetable intake, or high in meat/fat intake, higher alcohol consumption, high post-menopausal body mass index (BMI), lack of exercise and history of benign breast tumours (American Institute for Cancer Research/World Cancer Research Fund, 2002). The strength of the association with all known risk factors is in the same range, from 1.2- to 6-fold increased RR (Figure 5). In observational research, it is rather unlikely that one could distinguish causality from bias and residual confounding with risk estimates ranging from 0.5 to 2.0 with the use of epidemiological methods, and many breast cancer risk estimates are within this range. In addition, there is variability in the results of the observational studies: the risk estimates are not consistent, ranging from lowered risk of breast cancer to increased risk.

Interestingly, large geographic differences in breast cancer risk are unlikely to be explained by genetic differences alone. Incidence rates of breast cancer are as much as 5-fold higher comparing the average of developed with developing countries. Indeed, the highest breast cancer incidence rates in individual developed countries are up to 20-fold higher than those in some developing countries. The incidence is very high and increasing in Europe and North America (or levelling off now in some countries), but very low in African and Asian regions (American Institute for Cancer Research/World Cancer Research Fund, 2002).

There is not sufficient evidence to claim that family history of breast cancer or genetic differences can be the main cause of breast cancer (Wiseman, 2000). Family history of breast cancer has a low prevalence, affecting 10–15% of first degree relatives in cancer cases, and ~5% in non-cancer controls. Nevertheless, some studies of high risk families have demonstrated an impact on the occurrence of breast cancer and an interaction with hormone use at least in first degree relatives (Grabrick et al., 2000). Family history and mutations of the tumour suppressor genes BRCA1 and BRCA2 are obviously important correlates of the breast cancer lifetime risk. Approximately 4–8% of all breast cancer cases may be caused by germline mutations, although 92–96% are sporadic and 50% of carriers do not develop cancer by age 60 years (Wiseman, 2000). Also, there is evidence from other studies that the population-attributable risk of the above-mentioned factors (education, family history and a few reproductive and hormonal factors) may well account for up to 50% of the breast cancer risk—even if external hormone use is not considered (Henderson and Bernstein, 1996). Therefore it can be concluded from sometimes conflicting evidence that family history of breast cancer is indeed an important issue (La Vecchia et al., 2001; Clamp et al., 2002).

The results of individual studies of the effect of family history of breast cancer risk associated with use of external steroid hormones have been inconsistent (Wiseman, 2000; Sellers et al., 1997; Grabrick et al., 2000; Friedenson and Friedenson, 2002). Some results indicated that a positive family history would amplify the association between hormone use and breast cancer risk but in others there was no impact. Most of the studies lacked power to evaluate the question, and therefore it is useful to have estimates from the collaborative meta-analyses published in 1996 and 1997.

With respect to use of oral contraceptives, the impact of family history on the RR of breast cancer associated with oral contraceptive use could be assessed among 2044 breast cancer cases and 1731 control women who had a mother and/or a sister with a history of breast cancer (Table VII). For each category of oral contraceptive use, including current or recent use within the last 5 years, the RR of breast cancer was higher in women with no family history than in women with one or more primary relatives with a history of breast cancer. Although the lower risks with family history were not significantly different, there is no reason to expect that family history of breast cancer magnifies the risk of breast cancer with oral contraceptive use.

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**Figure 5.** Common risk factors for breast cancer (Singletary, 2003).
(Collaborative Group on Hormonal Factors in Breast Cancer, 1996a). With respect to use of menopause hormone treatment, the Collaborative analysis involved 566 breast cancer cases and 791 control women who had a mother and/or a sister with a history of breast cancer (Table VIII). In these analyses the RR also were not different for women with or without a family history as defined (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). This suggests that family history of breast cancer does not magnify the risk of breast cancer with menopause hormone treatment.

Family history of breast cancer, however, may reflect not only shared genes, but also shared environmental/lifestyle exposures. It is not trivial to disentangle both effects—even in family studies. The critical issue is how to advise patients with a strong family history of breast cancer about use of oral contraception or menopause hormone treatment. It is important to ensure that the patient recognizes the increased baseline risk of breast cancer due to the possibility of pre-existing malignant or pre-malignant changes, and shares in the decision about whether to use contraceptive or menopause hormone treatment.

Since germline mutations are relatively infrequent and few of the abnormal genes are known, genetic testing for all women is currently not favoured. It remains uncertain whether genetic testing should be done in women with a strong family history of breast cancer, because they may derive benefit from reduced fear of cancer and feel freer to consider hormone therapy if the results rule out known high risk genes (Sellers et al., 1997; Friedenson and Friedman, 2002; Ursin et al., 2002). As an alternative to genetic testing, mathematical models have been developed to predict the likelihood of developing breast cancer in individuals and these models have family history of breast cancer as one of the important variables (Clamp et al., 2002).

Thus, family history of breast cancer and hormone use are two factors among many potential known or unknown causal agents in the development of breast cancer. Family history is not involved in most cases of breast cancer, nor is family history alone an inevitable precursor of breast cancer. Family history is, however, an indication for counselling and, in some women, for special diagnostic tests.

### Selective estrogen receptor modulators and breast cancer

Knowledge about hormonal effects on breast cancer has expanded in the last three decades with the development of selective estrogen receptor modulators (SERM). This chemically diverse group of compounds involves a tertiary structure allowing them to bind to the estrogen receptor and to exert a specific set of agonist or antagonist effects on estrogen target tissues. Factors which influence agonist or antagonist activity in a given target tissue or circumstance include differences in estrogen receptor expression, receptor conformation on ligand binding and the expression of co-regulating proteins (Jordan, 2001). SERM are particularly useful in breast cancer management because they offer possible treatment and prevention through estrogen antagonism coupled with the potential for useful estrogen agonist effects on normal tissues including bone, the cardiovascular system, and perhaps the central nervous system.

Tamoxifen is the most widely used SERM in the treatment of breast cancer; tamoxifen and raloxifene are both used in prevention strategies. Both drugs have anti-estrogenic activity against breast cancer because they interfere with binding of the estrogen receptor to DNA structures, specifically by recruiting co-repressors that interact with the estrogen receptor at the estrogen response elements within target genes.

### Treatment of breast cancer

Tamoxifen is the cornerstone of adjuvant endocrine therapy for early breast cancer and causes a significant survival benefit in patients with estrogen positive disease (Breast Cancer Trialists Collaborative Group, 1998). Recent results from the adjuvant ATAC (Arimidex, Tamoxifen Alone or in Combination) trial have suggested that the aromatase inhibitor anastrozole alone achieves significantly greater disease-free survival than tamoxifen alone or in combination with anastrozole (ATAC Trialists Group, 2002). Follow-up is short, however, with insufficient long-term information on safety and efficacy of aromatase inhibitors. For this reason the American Society of Clinical Oncology Technology Assessment statement continues to recommend tamoxifen except in patients where there is a specific contraindication (Winer et al., 2002).

Also raloxifene has activity against advanced breast cancer but unlike tamoxifen it has been developed not for the treatment of this disease, but for osteoporosis.

### Effects on other target organs

Tamoxifen and raloxifene have effects on other target sites that may affect the balance of clinical benefits and risks.

#### Bone

Tamoxifen has an agonist effect on bone and promotes a gain in bone density at least in post-menopausal women (Powles et al., 1996). Raloxifene also has estrogen agonistic activity in bone and increases bone mineral density (Delmas et al., 1997). Raloxifene also decreases the risk of vertebral fractures in post-menopausal women with osteoporosis (Ettinger et al., 1999).
Both tamoxifen and raloxifene have estrogen agonist effects on serum lipids with an increase in high density lipoprotein and a decrease in low density lipoprotein cholesterol and total cholesterol. Raloxifene decreased cardiovascular events by 40% in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial (Barrett-Connor et al., 2002). Tamoxifen has been associated with a reduction in coronary artery disease in some but not all adjuvant or prevention trials (Smith and Dowsett, 2003). It is of interest that estrogen also increases high density lipoprotein cholesterol concentration, but does not decrease coronary artery disease events (Writing Group for the Women’s Health Initiative Investigators, 2002).

Endometrium
Tamoxifen has agonist effects on uterine endothelium and is associated with an increased risk of endometrial cancer in adjuvant trials (Breast Cancer Trialists Collaborative Group, 1998). In contrast, raloxifene appears to have neutral actions on uterine endothelium and is not associated with an increased risk of endometrial cancer.

Central nervous system
The brain is rich in estrogen receptors, particularly in the hypothalamus, and replacement estrogen is effective in reducing hot flushes in post-menopausal women. Unfortunately, none of the SERM so far studied has replicated this effect, and tamoxifen and raloxifene increase the incidence of hot flushes compared with placebo. Theoretically estrogen agonists could have a role in reducing the incidence of Alzheimer’s disease but estrogen–progestogen treatment does not reduce the incidence of senile dementia and there are no convincing data to indicate effects of tamoxifen or raloxifene on cognition (Shumaker et al., 2003).

Breast cancer prevention
Tamoxifen treatment in high risk women appears to prevent breast cancer. Previous trials of adjuvant tamoxifen have shown an almost 50% reduction in the development of contralateral breast cancer (Breast Cancer Trialists Collaborative Group, 1998). Also, two chemoprevention trials have shown that tamoxifen reduces the incidence of breast cancer (Fisher et al., 1998; IBIS Working Party and Principal Investigators, 2002).

Raloxifene has not been widely studied as an adjuvant therapy but it may have a significant role in prevention. In the MORE (Multiple Outcomes of Raloxifene Evaluation) trial, designed to assess anti-fracture efficacy, raloxifene reduced the risk of breast cancer by 76% (Cummings et al., 1999).

Trials are currently underway that involve comparisons of tamoxifen, raloxifene, anastrozole and selected combinations in reducing the incidence of breast cancer in women at increased risk.

Screening for breast cancer
Regular mammography examinations to detect early breast cancer have become a key component of national breast cancer screening programmes. Mammography is also required for balanced diagnostic surveillance in epidemiological studies and clinical trials that evaluate the effect of hormones on breast cancer incidence. Menopausal estrogen–progestogen hormones increase the density of breast tissue and may affect the accuracy of mammography interpretation (Greendale et al., 2003; Million Women Study Collaborators, 2003). It is therefore sensible to assess the overall results of breast cancer screening programmes to evaluate whether hormonal effects might cause a significant change in their effectiveness.

The case for breast cancer screening is based on the results of trials: the New York Health Insurance Plan (HIP) trials and four Swedish trials were the principal randomized trials. Combined results of the Swedish trials in particular show a 27% reduction in mortality from breast cancer in women aged 60–69 years invited for screening but failed to show a significant advantage for women aged 40–59 years (Nystrom et al., 2002) (Table IX).

As a result of these trials, several countries introduced population screening. In the UK the National Health Service Breast Screening Programme (NHS BSP) was introduced in 1988 after the preliminary Trial for the Early Detection of Breast Cancer (TEDBC) which compared breast self-examination (BSE), mammographic screening and no intervention; mammographic screening, but not BSE, was shown to be associated with a lower mortality from breast cancer. The NHS BSP in which women aged 50–64 years are screened every 3 years has been operating since 1988 (Blanks et al., 2000). From 1990 to 1998 in England and Wales, there was a 21% reduction in breast cancer mortality, which has been attributed to three factors: improvements in treatment; earlier symptomatic presentation; and mammography screening. Approximately 15% of the 21% reduction in breast cancer mortality in the age group at risk from 1990 to 1998 was due to treatment and other factors and 6% to mammography (Blanks et al., 2000).

Trials of technique showed advantage to double reading and to the taking of two views at prevalent screening. Otherwise screening in the UK has been based on the single lateral oblique view. A trial of the screening of younger women still awaits final analysis.

Trials on screening intervals were introduced in the UK, in particular because the length of the screening interval of 3 years was criticized as being too long. A study of the effect of breast cancer screening frequency on case survival in Nottingham illustrates the number of issues besides screening that must be considered in such an evaluation. The study made use of the Nottingham Prognostic Index (NPI) which has been well-validated among national and international centres. The index incorporates histological grade, lymph node stage and tumour

<table>
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<th>Control</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
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<tr>
<td>40–74</td>
<td>795</td>
<td>847</td>
<td>0.85</td>
<td>0.77–0.94</td>
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</tbody>
</table>

RR = relative risk; CI = confidence interval.
size to separate patients into groups with significantly differing good, medium and poor prognoses (Kollias et al., 1999).

The frequency of breast cancer screening trial, which made use of the NPI to predict survival, has shown no advantage with annual screening over triennial screening (Breast Screening Frequency Trial Group, 2002). In an economic evaluation, the screening frequency trial showed that annual screening cost £40 \times 10^6 more per annum than triennial screening. If a 20% reduction in mortality from breast cancer is assumed, then each breast cancer death averted by annual screening costs £60 000 rather than £30 000 per case. Among 40–49 year old women, trials have failed so far to demonstrate a significant fall in mortality. Should future trials demonstrate a reduction in this age group, the cost per life saved will be considerably higher than in the 50–64 year age group. The cost per life saved also will be higher in screening programmes for older women, because of their high rate of death from causes other than breast cancer.

Breast cancer screening has made an important contribution to public awareness of breast cancer, but reductions in mortality are due more to treatment than to screening. The small compromise in breast cancer screening that might be attributable to menopause hormone treatment is unlikely to have an impact on mortality. Current evidence indicates that breast cancer mortality has been reduced more by better use of existing treatments and by the introduction of new therapeutic agents than by breast cancer screening programmes.

**Conclusions**

Recent advances have begun to clarify the molecular origins of breast cancer, the influence of endogenous and exogenous hormones and the factors that determine the prognostic characteristics of a given tumour. The effect of hormonal contraception is small and occurs at an age when overall breast cancer risk remains low. The hormonal contraception risk declines after cessation of use, but this exposure remains low. The hormonal contraception risk declines after cessation of use, but this exposure remains low.

**Table Xa.** Ten year breast cancer survival age 50–64

<table>
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<td>Good</td>
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<td>22</td>
<td>42</td>
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<tr>
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<tr>
<td>Total</td>
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**Table Xb.** Ten year breast cancer survival age 50–64 years

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<tr>
<td>Total</td>
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estrogen treatment for menopause pose fewer risks than combined estrogen–progestogen treatment?

Acknowledgements

The secretarial assistance of Mrs Simonetta Vassallo is gratefully acknowledged.

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Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA and Haslam SZ (1999) Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. J Clin Endocrinol Metab 84,4559–4565.


