Chapter 2
Lifestyle Factors and Risk of Breast Cancer: A Review of Randomized Trial Findings

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Abstract Observational and pre-clinical studies suggest a role for multiple lifestyle factors in the etiology of breast cancer, but few of these have been tested in full-scale randomized trials and fewer still have been shown to affect breast cancer risk. The clearest evidence for a modifiable risk factor is use of menopausal estrogen plus progestin therapy, where randomized trial evidence confirms an increased risk with longer durations of exposure and studies in multiple populations document that a decrease in use results in reduced rates. The effects of estrogen alone on breast cancer risk are less clear as the only large trial on this topic suggests a possible reduction and that timeframe of exposure may be an important effect modifier. The role of diet has not been adequately resolved, in part because of the methodological difficulties. Randomized trial data are strongly suggestive of the benefits of a low-fat diet on breast cancer risk but no other nutrients tested in trials of dietary supplements have yielded benefits for breast cancer or total cancer in women. Similarly, one large randomized trial of low-dose aspirin has not shown an effect on breast cancer. The contrasts between the observational studies that motivated the randomized trials and the results of the trials emphasize the need for more efforts to test other lifestyle factors in full-scale randomized trials.

Keywords Diet · Nutritional supplements · Menopausal hormone therapy · Aspirin

Key Issues

- Lifestyle factors are behaviors or exposures that are modifiable at the individual level.
- Observational studies, and particularly international observational studies, point to lifestyle as likely having a role in breast cancer risk.
- Randomized trials are often required to assess the effects of lifestyle factors because of the methodologic challenges of the observational studies: measurement problems, modest effect sizes, confounding and differential screening/detection.
- Estrogen plus progestin therapy in postmenopausal women increases the risk of breast cancer and reductions in its use are associated with a rapid decline in incidence rates.
- The effect of unopposed estrogen therapy on breast cancer rates in postmenopausal women is less clear and the effects may vary by age at first use.

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- Randomized trial data strongly suggest that a low-fat diet provides a modest reduction in risk of breast cancer after menopause.
- None of the micronutrients tested, including β-carotene, vitamin C, vitamin E, folic acid, vitamin B6 and B12, calcium and vitamin D and selected multi-nutrient supplements have been shown to have an effect on either breast cancer or total cancer incidence in women.
- Low-dose aspirin offers women no protection for breast cancer or total cancer risk.

Introduction

The large international variation in breast cancer rates[1,2] and more specifically studies that demonstrate a change in breast cancer rates with migration from low incidence countries to high incidence countries[3,4] provide evidence that environmental and lifestyle factors modify breast cancer risk. Many lifestyle factors, here defined as risk factors that are amenable to change at the individual level, have been examined and found to be associated with breast cancer risk. The most commonly considered are diet, physical activity, smoking, and alcohol consumption, but choices such as regular use of dietary supplements or medications, reproductive choices and lactation represent aspects of women's lifestyle that are associated with breast cancer.

Definitive evidence to support a causal influence of most lifestyle factors on breast cancer or other health conditions is scarce. Most of our current understanding arises from observational studies. In addition to the usual limitations of non-experimental data, many observational studies of lifestyle are faced with additional methodological challenges: difficulties in measuring lifestyle choices, limited variability within populations for selected behaviors, modest effect sizes, and correlation among lifestyle factors and between lifestyle and other exposures, including cancer screening, in free-living populations. At best, these complexities constrain the inference that can be made; often they contribute to conflicting results. Thus, it is increasingly clear that unless a lifestyle factor has a very strong effect on health, definitive evidence requires a randomized trial.

The first trial to document a reduction in breast cancer risk with any intervention was a randomized, double-blind, placebo-controlled trial of tamoxifen.[5] Since that time a few other large scale studies have tested effects of diet, specific nutrient supplements, aspirin and hormone therapy on breast cancer incidence. Although some of these were motivated by other chronic disease hypotheses, these trials provide the clearest information regarding the role of these factors on breast cancer risk. The most noteworthy of these efforts include the Women's Health Initiative (WHI), a large randomized trial testing three disease prevention strategies, hormone therapy, a low-fat diet, and calcium and vitamin D supplementation in a partial factorial design,[6,7] the Women's Health Study (WHS), which tested low-dose aspirin, vitamin E and β-carotene[8] in a factorial design, and the Women's Antioxidant Cardiovascular Study (WACS), another randomized trial testing the effects of vitamin C, vitamin E and β-carotene in a $2\times2\times2$ factorial design.[9]

Nutrition and Breast Cancer

When one considers lifestyle and health, nutritional factors are often at the forefront. The diet and disease question can be posed in different terms: specific foods, macro or micro-nutrients, eating patterns (e.g., vegetarian, Mediterranean, religious), and food preparation methods. Variation in specific nutrient consumption or in eating patterns may be limited within a population and may be correlated with other lifestyle factors. Further, the relative risks associated with different dietary factors are

generally thought to be modest and the lifestyles must be sustained for some interval to reach their full effect. While various observational study designs have been used to examine these questions, all face noteworthy hurdles. Prospective studies require very large sample sizes and long-term follow-up to have adequate statistical power. Retrospective studies, though more efficient, generally rely on dietary recall over a long period of time, a particular concern since dietary behaviors and memory may be altered by the presence of the disease. Not surprisingly, inconsistencies in results are common.

Macronutrients

One of the strongest and longest posed hypotheses has been that a diet high in total fat is associated with increased breast cancer incidence. Analyses of international data found a strong association between breast cancer incidence and fat disappearance, which was well-summarized as a linear trend with a 50% lower fat consumption associated with a 50% lower breast cancer incidence.[10] A summary of case-control data showed a more modest but statistically significant increasing trend in breast cancer risk across quartiles of dietary fat intake.[11] Prospective cohort studies did not support this hypothesis.[12,13] A more recent review of the international data reported 11 case-control studies supporting increased breast cancer risk with greater fat intake, 5 showing decreased risk.[14] In the same review, nine cohort studies addressed this question; of these, six reported increased risk and three reported reduced risk with increased fat consumption.[14]

Between 1993 and 2005, the WHI tested the low-fat diet and breast cancer hypothesis in a large scale randomized primary prevention trial. The trial randomized 48,835 postmenopausal women aged 50–79 to their usual diet (60%) or to a dietary behavioral intervention (40%). Women in the intervention group were taught strategies to reduce their dietary fat intake to 20% of energy and to increase their consumption of fruits, vegetables, and grains. The design assumed that the difference in percent energy from fat intake between intervention women and women in the usual diet group would be 13% at 1 year and that most of this difference would be maintained throughout the planned 9-year follow-up period. In addition, a 10-year lag time to full effect was incorporated, as suggested by the international data.[10] Based on these assumptions, the trial was designed to detect a 14% reduction in breast cancer incidence.[7]

Statistically significant reductions in reported percent energy from fat were found (mean 10.7% at year 1, diminishing to 8.1% at year 6) but these did not reach trial goals. Intervention women also reported small but statistically significant increases in fruit and vegetable consumption (mean of one serving per day) and grain servings (mean < one serving per day).[15]

After a mean 8.1 years of follow-up, the hazard ratio (HR) for invasive breast cancer was 0.91 (95% confidence interval [CI] 0.83–1.01) in 1,727 cases (Fig. 2.1).[15] Total cancer incidence was not affected (HR 0.96; 95% CI 0.91–1.02 in 4,986 cases). No effect was seen on breast cancer mortality (HR 0.77; 95% CI 0.48–1.22 in 80 breast cancer deaths) or on total cancer mortality or total mortality. The 9% breast cancer risk reduction did not reach statistical significance ($p = 0.09$), but was consistent with the level of risk reduction projected from the trial design after accounting for the level of adherence, i.e., the trial achieved roughly 70% of intervention goals and observed approximately 70% of the expected 14% reduction in incidence[15] (Fig. 2.1).

In further analyses, the observed reduction appeared to be concentrated in progesterone receptor (PR) negative disease (HR 0.76; 95% CI 0.63–0.92) with no reduction observed in PR positive disease, and a suggestion of the strongest risk reduction in ER positive/PR negative disease. In exploratory analyses, an interaction ($p = 0.04$) with baseline fat intake was observed – among the women consuming the highest percent energy from fat at baseline (>36.8% calories from fat), the

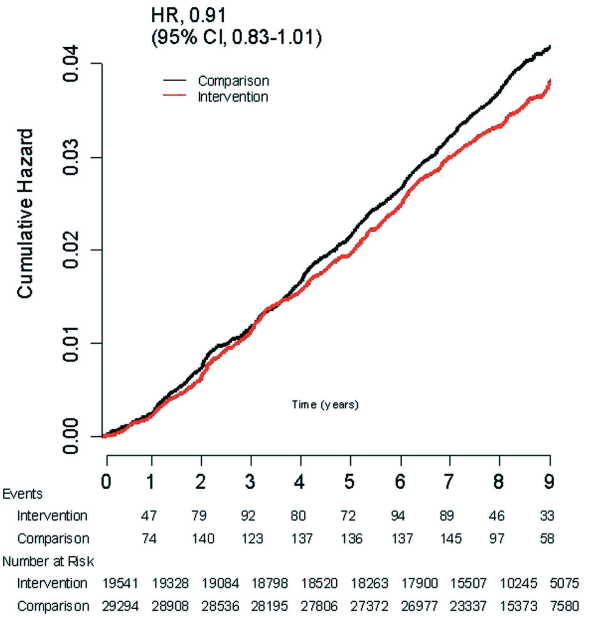

Fig. 2.1 Kaplan-Meier estimates of the cumulative hazard for invasive breast cancer. CI indicates confidence interval; HR, hazard ratio (Reprinted with permission from Prentice et al.[15] Copyright © 2006 American Medical Association. All rights reserved)

intervention group achieved the greatest absolute change in dietary fat intake (12.2% ± 7.0%) and experienced the largest risk reduction (HR 0.78; 95% CI 0.64–0.95). Evidence for a trend with baseline fruit and vegetable intake was not as significant and there was no evidence of interaction with baseline grain consumption.[15] Thus, while the trial does not provide definitive results, the data are strongly consistent with the underlying hypothesis.

Limitations of a behavioral intervention study such as the WHI dietary modification trial include lack of ability to control adherence to the intervention goals, and the inability to identify the specific component of this dietary intervention that may lead to risk reduction. In addition, this study included only postmenopausal women; it is unknown whether these dietary changes if made earlier in life, and in that sense more reflective of the international studies, would have a stronger effect on breast cancer risk.

Micronutrients

The most prominent micronutrient hypothesis over the last two decades has been in the role of antioxidants, with regard to both cancer risk and chronic disease prevention more generally. This hypothesis has been tested in several large scale prevention trials using dietary supplements, often with doses at or above the recommended daily allowance at the time for dietary consumption in the general population. The design of these trials was usually based on cardiovascular disease, total cancer, or other site-specific cancers but they provide some of the most reliable information to date on the effects of these agents on breast cancer risk.

Vitamin A/β-carotene

Several full-scale prevention trials of vitamin A or β-carotene (pro-vitamin A) have been conducted: the α-Tocopherol and β-Carotene Cancer Prevention Study (ATBC),[16] the Carotene and Retinol Efficacy Trial (CARET),[17] the Physician's Health Study (PHS),[18] and the Women's Health Study.[19]

Most of these trials were focused on men, however. The ATBC trial reported an increased risk of lung cancer (hazard ratio [HR] 1.18; 95% CI 1.03–1.36) and no effect on other cancer incidence with 20 mg β-carotene daily in this trial of 29,133 male smokers in Finland after 5–8 years of follow-up.[16] Shortly thereafter the US based CARET trial was stopped early, after a mean follow-up of approximately 4 years, based on the observation of an adverse effect of supplement use on lung cancer incidence (HR 1.28; 95% CI 1.04–1.57) in 18,314 male and female heavy smokers and asbestos-exposed men randomized to either 30 mg β-carotene plus 25,000 IU of retinol per day or placebo.[17] The PHS, which randomized 22,071 male physicians in the USA to 50 mg β-carotene every other day, reported no effect on lung cancer or other cancer incidence after an average 12 years of follow-up.[18] These results undermine the general antioxidant and cancer association but do not provide direct information on the effects of β-carotene on breast cancer.

The WHS randomized 39,876 women aged 45 and older to 50 mg β-carotene every other day or placebo in a factorial design that also tested aspirin and vitamin E.[8] The β-carotene arm was terminated early, after a median duration of exposure of 2.1 years, prompted mainly by the results of the preceding trials. Follow-up continued with the other trial interventions. With a median 4.1 years of follow-up, no effect of β-carotene was observed on total cancer incidence and specifically there was no difference in the number of reported breast cancer cases (Table 2.1).[19]

The WACS was a somewhat smaller trial that tested β-carotene as well as vitamins C and E in a 2×2×2 factorial design among women health professionals 40 years of age or older who were at increased risk of cardiovascular disease. The trial randomized 8,171 women to either 50 mg β-carotene every other day or placebo. In the subset of 7,627 who were cancer-free at baseline, no effect was seen for total cancer or breast cancer incidence after an average 9.4 years of follow-up (Table 2.1).[20]

Vitamin C

Two large scale prevention trials provide information on the role of vitamin C in cancer risk. In WACS, women were randomized to receive either 500 mg of ascorbic acid daily or a placebo. Vitamin C did not reduce the risk of breast cancer or total cancer (Table 2.1).[20] The only other large scale trial (PHS) tested this same dose in men and found a similar overall null finding for total cancer incidence (relative risk [RR] 1.01; 95% CI 0.92–1.10) after a mean 8.0 years of follow-up.[21]

Vitamin E

Vitamin E (or α-tocopherol), a potent antioxidant, has been tested in several prevention trials, primarily in men for its impact on incidence of lung cancer,[16] prostate cancer,[21,22] and cardiovascular disease.[23] None of these studies reported a significantly reduced risk of cancer. Both the WHS and the WACS randomized women to vitamin E (600 IU on alternate days) or placebo. In the WHS, there was no effect of vitamin E on breast cancer incidence or on total cancer incidence (Table 2.1) over an average 10.1 years of follow-up.[24] Similar results were found after the average 9.4 years of follow-up in the smaller WACS (Table 2.1).[19]

The HOPE trial and its extension, the HOPE-TOO trial, randomized 9,541 subjects with vascular disease or diabetes to 400 IU vitamin E per day or placebo. After a median follow-up of 7.0 years, no significant effect of supplements was observed on breast cancer or total cancer incidence (Table 2.1).[25]

Table 2.1 Findings from randomized, double-blind, placebo-controlled trials of micronutrients on breast and total cancer incidence in women

Nutrient(s)		Women	Mean or median	Cancer cases				
Study	Dose(s)	randomized	follow-up (yrs)	Site	Active	Placebo	RR	95% CI
β-Carotene								
WHS[19]	50 mg/2 days	39,816	4.1	Breast	169	168	NA	NA
				Total	378	369	1.03	0.89–1.18
WACS[20]	50 mg/2 days	8,171	9.4	Breast	129	128	1.01	0.79–1.30
				Total	311	313	1.00	0.85–1.17
Vitamin C								
WACS[20]	500 mg/day	8,171	9.4	Breast	135	122	1.11	0.87–1.41
				Total	329	295	1.11	0.95–1.30
Vitamin E								
WHS[24]	600 IU/2 days	39,876	10.1	Breast	616	614	1.00	0.90–1.12
				Total	1,437	1,428	1.01	0.94–1.08
HOPE[25]	400 IU/day	9,541	7	Breast	29	25	0.86	0.50–1.47
				Total	552	586	0.94	0.85–1.06
WACS[20]	600 IU/2 days	8,171	9.4	Breast	127	130	0.98	0.77–1.25
				Total	300	324	0.93	0.79–1.09
Antioxidant multivitamins								
SU.VI.MAX[29]	120 mg/day vit C 30 mg/day vit E 6 mg/day β-carotene 100 μg/day selenium 20 mg/day zinc	7,715	7.5	Breast	95	199	0.95	NA
				Total	179	171	1.04	0.85–1.29

Table 2.1 (continued)

Nutrient(s)				Cancer cases				
Study	Dose(s)	Women randomized	Mean or median follow-up (yrs)	Site	Active	Placebo	RR	95% CI
Folate and vitamin B								
WACS[34]	2.5 mg/day folic acid 50 mg/day vit B6 1 mg/day vit B12	5,442	7.3	Breast Total	70 187	84 192	0.83 0.97	0.60–1.14 0.79–1.18
Calcium and vitamin D								
WHI[39,41]	1,000 mg/day Ca 400 IU/day vit D	36,282	7.0	Breast Total	528 1,634	542 1,655	0.96 0.98	0.85–1.09 0.91–1.05
Lappe[42]	1,400 mg/day Ca 1,400 mg/day Ca^{+} 1,100 IU/day vit D	288 placebo 445 Ca 446 $Ca^{+}D$	4.0	Total	17 13	20	0.40 0.53	0.20–0.82 0.27–1.03

NA – Not available

Multiple Nutrient Supplements

In addition to these single nutrient trials, a few such efforts have tested the antioxidant hypothesis using micronutrient combinations. The first two trials were conducted in Linxian China, testing the effects of selected vitamins and minerals in the general population, where nutrient intake was generally low, and in a high risk population. Participants in the general population trial were randomized in a fractional factorial design to either placebo or one of seven arms, each with a different combination of vitamins and minerals including β-carotene, retinol, vitamin C, vitamin E, niacin, riboflavin, molybdenum, selenium and zinc daily for over 5 years.[26] No effect on cancer incidence or mortality was observed for any of these supplement combinations except those containing β-carotene, vitamin E and selenium, where a reduction in stomach cancer and total cancer mortality was observed, a difference that has persisted through 5 additional years of follow-up.[27,28] In the parallel trial in 3,318 participants with esophageal dysplasia, participants were randomized to placebo or a daily supplement containing 14 vitamins and 12 minerals. A reduction in rates of esophageal dysplasia for up to 6 years of follow-up was reported.[27]

The Supplementation en Vitamines et Mineraux Antioxydants trial (SU.VI.MAX) randomized 13,017 French adults, ages 45–60 years to placebo or a single daily capsule containing 120 mg vitamin C, 30 mg vitamin E, 6 mg of β-carotene, and 20 mg of zinc. After a median 7.5 years of follow-up, no effect of these supplements was found on total cancer incidence in the entire population (RR 0.90; 95% CI 0.76–1.06 in 562 cases). There was evidence of an interaction with sex ($p = 0.02$) however, suggesting that men experienced some benefit from the supplements but women did not (Table 2.1). The numbers of breast cancers observed among women in the two groups were similar (Table 2.1).[29]

The Heart Protection Study tested the antioxidant and cardiovascular disease hypothesis in 20,536 UK adults aged 40–80 with coronary disease or occlusive arterial disease or diabetes. Participants were randomized to daily supplementation with 250 mg vitamin C, 600 mg vitamin E and 20 mg β-carotene or a matching placebo. After 5 years of supplementation, there was no effect on total cancer incidence (RR 0.98; 95% CI 0.89–1.08 in 1,617 cases).[30] Neither breast cancer rates nor total cancer rates in women were reported.

Together these trials provide strong evidence that antioxidants, supplied through either single or multi-nutrient supplements, do not provide protection against breast cancer or cancer risk in general. Whether the discrepancy between the observational studies and these trials arises from the manner in which these vitamins were consumed, differences in duration, timing, dose, or lack of power to detect more modest effects in the trials or in residual confounding or systematic measurement error in the observational studies remains to be determined.

Vitamin B and Folate

Recent interest has turned to other micronutrients. Folate, methionine, riboflavin, and vitamins B-6 and B-12 are nutrients involved in one-carbon metabolism. Because grain products are routinely fortified with folic acid to help prevent neural tube defects, it is important to know the long-term effects of these supplements on other health conditions. Folate has been shown in case-control studies, but not prospective studies, to be associated with lower risk of breast cancer, with some evidence for a stronger benefit for women consuming moderate or high amounts of alcohol.[31] Further inconsistencies regarding the relationship with pre- and postmenopausal disease and with ER and PR status have been raised.[32,33]

The WACS was expanded to include a randomization to folic acid (2.5 mg/day), vitamin B6 (50 mg/day) and vitamin B12 (1 mg/day) vs placebo. In the 5,442 women aged 42 years and older

who were randomized, neither breast cancer incidence nor total cancer incidence rates were affected by supplements (Table 2.1).[34]

One smaller placebo-controlled trial of two doses of folate supplements in 2,928 pregnant women was conducted in the UK in 1966–1967. Using linkage to the National Health Service Central Registry to ascertain cause of death through 2002, a non-significant increased risk of breast cancer mortality was found with 0.2 mg/day (RR 1.56; 95% CI 0.38–3.41) and with 0.5 mg/day (RR 2.02; 95% CI 0.88–4.72) in 31 cases.[35] Limitations of this trial include the small sample size, limited duration of intervention, lack of data on breast cancer incidence and an unknown randomization scheme.

Calcium and Vitamin D

Another recent nutrient and cancer hypothesis is related to vitamin D and calcium levels. Serum vitamin D levels are influenced by exposure to sunlight, dietary supplements and dietary intake, primarily through fortified dairy products. Observational studies examining the relationship between breast cancer risk and dairy product consumption, use of supplements, and estimates of sunlight exposure through geographic residence and outdoor activity have found supportive evidence of a protective effect of vitamin D with some inconsistency in the effects before and after menopause.[36–38] Whether vitamin D or calcium or both are involved cannot be adequately determined from these studies.

The WHI randomized 36,202 postmenopausal women to either 1,000 mg of calcium combined with 400 IU of vitamin D daily or matching placebo in divided doses. The primary outcome for this trial was hip fracture incidence. With an average of 7 years of follow-up, no effect on breast cancer incidence was observed (HR 0.96; 95% CI 0.88–1.06 in 1,074 cases, Table 2.1),[39] nor was there an effect on benign proliferative breast disease[40] or total cancer incidence (Table 2.1).[41] Further, in a nested case-control study, baseline serum vitamin D levels were found to be correlated with total vitamin D intake, BMI and physical activity but were not associated with breast cancer risk after adjustment for BMI and physical activity, suggesting these other factors may be stronger predictors of risk than serum vitamin D levels.[39]

In a small single-center study conducted by Lappe and colleagues, 1,179 postmenopausal women were randomized to 1,400–1,500 mg supplemental calcium, supplemental calcium plus 1,100 IU vitamin D or placebo to test for effects on fracture rates. After 4 years of treatment, a significant difference was observed in total cancer incidence rates between groups, with a large but non-significant reduction found with calcium alone (RR 0.53, 95% CI 0.27–1.08) and a slightly larger reduction with the addition of vitamin D (RR 0.40; 95% CI 0.20–0.82).[42]

The WHI and Lappe trials differ in dose, duration, and study population. The Lappe study[42] supports the hypothesis that among women with relatively high baseline serum 25(OH)D levels (71.8 ± 20.3 nmol/L), a large daily dose of calcium and vitamin D may reduce cancer incidence but the estimates are imprecise. The WHI, with the large, national sample, and longer-term intervention provides a more complete assessment of effects of these supplements but at a dose of vitamin D considered by some to be ineffective. The adverse effect on kidney stones reported by the WHI[43] will need to be factored into any future trials looking at larger doses.

Medication Use

Hormone Therapy

The hypothesis that female hormones are associated with breast cancer risk developed out of the literature on reproductive factors (age at menarche, age at first birth, parity). The findings of higher

risk for women with earlier age at menarche, later age at first birth, and lower parity pointed to an adverse role of increasing levels of endogenous estrogens.

Menopausal hormone therapy (HT) was first approved by the US FDA to relieve menopausal symptoms in the early 1940s. Initially, the vast majority of hormone use was of a single preparation – conjugated equine estrogens (CEE). Its use grew over the next three decades with CEE being the main preparation used. In the mid-1970s, however, unopposed estrogens were shown to have a carcinogenic effect on the endometrium and its use rapidly declined. When the protective effect of progestin on the uterus was established in the mid-1980s, interest in HT was rekindled and guidelines for use were developed based on a stratified approach to care for women with menopausal symptoms: women who had had a hysterectomy were given estrogen alone and women with an intact uterus were either given a combination of estrogen and progestin or were given estrogen alone with frequent endometrial monitoring.[44–46] By the mid-1990s, approximately 90 million prescriptions were filled annually for 15 million women.[47]

Medroxyprogesterone acetate (MPA) has been the most commonly used progestin product though, again, many different forms of progestin are available.[47] Progestins have been prescribed in daily, cyclic, and sequential regimens at different doses in an attempt to balance endometrial safety, convenience and side effects.

The prevalence of HT use motivated a large number of observational studies examining its effects on chronic diseases. Early studies did not always distinguish between types of HT but generally captured women exposed to CEE. As the prevalence of progestin use increased, analyses began to examine unopposed estrogen and combined estrogen/progestin separately. Together these studies suggested an association between prolonged exposure to HT and an increased risk of breast cancer.[48] The analyses of progestin effects, somewhat limited in their interpretation because of the variability in progestin regimens and the shorter history of exposure, suggested a generally similar pattern of association.[48]

Between 1993 and 1998, the WHI enrolled 27,341 postmenopausal women aged 50–79 years of age from 40 US clinical centers into one of two hormone trials testing whether HT would reduce risk of coronary heart disease: 16,608 women with an intact uterus were randomized to combined estrogen plus progestin (CEE.625 mg/day + MPA 2.5 mg/day) vs placebo and 10,733 women with prior hysterectomy were randomized to estrogen alone (CEE.625 mg/day) vs placebo.[7]

Combination Estrogen/Progestin Therapy

The WHI estrogen plus progestin trial was stopped early, in 2002, based on the finding of an increased risk of breast cancer and an overall assessment of risks exceeding benefits.[49] The invasive breast cancer hazard ratio over the 5.6 year average follow-up was 1.24 (95% CI 1.01–1.54, weighted $p = 0.003$) (Table 2.2)[50] and was nearly identical to the breast cancer hazard ratio (HR:1.27; 95% CI 0.84–1.94) reported from the smaller Heart Estrogen/Progestin Replacement Study, a randomized secondary cardiovascular prevention trial in 2763 women that used the same combined hormone regimen.[51] Secondary analyses of the WHI trial suggested increasing risk with prior exposure, longer follow-up, and greater adherence to therapy.[49,50,52] There was no evidence of interactions with other breast cancer risk factors. Estrogen plus progestin increased the incidence rates for both ductal and lobular cancer as well as receptor positive and negative tumors. The risk of in situ disease was not significantly elevated (HR 1.18; 95% CI 0.77–1.82).[50] Estrogen plus progestin was also found to increase mammographic density[53] and the risk of benign proliferative breast disease (HR 1.74; 95% CI 1.35–2.25).[54]

Table 2.2 Results of the WHI randomized trials and observational study on estrogen plus progestin and estrogen alone on breast cancer incidence [60,61]

		Estrogen + Progestin		Estrogen-alone	
Study group		HR	95% CI	HR	95% CI
Clinical Trial (CT)		1.24	1.01–1.54	0.80	0.62–1.04
No prior HT use		1.13[a]		0.61[a]	
Prior HT use		1.86[a]		0.95[a]	
Observational Study (OS)					
No prior HT use		2.20[a]		1.09[a]	
Prior HT use		2.07[a]		1.11[a]	
Combined CT/OS[b]	Years since initiation of current HT				
No prior HT use	0–2	0.98	0.56–1.72	1.44	0.54–3.84
	2–5	2.01	1.41–2.86	1.15	0.57–2.32
	5+	2.85	2.29–3.54	1.00	0.54–1.84
Prior HT use	0–2	1.28	0.66–2.51	1.63	0.68–3.91
	2–5	2.56	1.54–4.24	0.82	0.42–1.57
	5+	3.30	1.90–5.73	0.91	0.49–1.69
5-year increase in gap time		0.81	0.71–0.91	0.85	0.73–0.98

[a]Age-adjusted incidence ratio.
[b]Based on multivariate models that controlled for age, body mass index, education, smoking, alcohol intake, general health, physical activity, family history of breast cancer, Gail model estimated risk of breast cancer, bilateral oophorectomy and for women with prior HT, duration of prior HT use (not including the current episode). These models restricted the CT and OS to have the same HT effects up to a factor estimated as 1.30 (95% CI 0.69–1.53) for estrogen + progestin and 1.07 (95% CI 0.60–1.93) for Estrogen alone.

Results of the WHI trial suggested that estrogen plus progestin treatment delays diagnosis. Tumors in women assigned to combined hormones were larger and at somewhat more advanced stage than those in the placebo group. Even though there was increased risk after 5 years, breast cancer incidence rates were non-significantly lower in the estrogen plus progestin group for the first 2 years of follow-up.[50] The active and placebo groups had comparable mammography rates throughout since these were required by protocol, but the frequency of abnormal mammograms and of biopsies was greater in the active hormone group.[55] Together these results suggest that estrogen plus progestin serves as an active agent in postmenopausal breast tissue to promote carcinogenesis and reduces the sensitivity and specificity of mammography, leading to delayed diagnoses as well as a higher rate of unnecessary biopsies.[55]

Estrogen Alone

The effect of unopposed estrogen on breast cancer risk is less clear. The WHI estrogen alone trial was also stopped early, after an average of 6.8 years of follow-up, based on an increased risk of stroke.[56] The hazard ratio for breast cancer over this interval was 0.80 (95% CI 0.62–1.04) (Table 2.2), narrowly missing statistical significance for a protective effect but ruling out an increased risk in this population.[57] Secondary analyses found statistically significant interactions with family history of breast cancer, history of benign breast disease, as well as a summary risk estimate based on the

modified Gail model, each suggesting some degree of protection among women at lower risk and an elevated hazard ratio among women with the established risk factor. The apparent protective effect was observed only in localized disease and ductal carcinoma; there was no evidence of a reduced risk in more advanced disease or lobular tumors. Hazard ratios for both receptor positive and negative disease were less than one. Women in the estrogen alone arm had slightly larger tumors than those in the placebo arm and were more likely to have positive lymph nodes.[57] Additional analyses showed that estrogen alone increased the risk of mammograms requiring early recall[57] and of benign proliferative disease.[58]

Further Analyses of Hormone Therapy Effects

The WHI trial results apply to the two HT regimens tested, yet many others are available. Since it is unlikely this effort will be repeated for other forms of HT, observational studies are needed to expand the inference beyond the specific interventions tested. The Million Women Study (MWS), the largest study of breast cancer conducted to date, examined the relationship between current and past use of HT and found that among 1,084,110 UK women aged 50–64 years, current users of combination hormones were twice as likely as non-users to develop breast cancer (relative risk [RR] 2.0; 95% CI 1.88–2.12). Current users of estrogen alone also had elevated risks relative to non-users but lower than estrogen plus progestin (RR 1.30, 95% CI 1.22–1.38). There was no evidence of variation in these estimated risks with type of estrogen (equine estrogens or estradiol), type of progestin (MPA, Norethisterone, or Norgestrel/levonorgesterel), regimen (sequential vs continuous) or formulation (oral, transdermal, or implanted estrogens). Both types of hormones showed increasing risks with duration of exposure but past users exhibited no elevation in risk relative to never users. In addition to the large sample size which afforded very precise estimates of risk, and the usual control for confounding, this study was able to address concerns of differential breast screening by enrolling women only through the United Kingdom's National Health Service Breast Screening Programme, assuring comparable breast screening among both HT users and non-users.[59]

The difference between the randomized trials and observational data with regard to the magnitude of effect associated with combined hormones and the direction of effect for estrogen alone is noteworthy. Most of the hormone use captured in the observational studies was of the same agents and doses tested in the WHI so differences in hormone preparations cannot explain these discrepancies. Changes in screening practices over time might explain the variation between the motivating studies and WHI, but the Million Women Study effectively controlled for screening practices. Other possible explanations are residual confounding or selection bias and differences in other aspects of exposure such as duration and timing.

To understand these differences, Prentice and colleagues conducted a series of analyses of pooled data from the WHI trials and the parallel WHI observational study (OS) of nearly 94,000 women.[60,61] For each trial, a corresponding sample was defined consisting of women in the observational study that were in general eligible for that trial but refused randomization. Specifically, for the cohort looking at estrogen plus progestin, women in the observational study were included if they had a uterus at entry, had a mammogram in the last 2 years and were either taking combined estrogen plus progestin therapy or were not taking any HT. For estrogen alone analyses, the observational study participants selected reported a prior hysterectomy and a mammogram in the past 2 years and used either unopposed estrogen or no HT. The trials and observational study were conducted in parallel in the same clinical centers with almost identical methods thereby facilitating data pooling. The observational study cohorts were analyzed as if they were trials – women were placed in the HT user or non-user groups depending on their reported use at baseline.

In simple age-adjusted analyses, the WHI observational study estimates of effects of hormones better aligned with MWS and other observational studies than with the WHI trials (Table 2.2). Adjusting for other confounders, and for time dependent effects reduced the discrepancies with the trials but important differences remained.[60,61] The identification of prior hormone use as an effect modifier[50,52] led to modeling of the so-called "gap-time," the interval between cessation of menses and first use of hormone therapy. By modeling gap time as well as prior hormone therapy and time since initiation of therapy (i.e., randomization for trial participants), the estimates from each trial and the corresponding observational study cohort were brought into excellent alignment.[60,61]

The resultant pooled analyses indicate that, among women who started HT at the time of menopause (gap time = 0) the risk of breast cancer associated with estrogen plus progestin therapy doubled after 2 years of exposure with some variation in level of risk by prior hormone use (Table 2.2). A delay in hormone initiation, i.e., an increase in gap time, would reduce these risks by an estimated 19% per 5-year increment.[60]

In analyses of estrogen alone the three time variables were again important. For women who started therapy at the time of menopause (gap time = 0), there is no clear evidence of a reduced risk of breast cancer; any reduction seems limited to those women with large gap times as each 5-year delay is associated with an estimated 15% reduction in risk (Table 2.2).[61]

The effect of these findings on breast cancer rates has been documented in multiple populations. In the first report from the US using SEER data, an 8.6% (95% CI 6.8–10.4) reduction in annual breast cancer incidence was reported for 2004 relative to 2001[62] that paralleled the substantial drop in hormone therapy prescriptions which occurred when the first WHI results were released.[47] Limitations of this study included the inability to link hormone use to cancer incidence on an individual basis or to control for screening mammography use. Subsequent reports from Australia,[63] Scandinavia,[64] and France[65] reported similar declines in incidence rates with changing HT use on the population level but not all analyses agreed,[66,67] raising the possibility that the decline in rates may be attributable to other factors, including change in use of screening mammography. Similar declines in cancer rates reported in a screening population lent support to the HT hypothesis.[68]

Further information from the WHI trials and observational study provides clear support for this finding. In the 3 years after WHI trial participants were asked to stop their study hormones, the breast cancer risk in women originally randomized to estrogen/progestin therapy remained elevated (HR 1.26; 95% CI 1.02–1.55),[69] suggesting some carry-over effect. More detailed analyses of the rates over time indicated that within 5 years of randomization to estrogen plus progestin the breast cancer rates nearly doubled, but within the 3 years after cessation of therapy, the adverse effect became non-significant (Fig. 2.2).[70] The parallel cohort of WHI observational study participants who used combined hormones at baseline also discontinued their use of hormones, similar to the general population; 75% of baseline users were still users in 2001 but only 41% reported HT use in 2003. Modeling the effect of hormone use over calendar time in this population with multivariate adjustment for potential confounders produced a hazard ratio function that was relatively constant over time at approximately 2.0 prior to 2001 and then dropped rapidly between 2001 and 2003 to a level not significantly greater than 1.0 (Fig. 2.3).[70]

The totality of the WHI data indicate that estrogen plus progestin increases breast cancer risk, with greater risk with longer exposure duration reaching a twofold increase after 5 years, with higher risk in women who initiate use soon after menopause. The increased risk appears to dissipate within approximately 3 years of cessation of therapy. Estrogen alone, however, does not have a clear effect on breast cancer risk in women initiating HT soon after menopause but may reduce risk among women starting HT at later ages. The contrast between these two trials suggests that MPA, the form of progestin used in WHI trials, may be the potent agent.

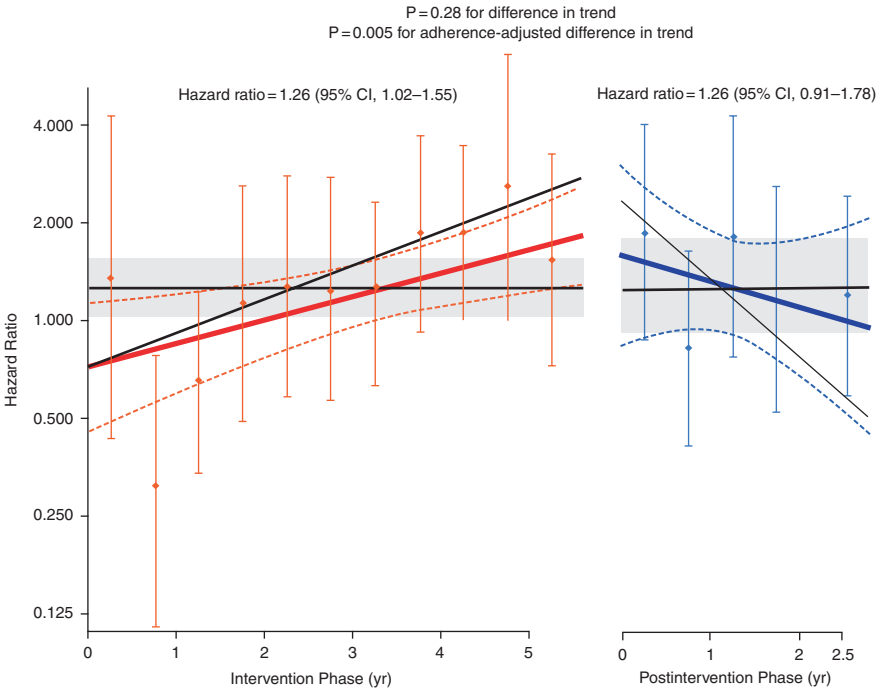

Fig. 2.2 Effects over time of estrogen plus progestin on the incidence of breast cancer in the WHI clinical trial (Reprinted with permission from Chlebowski et al.[70] Copyright © 2009 Massachusetts Medical Society. All rights reserved). Time-varying linear hazard ratios and 95% Cls (thick solid and dashed lines, respectively) are shown for the effect of conjugated equine estrogens plus medroxyprogesterone acetate on the risk of breast cancer as compared with placebo during the intervention and postintervention phases of the study. The shaded areas indicate the 95% Cls for the hazard ratios in the intervention and postintervention phases. The I bars show hazard ratios and 95% Cls according to an analysis based on events accumulated at 6-month intervals. The P value of 0.28 for a difference in trend is for the comparison of the hazard-ratio slopes in the two study phases in the primary, unadjusted analysis, and the P value of 0.005 is for a difference in trend from an analysis adjusted for adherence status, with censoring of events that occurred 6 months after a woman became nonadherent (defined as consuming < 80% of study pills or starting hormone therapy). The thin solid lines show the adherence-adjusted, time-varying linear hazard ratios

Aspirin and NSAIDS and Other Anti-inflammatory Medicine

The potential anti-carcinogenic effect of aspirin and non-steroidal anti-inflammatory medicines is based on their inhibition of the Cox-1 and Cox-2 pathways.[71] Observational studies have reported generally consistent modest risk reductions with aspirin use and to a lesser extent other nonsteroidal anti-inflammatory medications.[72]

To date, only one large scale trial has tested this hypothesis. The WHS randomized 39,876 women to low-dose aspirin (100 mg every other day) or a placebo between 1992 and 1996 and followed them until the planned termination in 2004. With an average of 10 years of follow-up, the overall invasive breast cancer HR was 0.98 (95% CI 0.87–1.09). No evidence was found for a differential effect by histology, grade, receptor status, tumor size or stage.[73]

Discussion

Large scale randomized trials examining lifestyle factors aimed at reducing the incidence of breast cancer or other chronic diseases have provided important answers to critical public health

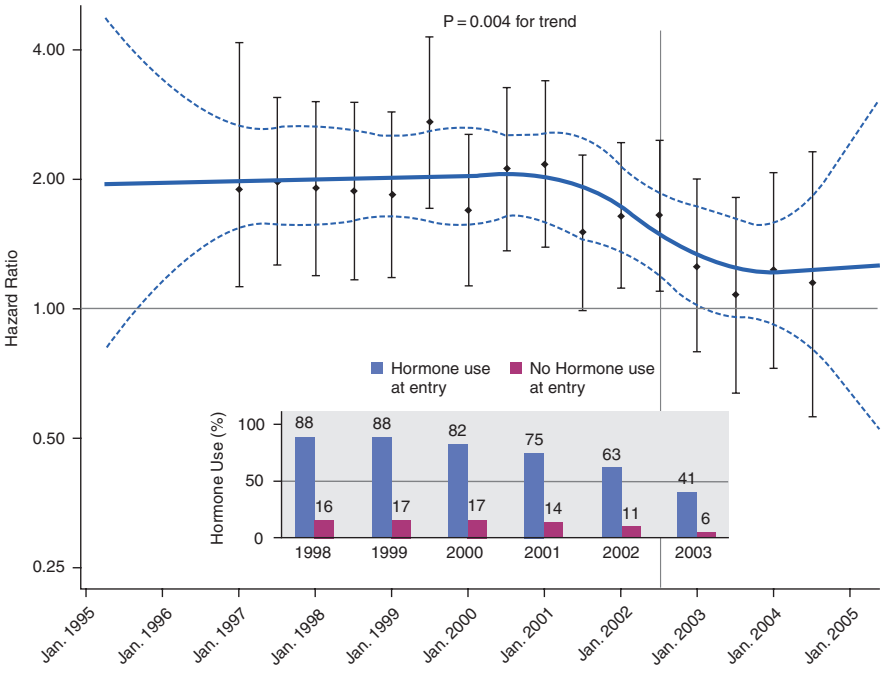

Fig. 2.3 Effects over time of estrogen plus progestin on the risk of breast cancer in the WHI observational study (Reprinted with permission from Chlebowski et al.[70] Copyright © 2009 Massachusetts Medical Society. All rights reserved). Smoothed time-varying, multivariable-adjusted hazard ratios and 95% confidence intervals (solid and dashed blue lines, respectively) for the comparison of participants who were taking estrogen plus progestin at study entry with those who were not are shown with the corresponding multivariable-adjusted hazard ratios and 95% confidence intervals from an analysis based on accumulated events at 6-month intervals (I bars). The vertical line indicates the announcement of the results of the clinical trial in July 2002. The bar graph shows the year-to-year percentages of participants who were taking hormones and those who were not

questions but have provided few clear choices women can make to reduce their risk of breast cancer.

The most definitive finding of these trials is the increase in breast cancer risk found with use of estrogen plus progestin therapy.[50] As demonstrated by both the follow-up after cessation of the intervention in the WHI trial[70] and in multiple other population-based studies,[62–65,68] reduction in estrogen plus progestin use resulted in a rapid and noteworthy decline in breast cancer rates.

The effects of estrogen alone on breast cancer risk are less clear. The suggestion of an overall protective effect of estrogen alone in the trial[57] may not apply to the average woman considering hormone use near the time of menopause.[61] Given the serious adverse health effects of estrogen on risk of stroke, blood clots,[56] and cognitive impairment in older women,[74] estrogen is an unacceptable breast cancer prevention approach for most women.

The preventive role of diet in breast cancer remains one of the more interesting and important areas for further study. Although the WHI low-fat diet trial did not provide definitive evidence on the fat and breast cancer incidence hypotheses, the totality of the evidence supports a modest risk reduction.[15] As a lifestyle change that is low in cost, without any serious adverse effects and therefore suitable for the majority of the population without close medical monitoring, it remains one of the more viable methods to address the public health question. Additional efforts are warranted to clarify this issue.

The multiple, large, high-quality randomized trials of dietary supplements[19,20,24,25,29,30,34,39] provide strong evidence that these agents, as delivered, have no appreciable effect either positive or negative, on breast cancer risk. While the lack of an adverse effect is reassuring given the high prevalence of use, the lack of benefit means there are few easy choices to effectively modify breast cancer risk.

Other aspects of diet deserve further consideration. To date, fruit and vegetable consumption, associated with cancer risk in observational studies, has been simplified into a limited set of micronutrients for testing in randomized trials. These trials provided rigorous tests of the specific supplement preparations in an easily implemented and monitored intervention but they differ from the motivating studies in the manner, form and timeframe in which the nutrients were consumed. Whether the reductionism employed in designing these trials resulted in loss of the critical risk modifying factor or other methodological factors confounded these results has not yet been determined.

The lack of an effect of low-dose aspirin on cancer risk reported by one trial, while disappointing, provides the important information that this very commonly used medication has no adverse effects on cancer risk but casts some doubt on the underlying hypothesis regarding the role of Cox-1/2 inhibitors. Further testing of other targeted agents may be warranted if safety concerns, such as those that have plagued other Cox-2 inhibitors[75] can be alleviated.

In addition to these important findings, these prevention trials provide an important cautionary reminder of the inference that can be derived from observational studies of lifestyle factors and cancer risk. The discrepancies observed between these two study designs are not easily resolved. Methodological limitations of each are generally recognized but in the context of lifestyle, the understanding of the issues may be critical in giving each their appropriate weight. Measurement problems and confounding of observational studies can be substantial. Limitations in clinical trials include timing and duration of the intervention. Additional efforts such as those pursued by Prentice and colleagues[60,61] and others[76] to analyze observational study data using the approach employed for clinical trial analyses provide some perspective on methodologic factors that may explain these differences. In addition, conducting more parallel observational studies and randomized trials may be useful to expand the inference that can be gained regarding a class of interventions when only one can be tested in a trial.

What do these trials imply for the role of other lifestyle factors on cancer risk? Current evidence regarding the relationship between breast cancer and lifestyle choices, such as alcohol use, smoking, physical activity, weight control/reduction, use of oral contraceptives, pregnancy and lactation is derived primarily from association studies with some supported by pre-clinical experiments. Some of these factors are not amenable to testing in randomized trials and, for these, the inference must be based on evidence accumulated from multiple sources and study designs. For others, such as physical activity, the lessons drawn from these randomized trials suggest that a full-scale randomized trial testing the effects of an exercise intervention on cancer incidence is needed to determine accurately and adequately the full range of potential health effects.

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