Management of risk of breast carcinoma in postmenopausal women

N Biglia, E Defabiani, R Ponzone, L Mariani, D Marenco and P Sismondi

Academic Department of Gynecological Oncology, Mauriziano 'Umberto I' Hospital (Torino) and Institute for
Cancer Research and Treatment (I.RCC) of Candiolo, Turin, Italy

(Requests for offprints should be addressed to P Sismondi; Email: sismondi@mauriziano.it)

Abstract

Breast carcinoma is the most frequent tumor in the female population. Many factors can influence the risk of breast cancer; some of them, such as old age and breast cancer 1/2 (BRCA1/BRCA2) gene mutations, are associated with a fourfold increase in risk. A previous diagnosis of atypical ductal or lobular hyperplasia or having a first-degree relative with a carcinoma are factors associated with a two- to fourfold increase in risk. A relative risk between 1 and 2 is associated with longer exposure to endogenous hormones as a result of early menarche, late menopause and obesity, or with recent and prolonged use of hormone replacement therapy (HRT) or with behavioural factors such as high alcohol and fat intake.

Is it possible to modify breast cancer risk in postmenopausal women? Risk factors related to lifestyle can be changed, even if it is not clear whether modifying these behavioural factors during the postmenopausal period will influence the overall breast cancer risk. For instance, the influence of exogenous hormones throughout life (both oral contraceptives and HRT) should be evaluated according to the individual risk–benefit ratio.

The problem is even more complex for women who carry genetic mutations and for those who have close relatives with breast cancer, who may be candidates for risk reduction strategies. Prophylactic bilateral mastectomy is still controversial, but is frequently offered to or requested by this group of women and may be indicated in BRCA1/BRCA2 carriers. Chemoprevention with tamoxifen and with the new selective estrogen receptor modulators, namely raloxifene, is very promising and deserves a thorough discussion for all high-risk women.

Endocrine-Related Cancer (2004) **11** 69–83

Introduction

Breast carcinoma is the most frequent female tumor in industrialized countries. It is generally less frequent in non-industrialized countries and the lowest rates are recorded among Asiatic populations. Interestingly, in Japan the incidence is very low despite its high degree of industrialization (Hulka & Moorman 2001).

Many of the risk factors for breast cancer are well known and some of them substantially affect a woman's chances of developing the disease. The most important factors are female gender and age. Approximately two out of three breast cancer cases are found after 55 years of age; among women between 75 and 79 years of age the incidence is one case for every 300 women per year (Ries *et al.* 1999). For a long time, the global death rate from breast cancer used to parallel incidence data. In 1990, there were approximately 300 000 breast cancer-related deaths in the world, more than half of which occurred in industrialized countries. At present, the annual death rate varies from 27/100 000 women in northern Europe to 4/100 000 women in Asia (Lacey *et al.* 2002). Since 1987, a 25% decrease in death rates has been recorded in the USA; this is probably due partly to earlier diagnosis and partly to the introduction of adjuvant therapies (Lacey *et al.* 2002).

Research has also been aimed at reducing the incidence of breast cancer, by changing the risk factors whenever possible, or by prescribing chemopreventive drugs. Surgical prophylaxis has been advocated and put in practice for women at very high risk, i.e. those who are carriers of genetic mutations.

Risk factors

The main risk factors for breast cancer are listed in Table 1.

Age

Age is the main risk factor for breast carcinoma. The incidence of the disease increases steadily from 29 up to 40–50 years of age; after the menopause, the risk continues to rise up to 75 years of age in the USA and in northern Europe, while in Japan there is a slow decrease of incidence after 45 years (Hulka & Moorman 2001). Multiple factors such as genetic susceptibility, differences in endogenous hormonal levels, lifestyle and dietary factors, hormone therapy and availability of mammography screening programmes can explain the variations observed in different countries (Fig. 1).

Family history

Family history of breast cancer is another important risk factor. Having a mother or a sister with breast cancer increases the risk of developing the disease by 2 to 3 times. If there is more than one affected relative, if the disease appears at a young age and if it is bilateral or associated with ovarian cancer, the risk increases further (Thompson 1994). Studies on families with high breast cancer incidence have shown that about 5–7% of all breast carcinomas are hereditary. It was previously thought that mutations of two genes, breast cancer 1 (BRCA1) and BRCA2, were associated with a 90% lifetime risk of developing the disease. Further population studies have shown that variants of these two genes have different penetrance. It is currently believed that women who are carriers of BRCA1 and BRCA2 mutations have a 37–85% cumulative risk of developing breast cancer before 70 years of age, as compared with a risk of 10% for the general population (Easton *et al*. 1993, Struewing *et al*. 1996, Fodor *et al*. 1998). BRCA-related tumors generally appear before 50 years of age, although it is not unusual to see patients diagnosed at a later age (Hulka & Moorman 2001).

Mammographic density

Mammographic density is a risk factor for breast cancer in both pre- and postmenopausal women. Based on data from the Breast Cancer Detection Demonstration Project (Byrne *et al*. 1995) and the Canadian National Breast Screening Study (Boyd *et al*. 1995), women with more than 75% of their breast area classified as 'dense' at mammography have an approximately fivefold greater risk of developing breast cancer than women with less than 5% of their breast area classified as dense. Breast density is increased in younger and thinner women and in both pre- and postmenopausal nulliparae. The use of hormone replacement therapy (HRT) in postmenopausal women doubles their chance of having dense breasts at mammography (Sala *et al*. 2000) compared with non-users (odds ratio (OR) 2.48, 95% confidence interval (CI) 1.32–4.61) and this may make early diagnosis more difficult. Consequently, it is still unclear if mammographic density modifications induced by HRT can be used as indicators of breast cancer risk for individual women.

Previous biopsy for benign breast disease

Benign breast disease (BBD) is a very common spectrum of conditions that include a wide range of clinical and histopathological aspects of the mammary gland, the most representative of which are cysts and fibroadenomas. Since most benign breast lumps are neither painful nor progressive and may regress spontaneously, women may be unaware that they carry palpable lumps in their breasts. Typically, women who do not self-examine their breasts have a lower breast cancer awareness. By contrast, women who present with cysts or fibroadenomas in the breasts are those who routinely practice self-examination and are well informed about breast cancer. The former group of women are likely to belong to a lower social class and to have families with no breast cancer cases, while the latter group is likely to include women of a higher social

Table 1 Risk factors for breast cancer (modified from Hulka & Moorman 2001).

RR > 4	RR 2–4	RR < 2
Advanced age	One first-degree affected relative (mother, sister)	Endogenous estrogens (nulliparity, first pregnancy after 30 years old)
BRCA1–BRCA2 genetic mutation	Atypical ductal or lobular hyperplasia	Recent or continuous use of HRT
Two first-degree affected relatives (mother, sister)	Breast exposure to high radiation doses	Lifestyle (smoking, physical activity)
> 75% of dense breast at mammography	High bone density	

RR, relative risk.
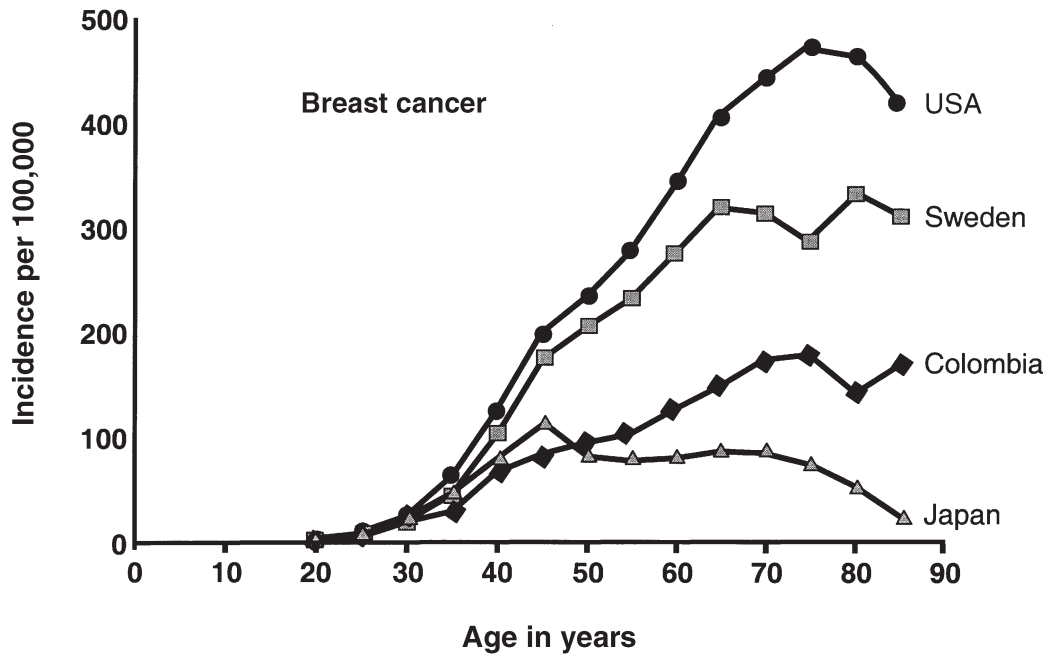
Figure 1 Age-adjusted incidence rates for breast cancer, 1988–1992, in four countries: USA (SEER registries), Sweden, Colombia (Cali) and Japan (Miyagi Prefecture) (modified from Hulka & Moorman 2001).

class or those with a positive family history of breast cancer. As a result, women who undergo biopsies for BBD are likely to be of a higher social class or to have a family history of breast cancer. This explains why the self-diagnosis of a benign lump may be considered as an indirect marker of the presence of established risk factors. Indeed, women who have undergone a breast biopsy for BBDs, independent of the histological outcome, have a relative risk (RR) of developing carcinoma of 1.5–1.8 (Amstrong *et al.* 2000). Only in cases of atypical ductal or lobular hyperplasia does the risk increase to three- to fourfold. It must be emphasized that although the relative risk associated with atypical lesions is high, their incidence is quite low (less than 5% of biopsies for BBD). Finally, women with a previous diagnosis of lobular or ductal carcinoma *in situ* have a relative risk of 8–10 of developing breast cancer as compared with the general population (Dupont & Page 1985).

Ionizing radiation

The exposure of the mammary gland to ionizing radiation is a well-recognized risk factor for breast carcinoma. Studies on populations surviving the nuclear explosions of Hiroshima and Nagasaki have demonstrated an inverse relationship between risk and age at radiation exposure. Furthermore, the risk is dose-dependent and tends to decrease progressively over time (Tokunaga *et al.* 1994). These data were confirmed by studies of infants receiving high radiation doses to reduce the size of the thymus, studies of the repeated use of fluoroscopy for tuberculosis (Hildreth *et al.* 1989, Miller *et al.* 1989) and, more recently, studies of women undergoing radiotherapy for the treatment of Hodgkin's disease (Clemons *et al.* 2000). Although modern mammographic equipment allows delivery of very modest radiation doses (200–400 mrad) to the breast, it is important to assess the radiation-risk side of the risk–benefit equation related to routine screening mammography over many years. Because of the low doses involved in screening mammography, the benefit–risk ratio for older women would still be expected to be large. Conversely, the estimated radiation risk for younger women requires careful assessment of every single risk factor, to identify those women who actually show a favorable risk–benefit ratio, before starting any routine mammography.

Bone density

Many epidemiological studies have shown a positive correlation between bone density and postmenopausal risk of breast carcinoma, probably mediated by the action of endogenous estrogens. Women with high bone density are also those who have a higher risk of developing breast carcinoma, with a relative risk that varies from 2.0 to 3.5 (Cauley *et al.* 1996, Zhang *et al.* 1997, Buist *et al.* 2001). To support this point, it has been observed that women who have had fractures in the last 5 years have a reduced

risk of breast cancer (RR = 0.85-0.55) (Persson *et al.* 1994, Newcomb *et al.* 2001).

Anthropometric variables

The influence of some anthropometric variables, such as height and weight, on the risk of developing breast cancer is still the subject of debate. A weak correlation between height in adulthood and risk of breast carcinoma has been reported in many studies, with RR values for postmenopausal women spanning from 1.3 to 1.9 (Friedenreich 2001). A recent analysis of seven prospective cohort studies reports a RR of 1.07 (CI = 1.03–1.12) for a 5 cm difference in height. Furthermore, women who reach their maximum height after 18 years have a lower risk of developing breast cancer compared with those reaching their maximum height before 13 years (OR = 0.7, 95% CI = 0.5–1.0) (van den Brandt *et al.* 2000). Height is correlated to genetic factors, diet, physical activity, age at menarche and exposure to endogenous estrogens; therefore, one could hypothesize that modifying these factors at a young age could reduce the risk of breast cancer in later years.

Many studies have shown that body weight is directly correlated to breast cancer risk in postmenopausal women; the RR varies, according to the individual studies, from 1.0 to 1.9 and up to 2.2 for patients with a positive family history of breast cancer (Friedenreich 2001). The association between body mass index (BMI) and cancer risk in postmenopausal women is not linear; the risk does not increase further when BMI reaches 28 kg/m^2 (RR = 1.26, 95% CI = 1.09–1.46) (van den Brandt *et al.* 2000). A slight weight gain is associated with an RR of 1.2 in postmenopausal women, whereas the increase is more pronounced for those who gain more weight (RR = 2.3) (Friedenreich 2001). Data retrieved from the Nurses' Health Study confirm a significant association between high BMI and low breast cancer incidence before the menopause, and much weaker association after the menopause. However, a positive relationship between BMI and breast cancer risk was also seen among postmenopausal women provided they never used HRT (RR = 1.59 for BMI > 31 kg/m^2 vs BMI ≤ 20 kg/m^2; 95% CI = 1.09–2.32; $P < 0.001$). In particular, a high BMI at the age of 18 years was found to be associated with a lower breast cancer incidence both before and after the menopause. Weight gain after the age of 18 years was unrelated to breast cancer incidence before the menopause, but was positively associated with breast cancer incidence after the menopause. This positive relationship between risk and weight gain was limited to women who never used postmenopausal hormones; among these women, the RR was 1.99 (95% CI = 1.43–2.76) for a weight gain of more than 20 kg vs unchanged weight ($P < 0.001$) (Huang *et al.* 1997).

Weight loss after the age of 45 only reduces the breast cancer risk in postmenopause in women who had reached their maximum weight before 45 years of age (OR = 0.90, CI = 0.84–0.98 for 5 kg weight loss). In contrast, for women who reach their maximum weight after 45 years of age, a decrease in weight does not modify their risk (OR = 1.00, CI = 0.95–1.05 for 5 kg weight loss). Finally, cyclic variations do not seem to modify the risk of breast cancer in postmenopausal women (Trentham-Dietz *et al.* 2000).

Lifestyle

Dietary fat intake

The association between dietary fat intake and breast cancer risk is highly debated. Although a reduction of circulating estradiol, both in pre- and postmenopausal women, has been observed after the reduction of fat in the diet (Wu *et al.* 1999), more recent epidemiological studies have not shown a correlation between fat intake and the risk of breast cancer (Lee & Lin 2000, Smith-Warner *et al.* 2001, Byrne *et al.* 2002, Horn–Ross *et al.* 2002). Considering the difficulty both in quantifying and qualifying fat intake and in comparing results of observational studies, the Women's Health Initiative in the USA has launched a randomized clinical trial that will allow calculation of the real value of this risk factor (The Women's Health Initiative Study Group 1998).

Alcohol consumption

Most epidemiological studies have highlighted a positive association between alcohol intake and the risk of developing breast carcinoma in both pre- and postmenopausal women, with a RR varying from 1.1 to 4.0 (Singletary & Gapstur 2001). The risk is dose-dependent as demonstrated by the experimental observation that starting from an intake of 60 mg/day, there is a 9% risk increase for every 10 g increase in daily alcohol consumption (Smith-Warner *et al.* 1998). It has also been estimated that about 2% of breast cancers in the USA can be attributed to alcohol consumption (Tseng *et al.* 1999); in Italy this figure rises to 15% (Mezzetti *et al.* 1998).

In postmenopausal women who are not using HRT, serum levels of estradiol and androgens are only slightly increased by a moderate alcohol intake. In women drinkers who take HRT, estradiol concentration is even more increased by alcohol, since it is around 3.3 times higher than that in non-drinkers (Ginsburg 1999).

Phytoestrogens

The incidence of some cancers, including those of the breast, endometrium, prostate and colon, is lower in eastern than in western countries. It has been hypothesized that different dietary habits may explain, at least in part, these differences. Attention has been focused on soy and its derivatives; these represent a fundamental diet component in eastern populations and contain many biologically active substances including isoflavones. Isoflavones are part of the wide phytoestrogen family, natural compounds of vegetable origin endowed with estrogen-like activity. The results of epidemiological studies evaluating the association between soy-rich diets and breast carcinoma are contradictory. Some authors have shown a protective effect only in premenopausal women (Lee *et al.* 1992); others report that the effect is independent of the menopausal status (Wu *et al.* 1996, Torres-Sanchez *et al.* 2000) and yet others do not find any significant effect of soy isoflavones (Horn-Ross *et al.* 2001). A meta-analysis has recently evaluated nine studies (eight case–controls, and one cohort) published in the last 10 years that are characterized by a huge variability both in RR values and in the definition of 'elevated intake of soy'. An analysis of all the data shows only a small risk reduction in women who had an elevated intake of soy. The favourable effect was limited to premenopausal women, while there appeared to be no association in postmenopausal women (Trock *et al.* 2000) (Table 2).

Smoking

No relevant relationship is reported by many studies evaluating the effect of smoking on the risk of breast carcinoma. Women smokers tend to be thinner, are more often infertile, go into earlier menopause and are prone to osteoporosis. All these factors should reduce the risk of breast carcinoma after the menopause. More recent studies have shown that smoking at younger ages (before 16–17 years) increases breast cancer risk by approximately 20%, independent of length of exposure (Baron *et al.* 1996, Marcus *et al.* 2000, Egan *et al.* 2002). The largest case–control study (based on 17 000 breast cancer cases) reports a slight risk increase (RR = 1.17, 95% CI = 0.96–

1.43) for postmenopausal women who started smoking before 16 years of age (Baron *et al.* 1996).

The effect of passive smoke is still debated; some authors report a positive correlation (Lash & Aschengrau 1999, Johnson *et al.* 2000), while others do not find any correlation (Wartenberg *et al.* 2000, Egan *et al.* 2002). A meta-analysis of 11 studies reported a RR of 1.41 (95% CI = 1.14–1.75), but given the available data it is difficult to establish a causal association (Khuder & Simon 2000).

Physical activity

The literature on the relationship between physical activity in the menopause and breast carcinoma is controversial. The problem is that there is no single method for quantifying physical activity and the period of life during which physical activity has a beneficial effect. Some recent data suggest, however, that an increase in physical activity can reduce the breast cancer risk of postmenopausal women (Dirx *et al.* 2001, Friedenreich *et al.* 2001, Lee *et al.* 2001).

Endogenous hormones

The correlation between estrogens and breast carcinoma has been known for a long time. Estrogens promote growth and progression of tumor cells *in vitro*. In women, early menarche and late menopause, and therefore longer exposure of the breast to estrogen, are associated with an increased breast cancer risk, whereas the risk is reduced by an early menopause, either natural or induced (Clemons & Goss 2001).

Women who have had one or more pregnancy and, in particular, if the first pregnancy was before 25 years of age, have a lower breast cancer risk compared with nulliparous women. The protective effect of pregnancy appears after 10–15 years, is maintained for a long time span and is probably the result of modifications of the mammary tissue during pregnancy. As a result, multiparity reduces breast cancer risk during the menopause (Hulka & Moorman 2001).

Conversely, there is a positive relationship between breast cancer risk after the menopause and concentration of estrogen and androgen in the serum and a negative relationship with the concentration of sex hormone binding globulin (The Endogenous Hormone and Breast Cancer Collaborative Group 2002).

Exogenous hormones

Oral contraceptives

A link between the use of oral contraceptives (OCs) and breast cancer risk was thought plausible for many years, despite the inconsistent results of epidemiological studies.

Table 2 Meta-analysis of studies on phytoestrogens and breast cancer risk (eight case controls and one cohort study) (modified from Trock *et al.* 2000).

		OR	CI (95%)
All women	⇓	0.87	0.89–0.96
Premenopausal	⇓	0.80	0.71–0.90
Postmenopausal	⇔	1.01	0.86–1.19
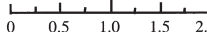
OR, odds ratio; CI, confidence interval.

Table 3 Relative risk (RR) of breast cancer for duration of use within categories of time since last use of HRT (from the Collaborative Group on Hormonal Factors in Breast Cancer 1997).

Duration of use and time since last use	Cases/controls	RR	RR and 99% CI
Never used	12 467/23 568	1.00	
Last use <5 years before diagnosis			
Duration <1 years	368/860	0.99	
Duration 1–4 years	891/2037	1.08	
Duration 5–9 years	588/1279	1.31	
Duration 10–14 years	304/633	1.24	
Duration ≥15 years	294/514	1.56	
Last use ≥ 5 years before diagnosis			
Duration <1 years	437/890	1.12	
Duration 1–4 years	566/1256	1.12	
Duration 5–9 years	151/374	0.90	
Duration ≥10 years	93/233	0.95	

0   0.5   1.0   1.5   2.0

The Collaborative Group on Hormonal Factors in Breast Cancer published a meta-analysis in 1996 on 54 epidemiological studies that showed a slight increase in risk (RR = 1.24, 95% CI = 1.15–1.33) in women taking OCs. The risk remained stable for 10 years after the end of treatment, and then returned to basal values. No correlation was observed to dose, different preparations, length of use, age at first use, age of diagnosis or family history of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1996a,b).

Most of these data consider cancers developing during the pre- or perimenopausal period; the possible correlation between OC use and breast carcinoma in postmenopausal women has still to be elucidated. Two cohort studies have shown that the RR is almost doubled in women with breast carcinoma diagnosed after 55 years and who had previously used OCs for long periods (Schuurman *et al.* 1995, Van Hoften *et al.* 2000).

Evidence is insufficient to give a conclusive opinion on the risk–benefit relationship of the ever-increasing use of OCs for treating premenopausal symptoms. A recent study showed no risk increase for women between 45 and 64 years of age who were taking OCs or had taken them in the past. These data are reassuring, but the number of women (40 cases, 26 controls) who used OCs over 45 years of age is too small to draw definite conclusions (Marchbanks *et al.* 2002).

The actual role of OC use in women with a positive family history or in carriers of BRCA1 and BRCA2 gene mutations is still to be investigated. A small study shows a RR of 3 for women with a first-degree relative (sister or mother) with breast cancer who took OCs before 1975 (i.e. with ethinylestradiol doses over 50 μg) (Grabrick *et al.* 2000). Another two studies, although small, found the same correlation for women carrying BRCA1 mutations (Ursin *et al.* 1997, Heimdal *et al.* 2002).

Hormone replacement therapy

There are over 50 epidemiological studies available today on HRT and breast tumors. Overall, the data are reassuring regarding short- to medium-term therapies (up to 5 years), while long-term HRT slightly increases breast cancer risk. The meta-analyses carried out in the last decade indicate a risk increase in the order of 20–30% for long-term treatments (over 8–15 years). The collaborative study that collected over 90% of the epidemiological data available in 1997 highlights how duration of treatment and time elapsed since last HRT use are crucial factors for determining the magnitude of the risk (Table 3). The risk increase for each year of HRT is very limited (RR = 1.023), and is slightly lower than that associated with each year of physiological ovarian activity in women who have never used HRT (RR = 1.028). Furthermore, it appears to be limited to slim women. Long-term HRT is responsible for only a moderate excess in breast tumors over those expected between the ages of 50 and 70 in the untreated population: 2 cases for every 1000 women taking HRT for 5 years from the age of 50 years (47 observed instead of 45 expected), 6 cases if HRT is used for 10 years and 12 cases if HRT is used for 15 years (Collaborative Group on Hormonal Factors in Breast Cancer 1997) (Fig. 2). Data from the recently published Women's Health Initiative (WHI) Randomized Controlled Trial are consistent with previous observations, reporting a RR of 1.26 (95% CI = 1.00–1.59) after 5 years treatment with combined HRT, which translates into an excess of eight breast carcinomas for 10 000 women per year of use (Writing Group for the Women's Health Initiative Investigators 2002).

The most debated issue today is the possible impact on breast tumor risk of the different treatment modalities, i.e. administration route, dosage and compound used.
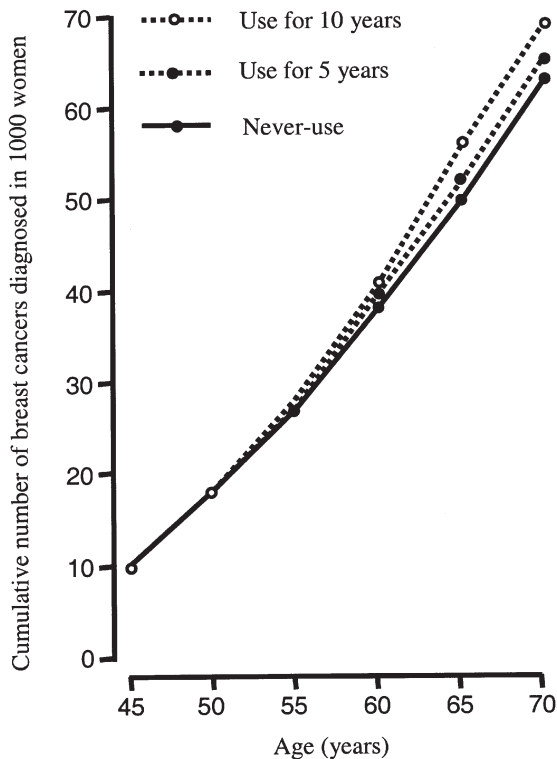
Figure 2 Estimated cumulative number of breast cancer cases diagnosed in 1000 women in each of the following groups: those who had never used HRT, those who had used HRT for 5 years and those who had used HRT for 10 years (from the Collaborative Group on Hormonal Factors in Breast Cancer 1997).

Different preparations have different metabolic and pharmacodynamic characteristics that could be important in modulating the proliferative effect of estrogens on the mammary gland. A positive relationship between breast cancer risk and estrogen dosage cannot be substantiated by data in the literature. Moreover, the majority of studies refer to oral estrogens; there are still limited epidemiological data on transdermal estrogens or nasal spray formulations. Recent studies suggest that the addition of a progestogen further increases the risk associated with estrogen-only regimens, independent of the drug and of the treatment scheme (Magnusson *et al*. 1999, Ross *et al*. 2000, Schairer *et al*. 2000).

Almost all epidemiological studies suggest that the prognosis is better for breast cancer patients who had previously used HRT or who were taking HRT at the time of diagnosis (Fig. 3). These data seem to suggest the existence of a favourable biological effect of hormonal therapy which could selectively induce the growth of less aggressive tumors. Nevertheless, it cannot be excluded that the better prognosis of HRT users derives from earlier diagnosis as a result of heightened clinical and radiological surveillance (Gapstur *et al*. 1999, Stallard *et al*. 2000).

At present, there is controversy about the use of HRT in women who are carriers of BRCA1 or BRCA2 gene mutations, especially for those who undergo premature menopause following prophylactic bilateral oophorectomy (Narod 2001). Some authors believe that the administration of exogenous estrogens should not significantly influence the breast cancer risk of BRCA carriers since they are more likely to develop undifferentiated and estrogen receptor negative tumors.

Management of the risk in postmenopausal women

Various factors can reduce the risk of breast carcinoma in postmenopausal women such as preventive surgery, chemoprevention and changes in lifestyle.

Prophylactic surgery

Prophylactic mastectomy is considered a potential approach to reduce the risk of breast carcinoma in women carriers of BRCA gene alterations. Recent studies report a 90% risk reduction after bilateral mastectomy in a group of carriers of BRCA1 and BRCA2 gene mutations, although breast cancer might still develop because of the presence of residual mammary tissue (Meijers-Heijboer *et al*. 2001). Prophylactic mastectomy, whether or not followed by reconstructive surgery, must be discussed case by case with the patient, who should be well informed about the risks related to the surgical operation, the psychological changes it may bring and the incomplete protection it provides. Nevertheless, several studies showed that proven BRCA mutation carriers did not express any regret if the prophylactic mastectomy followed adequate counselling nor did they report sexual function changes after surgery; conversely their fear of cancer was effectively relieved (Stefanek *et al*. 1995, Klijn *et al*. 1997, Borgen *et al*. 1998). Moreover, in another two studies, 35 and 17% of proven carriers of BRCA1 mutation declared an interest in prophylactic mastectomy, and 73 and 33% in prophylactic oophorectomy, shortly after disclosure of DNA-test results (results from Lerman *et al*. 1996 and Lynch *et al*. 1997 respectively). Women carriers of BRCA mutations must be informed that bilateral oophorectomy will normally also prevent ovarian cancer. Although salpingo-oophorectomy is highly effective, protection is not complete as peritoneal carcinomatosis may develop in peritoneal tissues sharing a common embryologic origin from the coelomic epithelium or micrometastases may have already been present before surgery. Furthermore, in premenopausal women, surgical castration reduces the risk of breast carcinoma as much as it lowers estrogen levels. The severe impact of an early
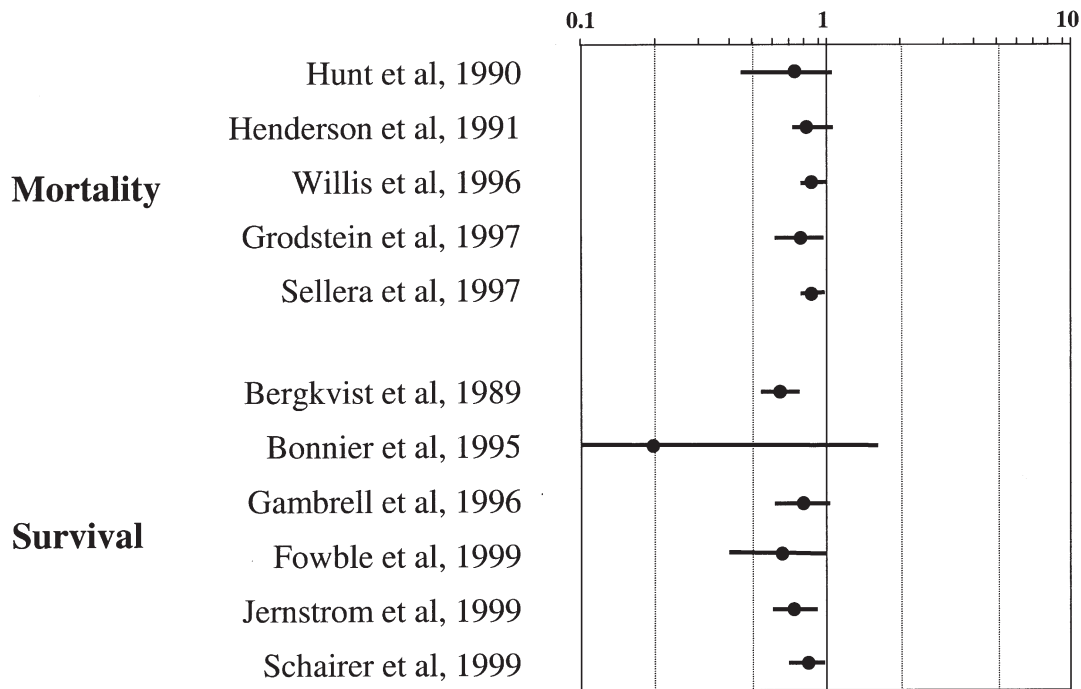
Figure 3 Risk estimates for death from breast cancer and breast cancer survival: ever users compared with never users of HRT (estrogen plus progestin) (modified from Bush *et al.* 2001).

menopause on quality of life should be considered and discussed with the patient.

Chemoprevention

In 1998, results from the National Surgical Adjuvant Breast and Bowel Project-Breast Cancer Prevention Trial (NSABP-BCPT) (Fisher *et al.* 1998) led to Food and Drug Administration approval of the use of tamoxifen for the chemoprevention of breast cancer in healthy women at high risk. This study showed a 50% risk reduction of invasive carcinoma and ductal carcinoma *in situ* (DCIS) in the group treated for 5 years with 20 mg tamoxifen/day as compared with controls. This reduction was observed for all age groups and was significant for women with previous diagnosis of lobular carcinoma *in situ* (LCIS) and atypical hyperplasia or in women with a family history of breast cancer; the protective effect was limited to tumors with positive estrogen receptors. Among the favorable events, a 19% reduction in osteoporotic fractures was reported in the group taking tamoxifen. Incidence of myocardial infarction was the same in the two groups, but there was an excess of deep venous thrombosis in postmenopausal women and an increased risk of endometrial carcinoma (RR = 2.5) in the treated group compared with the placebo group.

Results of the BCPT study were not confirmed by two European studies (Powles *et al.* 1998, Veronesi *et al.*

1998). Many reasons can explain this discrepancy: the small numbers of events (70 in the English study, 49 in the Italian study), different eligibility criteria, the higher proportion of carcinomas with negative estrogen receptors in the European studies as compared with the BCPT trial and the high drop-out rate. Furthermore, women taking HRT were excluded from the BCPT trial, while 41% of women in the UK study and 14% in the Italian study were taking hormones for menopausal symptoms, together with tamoxifen. Veronesi *et al.* 1998 observed a significant reduction in number of breast cancers in the group treated with tamoxifen compared with the placebo group (6 cases vs 17) only in the subgroup of women who had also taken HRT. This encouraged Italian researchers to begin a new trial to evaluate the efficacy of tamoxifen at low doses (5 mg/day) in preventing breast carcinoma in healthy postmenopausal women treated with every kind of HRT for problems related to the menopause (HRT Opposed to Low-dose Tamoxifen Study (HOT Study)) (Veronesi *et al.* 2002). The IBIS trial confirmed the effectiveness of tamoxifen in reducing the incidence of breast cancer in healthy women. The investigators found a reduction of 32% of invasive breast cancers and DCIS in the tamoxifen group; interestingly they also reported that women taking HRT and tamoxifen had fewer unfavorable endometrial and

Table 4 The use of tamoxifen for the reduction of breast cancer risk (modified from Vogel *et al.* 2001)

Women who may consider the use of tamoxifen for risk reduction
History of lobular carcinoma *in situ*
History of ductal carcinoma *in situ*
History of atypical ductal or lobular hyperplasia
Premenopausal women with mutations in either the BRCA1 or BRCA2 genes or other predisposing genetic mutations
Women aged > 35 years with Gail model 5-year probability of breast cancer > 1.66%

cardiovascular events than those who had been treated with tamoxifen alone (Cuzick 2001).

There is controversy on the efficacy of tamoxifen in reducing breast cancer incidence in women with BRCA mutations. A recent case–control study has shown that adjuvant tamoxifen is associated with a 50% reduction of contralateral carcinoma in breast cancer patients with BRCA1 and BRCA2 gene mutations (Narod *et al.* 2000). Using a simulated cohort, Grann *et al.* 2000 estimated that a 30-year-old woman with gene mutations can prolong survival by 0.9 years if she undergoes bilateral ovariectomy, by 3.4 years if she undergoes bilateral mastectomy, and by 4.3 years if she undergoes both procedures compared with a woman who simply undergoes clinical surveillance. A 5-year tamoxifen treatment, even if started late, between 40 and 50 years, extends survival by 1.6 years, with fewer side-effects and a better quality of life compared with early castration or bilateral mastectomy (Grann *et al.* 2000).

Before starting chemoprevention it is important to evaluate the individual absolute breast cancer risk over a definite period of time. To this aim, the Gail model is a widely used tool, although it has not been validated in European populations. Once the risk is assessed, several other factors such as age, co-morbidities and factors that may increase tamoxifen side-effects and toxicity should be thoroughly considered. Indications for use of tamoxifen are listed in Table 4 (Vogel 2001).

As for the onset of side-effects, an overview of all tamoxifen prevention trials reported a 38% reduction in breast cancer incidence along with an increase of venous thromboembolic events (RR = 1.9) and endometrial cancers, which were mostly of low or intermediate grade and stage I (consensus relative risk = 2.4). Nevertheless, there was no increase in death from endometrial cancer, or cardiac (i.e. myocardial infarction and transitory ischemia) and vascular events except for pulmonary embolism (6 vs 2 in the tamoxifen prevention trials). Therefore, particular attention should be paid when using tamoxifen in women with a positive history for deep vein thrombosis, pulmonary embolism, myocardial infarction and transitory ischemia or in the presence of factors that may increase the risk of developing endometrial cancer.

In conclusion, the data available from all the breast cancer prevention trials are very promising and tamoxifen should be considered as a preventive drug to be prescribed in clinical practice in women with a higher than average risk of breast cancer, for whom it has a more favourable risk–benefit ratio.

Retinoids, natural or synthetic vitamin A-like substances, have shown anti-tumor activity in animal models, but clinical results have proved disappointing. In one study (Veronesi *et al.* 1999), breast cancer patients taking fenretinide, one of the less toxic retinoids, had no reduction in risk of contralateral neoplasia as compared with controls. *Post-hoc* analyses, however, showed a possible favourable effect in preventing breast carcinoma in premenopausal women (RR = 0.66, 95% CI = 0.41–1.079) and a non-significant opposite effect in postmenopausal patients (RR = 1.32, 95% CI = 0.82–2.15). In the light of these data, fenretinide cannot be prescribed as a chemopreventive agent for breast carcinoma.

A wide group of compounds known as selective estrogen receptor modulators (SERMs) has been extensively studied. SERMs are able to bind to and activate estrogen receptors (ERs) with tissue-specific effects, acting as estrogen agonists or antagonists according to the organ, tissue and physiological context. Raloxifene has been widely studied; like tamoxifen, it is a competitive ER antagonist in breast tissue. It also acts as a competitive antagonist in uterine tissue and as an agonist in bone. In addition, raloxifene lowers total and low-density lipoprotein cholesterol levels, but does not increase high-density lipoprotein cholesterol levels as estrogen does.

The suggestion to use raloxifene as a chemopreventive agent for breast cancer arose from the safety data analysis of the MORE trial (Cummings *et al.* 1999), a randomized, double-blind study where the primary aim was to evaluate the effect of raloxifene treatment on fractures in postmenopausal women with osteoporosis. The study showed the effectiveness of raloxifene in reducing the incidence of vertebral fractures and in increasing bone mineral density (Ettinger *et al.* 1999). Furthermore, after an average treatment period of 36 months, raloxifene was also found to reduce by 90% (RR = 0.10, 95% CI = 0.04–0.24) the risk of developing ER-positive tumors (Fig. 4) (Cummings *et al.* 1999). These results were subsequently confirmed after 4 years of therapy, with an 84% reduction of ER-positive breast carcinomas (RR = 0.16, 95% CI = 0.09–0.30) (Cauley *et al.* 2001). In a further analysis of the MORE trial data, Cummings *et al.* 2002 showed that raloxifene reduced breast cancer incidence by 76% (95% CI = 53%–88%) in the group of women with high levels of endogenous estrogens, while
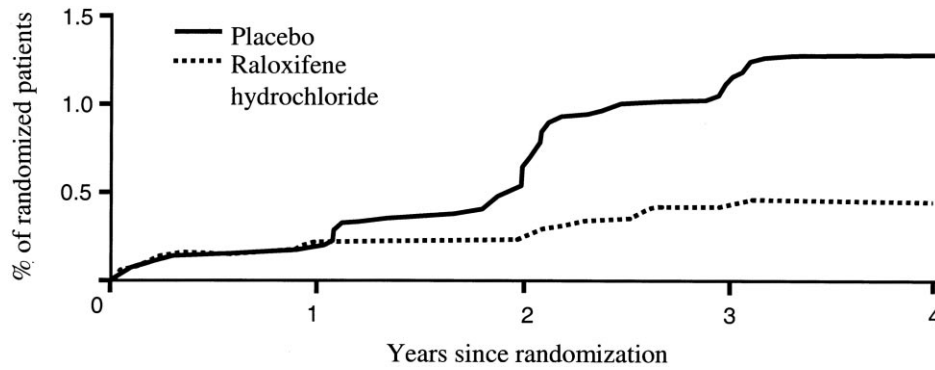
Figure 4 Cumulative incidence of all breast cancers in placebo and raloxifene-treated groups (modified from Cummings *et al.* 1999).

the risk of breast cancer did not change in the group of women with low endogenous estrogen levels. This finding led the authors to suggest that high estrogen concentrations are likely to stimulate breast cancer so that a greater impact of raloxifene is expected as compared with patients with low levels of endogenous estrogens.

Raloxifene is usually well tolerated and side-effects are limited to a higher frequency of hot flushes, cramps of the lower limbs and fluid retention. The most significant problem is the increased incidence of deep venous thrombosis and pulmonary embolism, similar to that observed with HRT and tamoxifen. Raloxifene has also elicited new cases of, or worsened, diabetes mellitus but it does not appear to increase the risk of endometrial carcinoma (Cummings *et al.* 2002). In a further analysis of the MORE trial data, the number of cardiovascular events (defined as all coronary and cerebrovascular events) did not increase after 1 year of raloxifene treatment. After 4 years, raloxifene also proved to be effective in reducing the risk of cardiovascular disease, at least in a series of 1035 high-risk patients (RR = 0.60, 95% CI = 0.38–0.95) (Barrett-Connor *et al.* 2002).

Based on these promising data, a new trial of chemoprevention comparing tamoxifen and raloxifene in high-risk women has been designed (STAR trial). This trial will allow a comparison of the benefits of these two drugs. An indirect comparison relying on the data obtained in the BCPT and MORE trials cannot be made as the populations in the two studies are completely different. In the American study women with a high risk of breast cancer were included and the power of the study derives from the large number of events (264 invasive tumors and 104 DCIS). In contrast, the MORE trial was carried out on women with osteoporosis and thus at lower risk of breast cancer. In the STAR trial, 22 000 postmenopausal women at high risk of breast cancer will be compared, but data will not be available for 7 years. As a consequence, despite the favourable data of

the MORE trial, raloxifene cannot be currently prescribed as a chemopreventive drug for breast cancer.

Modification in lifestyle

The association between changes in lifestyle and modification of breast cancer risk has yet to be confirmed. High alcohol intake (more than three glasses a day) is the only dietary component significantly related to the risk of breast cancer. Other components, including fat intake, do not show any significant correlation with the risk of the disease. Similarly, there are no clinical data to assert that an increased intake of phytoestrogens may cause a reduction in breast cancer risk.

Although available data are limited, it is possible to recommend that postmenopausal women do not increase their weight as, in this particular period in life, this may be associated with a modest increase of breast cancer incidence. Therefore, correct dietary habits and regular physical activity, besides improving general health, may reduce the risk of developing breast cancer in postmenopausal women.

Smoking after the menopause does not seem to increase the risk of breast cancer; however, the benefits of giving up, as far as cardiovascular and lung disease risk are concerned, are enough to advise against continuing such activity.

Conclusions

The prevalence of breast carcinoma after the menopause is expected to increase in the future. Is it possible to give indications aimed at modifying the risk of breast cancer in this age group? Is it worthwhile to suggest a change in lifestyle? It has been calculated that about 10–16% of all breast cancers in postmenopausal women can be attributed to obesity and weight increase (Mezzetti *et al.* 1998). Women should, therefore, be encouraged not to increase their weight during the menopause, and to lose weight if

they are over their ideal size. Losing weight helps to lower breast cancer risk only for postmenopausal women who reached their maximum weight before 45 years, but has no impact if their weight increased after this age. In order to prevent obesity, an increase of physical activity and a reduction in caloric intake is recommended. At present, the only suggestion that can be made regarding the type of diet, is to decrease alcohol intake if it is currently more than one glass a day. Abstinence or drinking less than one glass a day are not necessarily advisable because of the beneficial effect that moderate alcohol intake has on the risk of cardiovascular disease, which represents the main cause of morbidity and mortality in women during the menopause. Some preliminary data also suggest that a higher emphasis should be placed on these recommendations for women on HRT. There are currently no scientific grounds to suggest that other dietary modifications in postmenopausal women, such as lowering fat intake or increasing the intake of foods rich in soy, can alter the risk of breast cancer.

The association between HRT use and breast cancer risk is not yet completely clear, but it is biologically reasonable that long-term treatments may influence, at least modestly, the incidence of the disease. Therefore, the risk–benefit ratio in cases of long-term treatments must be evaluated for each individual woman.

The possibility of modifying the risk of breast cancer in women at high risk because of genetic susceptibility, family history or previous atypical hyperplasia is today one of the most important fields of research. Prophylactic surgery and chemoprevention should be considered on a case-by-case basis taking into account the risk–benefit profile, and must be thoroughly discussed with each woman. In the USA, tamoxifen is registered as a preventive drug for breast cancer in healthy women, whereas in Europe this indication is still the subject of clinical research. Conversely, tamoxifen remains a mainstay in the treatment of advanced breast cancer both in the adjuvant and advanced settings. Therefore, the use of tamoxifen for breast cancer prevention in healthy postmenopausal women, outside controlled clinical trials, should be taken into consideration after a careful evaluation of risks and benefits; these should include absolute breast cancer risk and the presence of risk factors for endometrial carcinoma and cardiovascular and thromboembolic diseases. Studies are underway to evaluate the efficacy of low-dose tamoxifen with HRT for the prevention of breast carcinoma in healthy postmenopausal women. Although available data show an antagonistic estrogen action, raloxifene cannot be used to reduce the risk of breast carcinoma and should be prescribed at present only as a preventive measure and for the treatment of osteoporosis.

References

Armstrong K, Eisen A & Weber B 2000 Assessing the risk of breast cancer. *New England Journal of Medicine* **342** 564–571.

Baron JA, Newcomb PA, Longnecker MP, Mittendorf R, Storer BE, Clapp RW, Bogdan G & Yuen J 1996 Cigarette smoking and breast cancer. *Cancer Epidemiology Biomarkers and Prevention* **5** 399–403.

Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, Rautaharju P & Harper KD 2002 Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four-years results from MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *Journal of the American Medical Association* **287** 847–857.

Bergkvist L, Adami HO, Persson I, Bergstrom R & Krusemo UB 1989 Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *American Journal of Epidemiology* **130** 221–228.

Bonnier P, Romain S, Giacalone PL, Laffargue F, Martin PM & Piana L 1995 Clinical and biological prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. *Obstetrics and Gynecology* **85** 11–17.

Borgen PI, Hill AD, Tran KN, Van Zee KJ, Massie MJ, Payne D & Biggs CG 1998 Patients regrets after bilateral prophylactic mastectomy. *Annals of Surgical Oncology* **7** 603–606.

Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL & Yaffe MJ 1995 Quantitative classification of mammographic densities and breast cancer risk: results from Canadian National Breast Cancer Screening Study. *Journal of the National Cancer Institute* **87** 670–675.

Buist DS, LaCroix AZ, Barlow WE, White E & Weiss NS 2001 Bone mineral density and breast cancer risk in postmenopausal women. *Journal of Clinical Epidemiology* **54** 417–422.

Bush TL, Whiteman M & Flaws JA 2001 Hormone replacement therapy and breast cancer: a qualitative review. *Obstetrics and Gynecology* **98** 498–508.

Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R & Haile R 1995 Mammographic features and breast cancer risk: effects with time, age, and menopause status. *Journal of the National Cancer Institute* **87** 1622–1629.

Byrne C, Rockett H. & Holmes MD 2002 Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. *Cancer Epidemiology Biomarkers and Prevention* **11** 261–265.

Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS & Cummings SR 1996 Bone mineral density and risk of breast cancer in older women. The Study of Osteoporotic Fractures. Study of Osteoporotic Fractures Research Group. *Journal of the American Medical Association* **276** 1404–1408.

Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW *et al.* 2001 Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple Outcomes of Raloxifene

Evaluation. *Breast Cancer Resources and Treatment* **65** 125–134.

Clemons M & Goss P 2001 Estrogen and the risk of breast cancer. *New England Journal of Medicine* **344** 276–285.

Clemons M, Loijens L & Goss P 2000 Breast cancer risk following irradiation for Hodgkin's disease. *Cancer Treatment Reviews* **26** 291–302.

Collaborative Group on Hormonal Factors in Breast Cancer 1996*a* Breast cancer and hormonal contraceptives: collaborative study of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* **347** 1713–1727.

Collaborative Group on Hormonal Factors in Breast Cancer 1996*b* Breast cancer and hormonal contraceptives: further results. *Contraception* **54** (Suppl. 3) 1–106.

Collaborative Group on Hormonal Factors in Breast Cancer 1997 Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 10 8411 women without breast cancer. *Lancet* **350** 1047–1059.

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M *et al.* 1999 The effect of raloxifene on the risk of breast cancer on postmenopausal women: results from the MORE randomized trial. *Journal of the American Medical Association* **281** 2189–2197.

Cummings SR, Duong T, Kenyon E, Cauley JA, Whitehead M & Krueger KA 2002 Serum estradiol level and risk of breast cancer during treatment with raloxifene. *Journal of the American Medical Association* **287** 216–220.

Cuzick J 2001 A brief review of the International Breast Cancer Intervention Study (IBIS), the other current breast cancer prevention trials, and proposals for future trials. *Annals of New York Academy of Sciences* **949** 122–133.

Dirx MJ, Voorrips LE, Goldbohm RA & Van Der Brandt PA 2001 Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. *Cancer* **92** 1638–1649.

Dupont WD & Page DL 1985 Risk factors for breast cancer in women with proliferative breast disease. *New England Journal of Medicine* **312** 146–151.

Easton DF, Bishop DT, Ford D & Crockford GP 1993 Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *American Journal of Human Genetics* **52** 678–701.

Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willet WC & Colditz GA 2002 Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* **13** 138–145.

Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J *et al.* 1999 Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *Journal of the American Medical Association* **282** 637–645.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J *et al.* 1998 Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* **90** 1371–1388.

Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, Brower ST & Eng CM 1998 Frequency and carrier risk associated with common BRCA 1 and BRCA 2 mutations in Ashkenazi Jewish breast cancer patients. *American Journal of Human Genetics* **63** 45–51.

Fowble B, Hanlon A, Freedman G, Patchefsky A, Kessler H, Nicolaou N, Hoffman J, Sigurdson E, Boraas M & Goldstein L 1999 Postmenopausal hormone replacement therapy: Effect on diagnosis and outcome in early-stage invasive breast cancer treated with conservative surgery and radiation. *Journal of Clinical Oncology* **17** 1680–1688.

Friedenreich CM 2001 Review of anthropometric factors and breast cancer risk. *European Journal of Cancer Prevention* **10** 15–32.

Friedenreich CM, Courneya KS & Bryant HE 2001 Influence of physical activity in different age and life periods on the risk of breast cancer. *Epidemiology* **12** 604–612.

Gambrell RD Jr 1996 Hormone replacement therapy and breast cancer risk. *Archives of Family Medicine* **5** 341–348.

Gapstur SM, Morrow M & Sellers TA 1999 Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Heatlth Study. *Journal of the American Medical Association* **281** 2091–2097.

Ginsburg ES 1999 Estrogen, alcohol, and breast cancer risk. *Journal of Steroid Biochemistry and Molecular Biology* **69** 299–306.

Grabrick DM, Hartmann LC, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM, Olson JE, Couch FJ, Anderson KE, Pankratz VS & Sellers TA 2000 Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *Journal of the American Medical Association* **284** 1791–1798.

Grann VR, Jacobson JS, Whang W, Hershman D, Heitjan DF, Antman KH & Neugut AI 2000 Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2 positive women: a decision analysis. *Cancer Journal from Scientific American* **6** 13–20.

Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, Rosner B, Fuchs C, Hankinson SE, Hunter DJ, Hennekens CH & Speitzer FE 1997 Postmenopausal hormone therapy and mortality. *New England Journal of Medicine* **336** 1769–1775.

Heimdal K, Skovlund E & Moller P 2002 Oral contraceptives and risk of familial breast cancer. *Cancer Detection and Prevention* **26** 23–27.

Henderson BE, Paganini-Hill A & Ross RK 1991 Decreased mortality in users of estrogen replacement therapy. *Archives of Internal Medicine* **151** 75–78.

Hildreth NG, Shore RE & Dvoretsky PM 1989 The risk of breast cancer after irradiation of the thymus in infancy. *New England Journal of Medicine* **321** 1281–1284.

Horn-Ross PL, John EM, Lee M, Stewart SL, Koo J, Sakoda LC, Shiau AC, Goldstein J , Davis P & Perez-Stable EJ 2001 Phytoestrogen consumption and breast cancer risk in a

multiethnic population: the Bay Area Breast Cancer Study. *American Journal of Epidemiology* **154** 434–441.

Horn-Ross PL, Hoggatt KJ, West DW, Krone MR, Stewart SL, Anton H, Bernstei CL, Deapen D, Peel D, Pinder R *et al.* 2002 Recent diet and breast cancer risk: the California Teachers Study (USA). *Cancer Causes Control* **13** 407–415.

Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE & Willett WC 1997 Dual effects of weight and weight gain on breast cancer risk. *Journal of the American Medical Association* **278** 1407–1411.

Hulka BS & Moorman PG 2001 Breast cancer: hormones and other risk factors. *Maturitas* **38** 103–116.

Hunt K, Vessey M & McPherson K 1990 Mortality in a cohort of long-term users of hormone replacement therapy: An updated analysis. *British Journal of Obstetrics and Gynaecology* **97** 1080–1086.

Jernstrom H, Frenander J, Ferno M & Olsson H 1999 Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. *British Journal of Cancer* **80** 1453–1458.

Johnson KC, Hu J & Mao Y 2000 Passive and active smoking and breast cancer risk in Canada, 1994–1997. The Canadian Cancer Registries Epidemiology Research Group. *Cancer Causes and Control* **11** 211–221.

Khuder SA & Simon VJ Jr 2000 Is there an association between passive smoking and breast cancer? *European Journal of Epidemiology* **16** 1117–1121.

Klijn JGM, Janin N, Cortes-Funes H & Colomer R 1997 Should prophylactic surgery be used in women at high risk of breast cancer? *European Journal of Cancer* **33** 2149–2159.

Lacey JV Jr, Devesa SS & Brinton LA 2002 Recent trends in breast cancer and mortality. *Environmental and Molecular Mutagenesis* **39** 82–88.

Lash TL & Aschengrau A 1999 Active and passive cigarette smoking and the occurence of breast cancer. *American Journal of Epidemiology* **149** 5–12.

Lee HP, Gourley L, Duffy SW, Esteve J, Lee J & Day NE 1992 Risk factors for breast cancer by age and menopausal status: a case–control study in Singapore. *Cancer Causes and Control* **3** 313–322.

Lee IM, Rexrode KM, Cook NR, Hennekens CH & Burin JE 2001 Physical activity and breast cancer risk: the Women's Health Study (United States). *Cancer Causes and Control* **12** 137–145.

Lee MM & Lin SS 2000 Dietary fat and breast cancer. *Annual Review of Nutrition* **20** 221–248.

Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, Gold K, Trock B, Main D, Lynch J *et al.* 1996 BRCA1 testing in families with hereditary breast–ovarian cancer: a prospective study of patient decision making and outcomes. *Journal of the American Medical Association* **275** 1885–1892.

Lynch HT, Lemon SJ, Durham C, Tinley ST, Connolly C, Lynch SF, Surdam J, Orinion E, Slominski-Caster S, Watson P *et al.* 1997 A descriptive study of BRCA1 testing and reactions to disclosure of test results. *Cancer* **79** 2219–2228.

Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO & Persson I 1999 Breast cancer risk following long-term oestrogen and oestrogen-progestin-replacement therapy. *International Journal of Cancer* **88** 339–344.

Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, Bernstein L, Malone KE, Ursin G, Strom BL *et al.* 2002 Oral contraceptives and the risk of breast cancer. *New England Journal of Medicine* **346** 2025–2032.

Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD & Qaqish B 2000 The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes and Control* **11** 271–278.

Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, Bartels CC, Verhoog LC, van den Ouweland AM, Niermeijer MF *et al.* 2001 Breast cancer risk following long-term oestrogen and oestrogen–progestin-replacement therapy. *International Journal of Cancer* **88** 339–344.

Mezzetti M, La Vecchia C, De Carli A, Boyle P, Talamini R & Franceschini S 1998 Population attributable risk for breast cancer: diet, nutrition, and physical exercise. *Journal of the National Cancer Institute* **90** 389–394.

Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, Risch HA & Preston DL 1989 Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. *New England Journal of Medicine* **321** 1285–1289.

Narod SA 2001 Hormonal prevention of hereditary breast cancer. *Annals of the New York Academy of Sciences* **952** 36–43.

Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, Stoppa-Lyonnet D, Lerman C, Pasini B, de los Rios P *et al.* 2000 Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case–control study. *Lancet* **356** 1876–1881.

Newcomb PA, Trentham-Dietz DA, Egan KM, Titus-Ernstoff L, Baron JA, Storer BE, Willet WC & Stampfer MJ 2001 Fracture history and risk of breast cancer and endometrial cancer. *American Journal of Epidemiology* **153** 1071–1078.

Persson I, Adami HO, McLaughlin JK, Naessen T & Fraumeni JF Jr 1994 Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). *Cancer Causes and Control* **5** 523–528.

Powles T, Eeles R, Asheley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J & Davey J 1998 Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* **352** 98–101.

Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg LX & Edwards BK 1999 *SEER Cancer Statistics Review, 1973–1996*. Bethesda, MD: National Cancer Institute.

Ross RK, Paganini-Hill A, Wan PC & Pike MC 2000 Effect of hormone replacement therapy on breast cancer risk: estrogens versus estrogen plus progestin. *Journal of the National Cancer Institute* **92** 328–332.

Sala E, Warren R, Mc Cann J, Duffy S, Luben R & Day N 2000 High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case–control study. *International Journal of Epidemiology* **29** 629–636.

Schairer C, Gail M, Byrne C, Rosenberg PS, Sturgeon SR, Brinton LA & Hoover RN 1999 Estrogen replacement therapy and breast cancer survival in a large screening study. *Journal of the National Cancer Institute* **91** 264–270.

Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L & Hoover R 2000 Menopausal estrogen and estrogen–progestin replacement therapy and breast cancer risk. *Journal of the American Medical Association* **283** 485–491.

Schuurman AG, van den Brandt PA & Goldbohm RA 1995 Exogenous hormone use and risk of postmenopausal breast cancer: results from the Netherlands Cohort Study. *Cancer Causes and Control* **6** 416–424.

Sellera TA, Mink PJ, Cerhan JR, Zheng W, Anderson K, Kushi LH & Folsom AR 1997 The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Annals of Internal Medicine* **127** 973–980.

Singletary KW & Gapstur SM 2001 Alcohol and breast cancer. Review of epidemiologic and experimental evidence and potential mechanism. *Journal of the American Medical Association* **286** 2143–2151.

Smith-Warner S, Spiegelman D, Yaun SS, Van Den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR *et al.* 1998 Alcohol and breast cancer in women: a pooled analysis of cohort studies. *Journal of the American Medical Association* **279** 535–540.

Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, Van Den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S *et al.* 2001 Types of dietary fat and breast cancer: a pooled analysis of cohort studies. *International Journal of Cancer* **92** 767–774.

Stallard S, Litherland JC, Cordiner C, Dobson HM, George WD, Mallon EA & Hole D 2000 Effect of hormone replacement therapy on the pathological stage of breast cancer: population based, cross sectional study. *British Medical Journal* **320** 348–349.

Stefanek ME, Helzlsouer KJ, Wilcox PM & Houn F 1995 Predictors of and satisfaction with bilateral prophylactic mastectomy. *Preventive Medicine* **24** 412–419.

Struewing JP, Tarone RE, Brody LC, Li FP & Boice JD Jr 1996 BRCA1 mutations in young women with breast cancer. *Lancet* **347** 1493.

The Endogenous Hormones and Breast Cancer Collaborative Group 2002 Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *Journal of the National Cancer Institute* **94** 606–616.

The Women's Health Initiative Study Group 1998 Design of the Women's Health Initiative clinical trial and observational study. *Controlled Clinical Trials* **19** 61–109.

Thompson WD 1994 Genetic epidemiology of breast cancer. *Cancer* **74** (Suppl 1) 279–287.

Tokunaga M, Land CE, Tokuoka S, Nishimori I, Soda M & Akiba S 1994 Incidence of female breast cancer among atomic bomb survivors,1950–1985. *Radiotherapy Resources* **138** 209–223.

Torres-Sanchez L, Lopez Carrillo L, Lopez-Cervantez M, Rueda-Neria C & Wolff MS 2000 Food sources of phytoestrogens and breast cancer risk in Mexican women. *Nutrition and Cancer* **37** 134–139.

Trentham-Dietz A, Newcomb PA, Egan KM, Titus-Ernstoff L, Baron JA, Storer BE, Stampfer M & Willet WC 2000 Weight change and risk of postmenopausal breast cancer (United States). *Cancer Causes Control* **11** 533–542.

Trock B, Butler W, Clarke R & Hilakivi-Clarke L 2000 Meta-analysis of soy intake and breast cancer risk. *Journal of Nutrition* **130** 690–691.

Tseng M, Weinberg CR, Umbach DM & Longnecker MP 1999 Calculation of population attributable risk for alcohol and breast cancer (United States). *Cancer Causes and Control* **10** 119–123.

Ursin G, Henderson BE, Haile RW, Pike MC, Zhou N, Diep A & Bernstein A 1997 Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? *Cancer Resources* **57** 678–3681.

van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, Fraser G, Goldbohm RA, Graham S, Kushi L *et al.* 2000 Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *American Journal of Epidemiology* **152** 514–527.

Van Hoften C, Burger H, Peeters PH, Grobbe DE, Van Noord PA & Leufkens HG 2000 Long-term oral contraceptives use increases breast cancer risk in women over 55 years of age: the DOM Cohort. *International Journal of Cancer* **87** 591–594.

Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N & Boyle P 1998 Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* **352** 93–97.

Veronesi U, De Palo G, Marubini E, Costa A, Formelli F, Mariani L, Decensi A, Camerini T, Del Turco MR, Di Mauro MG *et al.* 1999 Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *Journal of the National Cancer Institute* **91** 1847–1856.

Veronesi U, Maisonneuve P, Sacchini V, Rotmensz N & Boyle P 2002 Tamoxifen for breast cancer among hysterectomised women. *Lancet* **359** 1122–1124.

Vogel VG 2001 Reducing the risk of breast cancer with tamoxifen in women at increased risk. *Journal of Clinical Oncology* **19** (Suppl 18) 87–92.

Wartenberg D, Calle E, Thun MJ, Heath CW Jr, Lally C & Woodruff T 2000 Passive smoking exposure and female breast cancer mortality. *Journal of the National Cancer Institute* **92** 1666–1673.

Willis DB, Calle EE, Miracle-McMahill HL & Heath CW Jr 1996 Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control* **7** 449–457.

Writing Group for the Women's Health Initiative Investigators 2002 Risks and benefits of estrogen plus progestin in healthy

postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *Journal of the American Medical Association* **288** 321–333.

Wu AH, Ziegler RG, Horn-Ross PL, Nomura AM, West DW, Kolonel LN, Rosenthal JF, Hoover RN & Pike MC 1996 Tofu and risk of breast cancer in Asian-Americans. *Cancer Epidemiology Biomarkers and Prevention* **5** 901–906.

Wu AH, Pike MC & Stram DO 1999 Meta-analysis: dietary fat intake, serum estrogen levels, and risk of breast cancer. *Journal of the National Cancer Institute* **91** 529–534.

Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, Schatzkin A, Levy D & Felson DT 1997 Bone mass and the risk of breast cancer among postmenopausal women. *New England Journal of Medicine* **336** 611–617.