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Factors that modify breast cancer risk in women

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INTRODUCTION

Globally, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women [1]. As an example, breast cancer is the most common cancer in females in the United States and the second most common cause of cancer death in women [2]. Approximately half of breast cancers can be explained by known risk factors, like reproductive factors and proliferative breast disease. An additional 10 percent are associated with family history and genetics. In addition, risk may be modified by demographic, lifestyle, and environmental factors.

This topic will review risk factors that modify breast cancer risk in women. Breast cancer chemopreventive medications (tamoxifen, raloxifene, aromatase inhibitors) are reviewed separately. Screening for breast cancer and risk prediction models that can help tailor screening recommendations for breast cancer are discussed separately.

- (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)
- (See "Screening for breast cancer: Strategies and recommendations", section on 'Breast cancer risk determination'.)
- (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Risk assessment models'.)

FACTORS ASSOCIATED WITH GREATER BREAST CANCER RISK

Increasing age — The risk of breast cancer increases with older age. Using data from the Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman developing breast cancer in the United States between 2013 and 2015 was [2]:

- Birth to age 49 – 2.1 percent (1 in 49 women)
- Age 50 to 59 – 2.4 percent (1 in 42 women)
- Age 60 to 69 – 3.5 percent (1 in 28 women)
- Age 70 and older – 7.0 percent (1 in 14 women)
- Birth to death – 12.9 percent (1 in 8 women)

Female sex — Breast cancer occurs 100 times more frequently in women than in men. In the United States, over 280,000 women are diagnosed with invasive breast cancer each year, compared with fewer than 3000 cases that occur annually in men [2].

Race/ethnicity — In the United States, the highest breast cancer risk occurs among White women, although breast cancer remains the most common cancer among women of every major ethnic/racial group [2].

Many of the racial differences in breast cancer rates are attributable to factors associated with lifestyle. In analyses in a cohort of over 156,000 postmenopausal women, the age-adjusted incidence of breast cancer for White women was higher than for other groups, but adjustment for breast cancer risk factors accounted for the differences for all but African Americans [3].

In a separate analysis, using population-based cancer registries from the National Program of Cancer Registries and SEER, the rate of newly diagnosed breast cancer (per 100,000 women) was 124 and 122 for White and Black women, respectively [4]. Despite this, Black women more commonly presented with regional or advanced disease (46 versus 36 percent) and had a 41 percent higher breast cancer-specific mortality rate (30 versus 21 deaths per 100,000 women). One analysis has also suggested that breast cancer in women less than 40 years old and triple-negative breast cancers are more common among African Americans than White Americans [5].

Weight and body fat in postmenopausal women — Obesity (defined as body mass index [BMI] ≥30 kg/m^2) is associated with an overall increase [6] in morbidity and mortality. However, the risk of breast cancer associated with BMI differs by menopausal status. (See "Overweight and obesity in adults: Health consequences".)

- **Postmenopausal women –** A higher BMI and/or perimenopausal weight gain have been consistently associated with a higher risk of breast cancer among postmenopausal women [7-9]. As examples:

- In a meta-analysis of more than 1000 epidemiologic studies, women with a higher BMI experienced a higher risk of postmenopausal breast cancer (relative risk [RR] 1.1 per 5 BMI units, 95% CI 1.1-1.2), particularly estrogen receptor (ER)-positive breast cancer [10].

- In a separate meta-analysis of 50 studies, for each 5-kg increase in adult weight gain, the RR for postmenopausal breast cancer among no- or low-menopausal hormone therapy users was 1.11 (95% CI 1.08-1.13) [11].

The association between a higher BMI and postmenopausal breast cancer risk may be mediated by higher estrogen levels resulting from the peripheral conversion of estrogen precursors (from adipose tissue) to estrogen [12,13]. Arguing for this mechanism are data suggesting that, even among women with normal BMI, a higher body-fat percentage is associated with higher breast cancer risk. In a secondary analysis of the Women's Health Initiative (WHI) cohort, among 3460 postmenopausal women with normal BMI, the multivariable-adjusted hazard ratios (HRs) for breast cancer risk among those with the highest quartile of body fat versus the lowest was 1.89 (95% CI 1.21-2.95) [13].

In addition, hyperinsulinemia may also contribute to the obesity-breast cancer relationship because a high BMI is associated with higher insulin levels [14]. (See 'Others' below.)

Of note, estrogen plus progestin increased breast cancer risk in all BMI groups in the WHI randomized trial [15]. (See "Menopausal hormone therapy: Benefits and risks".)

- **Inverse relationship in premenopausal women** – Unlike postmenopausal women, an increased BMI is associated with a **lower** risk of breast cancer in premenopausal women, particularly in early adulthood [16,17]. In a multicenter analysis using pooled individual-level data from approximately 760,000 premenopausal women from 19 prospective cohorts, there was a 4.2-fold increased risk between the lowest and highest BMI categories (BMI <17 versus ≥35) at ages 18 to 24 years [17]. The explanation of this finding remains unclear.

Tall stature — Increased height is associated with a higher risk of breast cancer in both premenopausal and postmenopausal women [18,19]. In one study, women who were >175 cm (69 inches) tall were 20 percent more likely to develop breast cancer than those <160 cm (63 inches) tall [20]. The mechanism underlying this association is unknown but may reflect the influence of nutritional exposures during childhood and puberty [21].

Benign breast disease — A wide spectrum of pathologic entities is included in the category of benign breast disease. Among these, proliferative lesions (especially those with histologic

atypia) are associated with an increased risk of breast cancer. (See "Overview of benign breast diseases".)

Dense breast tissue — The density of breast tissue reflects the relative amount of glandular and connective tissue (parenchyma) to adipose tissue [22]. Women with mammographically dense breast tissue, generally defined as dense tissue comprising ≥75 percent of the breast, have a higher breast cancer risk compared with women of similar age with less or no dense tissue [22-26]. (See "Breast density and screening for breast cancer", section on 'Breast density and breast cancer risk'.)

In addition, longitudinal increases (or slower decreases in breast density) are associated with an increased risk of breast cancer, while decreases (particularly more rapid ones) are associated with a decreased risk [27,28]. It is unclear whether screening recommendations should differ for women with dense breasts. (See "Screening for breast cancer: Strategies and recommendations".)

Breast density does not appear to be associated with a specific breast cancer subtype [29,30] or with higher breast cancer mortality [31].

Although breast density is a largely inherited trait, other factors can influence density [32-35]. For example, lower density has been associated with higher levels of physical activity [34] and with a low-fat, high-carbohydrate diet [35]. In postmenopausal women, estrogen and progesterone increase breast density [36-38], while the ER antagonist tamoxifen decreases breast density [39,40]. Despite the association of exogenous hormones with breast density, breast density is not strongly correlated with endogenous hormone levels [41].

Bone mineral density — Because bone contains ERs and is highly sensitive to circulating estrogen levels, bone mineral density (BMD) is considered a surrogate for long-term exposure to endogenous and exogenous estrogen. In multiple studies, women with higher bone density have a higher breast cancer risk [42-44].

In a meta-analysis of eight prospective cohort and two nested-control studies that included over 70,000 postmenopausal women, of whom 1889 developed breast cancer, women in the highest hip BMD category were more likely to develop breast cancer compared with women in the lowest BMD category (RR 1.62, 95% CI 1.17-2.06) [45]. In a 2008 study from the WHI (including 9941 postmenopausal women), each unit increase in the total hip BMD T-score was associated with a higher breast cancer risk (HR 1.25, 95% CI 1.11-1.40) [44]. (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women", section on 'T-score'.)

Hormonal factors

Endogenous estrogen and hormone therapy

- **Higher endogenous estrogen levels –** Higher endogenous estrogen levels are associated with higher breast cancer risk (particularly hormone receptor-positive disease) in both postmenopausal and premenopausal women. For postmenopausal women, the correlation between a higher breast cancer risk and higher hormone levels (eg, estradiol, estrone) has been consistent [46-49]. Supporting this concept is the finding that reducing estrogen levels with aromatase inhibitors in postmenopausal women reduces breast cancer risk.

  Estrogen level associations with breast cancer risk among premenopausal women can be difficult to measure due to menstrual cycle variations. In a pooled analysis from seven studies, including 767 premenopausal women with breast cancer and 1699 controls, concentrations of estradiol, calculated free estradiol, estrone, androstenedione, dehydroepiandrosterone, and testosterone were positively associated with breast cancer risk [50]. For example, every twofold increase in estradiol concentration was associated with an odds ratio for breast cancer of 1.19 (95% CI 1.06-1.35). Concentrations of luteal-phase progesterone and calculated free testosterone were not significantly associated with such risk.

- **Menopausal hormone therapy –** Combined estrogen/progesterone replacement in women with intact uteri has been shown to increase risk of subsequent ER-positive breast cancer. However, in women with prior hysterectomy, single-agent estrogen replacement has not been associated with increased risk of breast cancer (and is actually associated with reduced risks). The relationship between menopausal hormone therapy and breast cancer is reviewed elsewhere. (See "Menopausal hormone therapy and the risk of breast cancer".)

- **Contraceptives –** Breast cancer risk is temporarily increased with current or recent use of combined oral contraceptives, but this association disappeared within two to five years of discontinuation. Additional data on the risks of hormone therapy in young women, particularly centered on estrogen-progestin contraceptives, are discussed separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Breast cancer'.)

Others

- **Androgens –** Preclinical data suggest that androgens (in particular, testosterone) exert dual effects on mammary tumor development, with a proliferative effect mediated by the ER and an antiproliferative effect mediated by the androgen receptor [51]. Elevated androgen (ie, testosterone) levels have been associated with an increased risk of postmenopausal and premenopausal breast cancer [46,50,52].

Testosterone association with breast cancer subtypes has not been consistently seen. Some studies suggest that elevated testosterone levels increase the risk of breast cancer specifically for hormone receptor-positive breast cancers [52-55], while one study suggests elevated testosterone levels are associated with a lower risk of hormone receptor-negative breast cancers [49].

- **Insulin pathway and related factors –** In reports from the Women's Health Initiative, higher insulin resistance levels were associated with higher breast cancer incidence (HR 1.34, 95% CI 1.12-1.61), as well as higher all-cause mortality and higher all-cancer-specific mortality [56,57]. In addition, although diabetes is not considered a breast cancer risk factor [58], a large pooled analysis drawing from 17 prospective studies suggested that insulin growth factor-1 was associated with breast cancer risk in both premenopausal and postmenopausal women [59].

Reproductive factors

Earlier menarche or later menopause — Early age at menarche is associated with a higher breast cancer risk [21,60]. Women with menarche at or after 15 years of age were less likely to develop hormone receptor-positive breast cancer compared with women who experienced menarche before the age of 13 years (HR 0.76, 95% CI 0.68-0.85) [21]. They also had a 16 percent lower risk of hormone receptor-negative breast cancer.

In one study, for every one-year delay in the onset of menarche, breast cancer risk was 5 percent lower [60]. In addition, later age at menopause is associated with higher breast cancer risk.

Nulliparity — Nulliparous women are at higher risk for breast cancer compared with parous women (RR from 1.2 to 1.7) [61,62]. Although parous women have an increased risk for developing breast cancer within the first few years of delivery relative to nulliparous women, parity confers a protective effect decades after delivery.

Whether multiparity confers protection against breast cancer is controversial, because it is difficult to separate the effects of multiparity from early first full-term pregnancy; however, studies suggest a decreased risk with increasing number of pregnancies [60,62,63].

Increasing age at first full-term pregnancy — The effect of parity also differs depending upon the age of first full-term birth. Women who become pregnant later in life have an increased risk of breast cancer [60,62,63]. In the Nurses' Health Study, compared with nulliparous women at or near menopause, the cumulative incidence of breast cancer (up to age 70) was 20 percent lower among women who delivered their first child at age 20; 10 percent lower for those delivering their first child at age 25 years; and 5 percent higher among those delivering their first child at 35 years [61]. The risk for a nulliparous woman of any age was similar to that of a woman with a first full-term birth at age 35.

It has been proposed that full cellular differentiation, which occurs in the gland during and after pregnancy, protects the breast from breast cancer development [64]. A later age at first birth may confer a greater risk than nulliparity because of the additional proliferative stimulation placed on breast cells that are more likely to be fully developed and perhaps more prone to cell damage.

The relationship between infertility and breast cancer is controversial and is discussed below. (See 'Infertility' below.)

In vitro fertilization does not appear to be associated with breast cancer risks. (See "Assisted reproductive technology: Pregnancy and maternal outcomes", section on 'Breast cancer'.)

Personal and family history of breast cancer

- **Personal history of breast cancer –** A personal history of either invasive or in situ breast cancer increases the risk of developing an invasive breast cancer in the contralateral breast.

  A 2010 study using SEER data that included almost 340,000 women with a primary breast cancer found the incidence of invasive contralateral breast cancer (CBC) was 4 percent during an average follow-up of 7.5 years [65]. The risk of a CBC varied by age at the time of the index breast cancer diagnosis (those <30 years at diagnosis and those with ER-negative cancers were at higher risk; however, these rates have been decreasing over time, most likely due to advances in adjuvant breast cancer therapy).

  In a separate study, risks of CBC among those with hormone receptor-positive breast cancer were approximately 0.2 percent per year for the first five years after diagnosis (during adjuvant endocrine therapy), 0.5 percent per year for the subsequent five years (after endocrine treatment), and somewhere between these estimates for the following 5 to 10 years [66].

  In the setting of a personal history of breast cancer, a family history of breast cancer further increases CBC risk. For example, in a case-control study of women with CBC matched with women with unilateral breast cancer as controls, having a first-degree relative with breast cancer increased risk of CBC by almost twofold [67]. Risks were further increased if the relative was diagnosed at age <40 years.

- **Family history and genetic mutations –** The risk associated with a positive family history of breast cancer is strongly affected by the number of female first-degree relatives with and without cancer, and the age when they were diagnosed.

  In a pooled analysis of over 50,000 women with breast cancer and 100,000 controls, the risk of breast cancer was [68]:

- Increased almost twofold if a woman had one affected first-degree relative
- Increased threefold if she had two affected first-degree relatives

The age at diagnosis of the affected first-degree relative also influences the risk for breast cancer [68]. Women have a threefold higher risk if the first-degree relative was diagnosed before age 30 (RR 3.0, 95% CI 1.8-4.9), but the risk is only 1.5-fold higher if the affected relative was diagnosed after age 60. (See "Screening for breast cancer: Strategies and recommendations", section on 'Models predicting pathogenic BRCA1/2 mutations'.)

However, family history is still an important risk factor even with relatives with a later age at diagnosis. In a prospective cohort study of over 400,000 women, family history of breast cancer in a first-degree relative was associated with a higher risk of breast cancer, regardless of whether the relative was diagnosed before or after 50 years of age [69]. Criteria for genetic screening are discussed elsewhere. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Criteria for genetic risk evaluation'.)

Specific genetic mutations that predispose to breast cancer are rare; as an example, only approximately 6 percent of all breast cancers are directly attributable to inheritance of a *BRCA1/2* pathogenic variant. These and other variants are discussed in more detail elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer" and "Overview of hereditary breast and ovarian cancer syndromes".)

Alcohol use and smoking — Alcohol consumption is associated with a higher risk of breast cancer. This topic is discussed in detail elsewhere. (See "Overview of the risks and benefits of alcohol consumption", section on 'Breast cancer'.)

Although results have not been uniform, multiple studies suggest there is a modestly increased risk of breast cancer in smokers [70-75]. For example, in a meta-analysis of 27 prospective observational studies, the risk of breast cancer was higher among women with any history of smoking (summary RR 1.10, 95% CI 1.02-1.14) [70]. The relationship between cigarette smoking and breast cancer is complicated; as many as 50 percent of women who smoke also consume alcohol, a known breast cancer risk factor [70]. However, even in women who did not drink alcohol, there was still a higher breast cancer risk associated with smoking [70].

Studies regarding passive smoking and breast cancer risk have been inconclusive, but evidence for an increase in risk with passive smoking is emerging [72,76,77].

Exposure to therapeutic ionizing radiation — Exposure to ionizing radiation of the chest at a young age, as occurs with treatment of Hodgkin lymphoma or in survivors of atomic bomb or nuclear plant accidents, is associated with an increased risk of breast cancer [78-80]. The

most vulnerable ages appear to be between 10 to 14 years (prepuberty), although excess risk is seen in women exposed as late as 45 years of age [81]. After age 45, risk is attenuated. (See "Second malignancies after treatment of classic Hodgkin lymphoma".)

FACTORS ASSOCIATED WITH DECREASED BREAST CANCER RISK

Medical and surgical risk reduction strategies — Chemoprevention with aromatase inhibitors in postmenopausal women, or tamoxifen in pre- or postmenopausal women, reduces breast cancer risks. Mastectomy also greatly decreases breast cancer risks, and is an appropriate option for select patients at high risk, for example *BRCA* carriers. These strategies, as well as appropriate candidates, are discussed in detail elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer" and "Overview of hereditary breast and ovarian cancer syndromes" and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention" and "Contralateral prophylactic mastectomy".)

The effect of oophorectomy on breast cancer risk in the general population and among *BRCA* carriers is discussed elsewhere. (See "Elective oophorectomy or ovarian conservation at the time of hysterectomy" and "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Bilateral salpingo-oophorectomy'.)

Breastfeeding — A protective effect of breastfeeding has been shown in multiple case-control and cohort studies and meta-analyses, the magnitude of which depends on the duration of breastfeeding and on the confounding factor of parity [82,83].

A large pooled analysis that included individual data from 47 epidemiologic studies (approximately 50,000 women with invasive breast cancer and 97,000 controls) estimated that for every 12 months of breastfeeding, there was a 4.3 percent reduction in the relative risk (RR) of breast cancer [82]. Another meta-analysis suggested that this association was stronger for hormone receptor-negative breast cancers [83]. A postulated mechanism for the protective effect of breastfeeding is that it may delay the re-establishment of ovulatory cycles.

Physical activity — While there is no prospective clinical trial evidence, the observational studies strongly suggest that physical activity is associated with lower breast cancer risk [84-86]. A 2016 review of epidemiologic studies estimated that risk of breast cancer was lower among the most physically active women compared with the least active women (RR 0.88, 95% CI 0.85-0.90) [84]. Another meta-analysis of 139 prospective and retrospective studies evaluated physical activity and weight loss in approximately 237,000 breast cancer cases and 4 million controls. Higher physical activity levels were associated with lower breast cancer

risk (odds ratio [OR] 0.78, 95% CI 0.76-0.81). The findings were similar in pre-and postmenopausal women and for light- and high-intensity physical activity [87].

Given the paradoxical effect of weight in premenopausal and postmenopausal women, the reduction in breast cancer risk seen with exercise is likely not mediated through weight control alone [88-91]. Increased physical activity may reduce breast cancer risk through hormonal influences such as reducing serum estrogens, insulin, and insulin growth factor-1 levels [92-94]. (See 'Weight loss in postmenopausal women' below and 'Low-fat dietary pattern in postmenopausal women' below and 'Hormonal factors' above.)

Weight loss in postmenopausal women — While not seen in all studies [13,95], weight loss in postmenopausal women may reduce breast cancer risk [8,87,96-101], as observed in the examples below:

- In the meta-analysis of prospective and retrospective studies discussed above, including approximately 237,000 cases and 4 million controls, weight loss was associated with lower breast cancer risk (OR 0.82, 95% CI 0.67-0.97) [87].

- Among prospective studies, the Nurse's Health Study assessed weight change since menopause among approximately 50,000 women followed for up to 24 years. Women with no prior hormone therapy use who maintained a weight loss of ≥10 kg were at lower breast cancer risk than women who did not (RR 0.43, 95% CI 0.21-0.86) [8]. More recently, in roughly 61,000 postmenopausal women in the Women's Health Initiative (WHI), those who lost ≥5 percent of body weight in the three years from study entry had a lower breast cancer incidence over a mean of 11.4 years compared with women who did not (hazard ratio [HR] 0.88, 95% CI 0.78-0.98) [96].

- Retrospective studies have shown similar results. Among almost 34,000 participants in the Iowa Women's Health Study reporting recalled weight over a 35 year period, those with intentional weight loss ≥20 pounds had lower breast cancer risk (RR 0.81, 95% CI 0.66-1.00) [100], with similar significant findings in a subsequent analysis (RR 0.77, 95% CI 0.55-0.93) [99].

Low-fat dietary pattern in postmenopausal women — The low-fat eating pattern involves dietary moderation, and is similar to the Dietary Approaches to Stop Hypertension diet, but with somewhat more emphasis on fat intake reduction [102,103]. This pattern has been associated with reducing deaths following breast cancer diagnosis [104], with potential mediating mechanisms including reducing metabolic syndrome components and estradiol [13,105].

The WHI Dietary Modification trial randomly assigned almost 49,000 postmenopausal women with no previous breast cancer to a usual diet comparison group or a low-fat dietary pattern, with every-three-week group sessions in the first year, and quarterly maintenance

sessions throughout the 8.5-year intervention period [105,106]. The dietary intervention reduced fat intake to 24 percent calories from fat, and increased the intake of fruit, vegetables, and grains, resulting in modest weight loss (3 percent). After cumulative follow-up of nearly 20 years, the dietary group experienced fewer deaths from breast cancer (0.037 versus 0.047 percent; HR 0·79, 95% CI 0·64-0·97). This finding did not change by addition of time-dependent weight change and was mediated, in part, by a reduction in poor prognosis, estrogen receptor-positive, progesterone receptor-negative breast cancers (HR 0.77, 95% CI 0.64-0.94).

The influence of dietary fat, as a single component of diet, on breast cancer risks is discussed below. (See 'Other dietary factors' below.)

INCONCLUSIVE FACTORS

Diet rich in fruits and vegetables, fish, and olive oil (eg, Mediterranean diet) — A Mediterranean diet, characterized by an abundance of plant foods, fish, and olive oil, may decrease breast cancer risk, but further study is needed.

In one clinical trial, almost 4300 women aged 60 to 80 years were randomly assigned to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet with a primary outcome of cardiovascular disease [107]. Over 4.8 years of follow-up, there were 35 cases of breast cancer (33 of which were hormone receptor positive). There were fewer breast cancer cases in the Mediterranean diet supplemented with olive oil versus the control group (hazard ratio [HR] 0.32, 95% CI 0.13-0.79). Limitations include small event number and an absence of mammography information. Thus, findings would need to be confirmed in a larger study.

Studies have been conflicting in regards to whether a Mediterranean diet is associated with a decrease in incidence of all breast cancer, or estrogen receptor (ER)-negative breast cancers only.

- In a systematic review, three of four cohort studies examining Mediterranean diet adherence and breast cancer showed inverse associations with postmenopausal ER-negative, but not ER-positive, breast cancers [108].
- In the same time frame, a meta-analysis of five cohort studies examining Mediterranean diet and breast cancer in postmenopausal women found a 6 percent lower risk for all breast cancers, which was of borderline significance (relative risk [RR] 0.94, 95% CI 0.88-1.01) [109].
- In the Nurses' Health Study, the association of alternate Mediterranean Diet score (aMed) with breast cancer risk was examined [110]. With 3580 cases of breast cancer,

the highest quintile of aMed was associated with similar rates of total and ER-positive breast cancer to the lowest quintile, but lower rates of ER-negative breast cancer.

Other dietary factors — With rare exception, data gathered largely from observational studies suggest that certain dietary factors may modify breast cancer risk. However, methodologic issues regarding the measurement of nutritional intake and the contribution of other factors (eg, alcohol use) complicate these analyses and the interpretation of studies. The concept of studies designed to evaluate foods and/or nutrients in isolation is being challenged by the concept that evaluation of overall dietary patterns may better reflect the nature of the actual dietary exposure in a population [111]. Information regarding dietary patterns and breast cancer risk is found above. (See 'Low-fat dietary pattern in postmenopausal women' above and 'Diet rich in fruits and vegetables, fish, and olive oil (eg, Mediterranean diet)' above.)

A summary of what is known about specific dietary factors and breast cancer risk is discussed below.

- **Fruits and vegetables –** Data regarding the contribution of fruits and vegetables on breast cancer risk are inconclusive, with some evidence suggesting no effect and other studies suggesting a lower breast cancer risk in women with higher fruit and vegetable intakes.

  In a prospective study of over 993,000 women observed for 11 to 20 years, no association between total fruit and vegetable intake and overall risk of breast cancer was identified [112]. However, other studies have suggested a decreased breast cancer risk in diets high in fruits and vegetables [105,113-115]. A 2010 meta-analysis of studies evaluating breast cancer risk reported that high consumption of a diet composed predominantly of fruits and vegetables was associated with lower breast cancer risk (odds ratio [OR] 0.89, 95% CI 0.82-0.99) [114].

  Randomized clinical trials incorporating a pattern of increased fruits and vegetables are discussed above. (See 'Low-fat dietary pattern in postmenopausal women' above and 'Diet rich in fruits and vegetables, fish, and olive oil (eg, Mediterranean diet)' above.)

- **Fat intake –** Observational studies evaluating dietary fat intake as a single dietary component provide inconsistent results regarding breast cancer risk [116]. However, a low-fat dietary pattern including increase in fruit, vegetables, and grains may reduce breast cancer mortality, as discussed above [105]. (See 'Low-fat dietary pattern in postmenopausal women' above.)

  A meta-analysis of cohort studies found no significant association between dietary fat intake and breast cancer risk (RR 1.03, 95% CI 0.76-1.40) [116]. However, in the AARP Diet and Health Study, women in the highest fat intake quintile had breast cancer rates

11 to 22 percent higher compared with women in the lowest quintile [117]. In a more recent meta-analysis of 15 prospective cohort studies evaluating dietary fat and breast cancer mortality, breast cancer-specific death was higher for women with the highest compared with lowest saturated fat intake (HR 1.5, 95% CI 1.09-2.09; p <0.01), but there is no such association with total fat intake [118].

These inconsistent results could reflect limitations of the dietary assessment methodology [119]. In this regard, one study found dietary fat intake significantly associated with breast cancer incidence only when intake was based on food diaries rather than the food frequency questionnaires most commonly used in observational studies [120]. (See "Dietary fat", section on 'Cancer'.)

- **Soy/phytoestrogens** – Phytoestrogens are naturally occurring plant substances with a chemical structure similar to 17-beta estradiol. They consist mainly of isoflavones (found in high concentrations in soybeans and other legumes) and lignans (found in a variety of fruits, vegetables, and cereal products). There is only low-quality evidence that soy-rich diets in Western women prevent breast cancer.

  A 2014 meta-analysis of eight studies evaluating the impact of soy food intake and breast cancer risk reported the following results [121]: pooled studies in Asian countries suggested that soy isoflavone has a protective effect in both pre- and postmenopausal women (OR 0.59, 95% CI 0.48-0.69; OR 0.59, 95% CI 0.44-0.74, respectively). Pooled studies on postmenopausal women in Western countries found that soy isoflavone intake has only a marginally protective effect (OR 0.92, 95% CI 0.83-1.00). However, further analyses stratifying by study design found no statistically significant association.

- **Red meat and processed meat** – Red meat and processed meat have been suggested to increase breast cancer risk, but data are inconclusive. Two meta analyses found processed meat to be associated with higher breast cancer incidence, but there was no observed association with red meat [122,123]. In the 2010 meta-analysis discussed above, there was no influence on the risk of breast cancer among women who reported a high intake of a diet rich in red/processed meats. Meanwhile, an association between intake of red meat (>5 servings per week) and premenopausal breast cancer has been reported in a few studies, but the evidence linking this to breast cancer risk is weaker than that for other cancers [124-126].

  The suggested relationship has been based on iron content, estrogen use as a supplement for cattle, and mutagens created by cooking. However, further data are needed.

- **Fiber intake** – In a meta-analysis of 24 epidemiologic studies, dietary fiber intake was associated with a 12 percent relative risk reduction in breast cancer incidence, with

dose-response analysis suggesting that every 10 gram/day increment in dietary fiber intake was associated with a 4 percent relative risk reduction in breast cancer [127]. However, randomized trials are necessary to confirm this finding.

Geographic residence — Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females. Breast cancer incidence rates are highest in North America, Australia/New Zealand, and in western and northern Europe and lowest in Asia and sub-Saharan Africa [1]. Despite the decreases in incidence rates in North America, breast cancer incidence has been increasing in other parts of the world, such as Asia and Africa. These international differences are thought to be related to societal changes occurring during industrialization (eg, changes in fat intake, body weight, age at menarche, and/or lactation and reproductive patterns such as fewer pregnancies and later age at first birth).

Even within the United States, the breast cancer risk varies substantially among regions. Geographic cluster regions with high breast cancer incidence rates have been identified, such as Cape Cod, Massachusetts; Long Island, New York; and Marin County, California [128-130]. These clusters are most likely due to regional differences in established breast cancer risk factors, but studies are ongoing to better understand these clusters [131]. Studies of migration patterns of women from low-risk areas to the United States are consistent with the importance of cultural and/or environmental changes [132]. In general, incidence rates of breast cancer are greater in second-generation migrants and increase further in third- and fourth-generation migrants.

Exposure to diagnostic radiation — Whether there is a link between breast cancer risk and diagnostic levels of irradiation (eg, mammography, chest radiographs, diagnostic spine imaging, computed tomography scans) in women without an inherited predisposition is controversial [133-135]. However, the risk of breast cancer associated with diagnostic radiation in women with an inherited *BRCA1/2* mutation appears to be increased [136-138]. (See "Screening for breast cancer: Evidence for effectiveness and harms", section on 'Radiation'.)

Medications — Several medication classes may have a modifying effect on breast cancer risk. However, the evidence to support their association to breast cancer is weak. These include the following:

Calcium/vitamin D — Although observational studies have suggested that higher plasma 25-hydroxyvitamin D levels may be associated with lower breast cancer risk in postmenopausal (but not premenopausal) women [139], randomized trials of vitamin D supplementation have not shown a protective effect [140].

In a Women's Health Initiative (WHI) randomized trial, among over 36,000 postmenopausal women, those assigned to 1000 mg of elemental calcium with 400 international units (IU) of vitamin D3 did not have higher rates of invasive breast cancer relative to placebo, during the seven years of intervention and 4.9 years of post-intervention follow-up [141,142]. Similarly, the randomized VITAL trial of over 25,000 men and women found no significant effect of vitamin D (2000 IU) with or without omega-3 supplements on breast cancer incidence, or on total invasive cancer and major cardiovascular disease events (the coprimary study outcomes) [143,144].

Nonsteroidal anti-inflammatory drugs — The data regarding a possible protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on breast cancer risk are mixed:

- A meta-analysis of 49 studies concluded that use of any NSAID was associated with a lower breast cancer risk of approximately 20 percent (OR 0.82, 95% CI 0.77-0.88), with similar findings for aspirin, acetaminophen, cyclooxygenase-2 inhibitors, and, to a lesser extent, ibuprofen [145].

- However, a 2012 report from the Nurses' Health Study found no association between the use of aspirin, NSAIDs, or acetaminophen and the incidence of breast cancer (overall or by hormone receptor status) [146]. In addition, in the only randomized trial in which the impact of low-dose aspirin (100 mg every other day) on cancer prevention was evaluated, no effect on breast cancer or total cancer was seen after an average of 10 years of follow-up [147].

Bisphosphonates — Oral bisphosphonates are commonly used for the treatment of osteoporosis and for women with breast cancer with evidence of bone loss attributed to aromatase inhibitors. Whether their use is a true protective factor for those without a history of breast cancer is unclear. (See "Bisphosphonate therapy for the treatment of osteoporosis".)

Although some studies have shown a decreased risk of breast cancer with bisphosphonates by approximately one-third [148-151], other studies, including a large observational cohort of over 64,000 postmenopausal women followed for approximately seven years, have not seen an association [152]. Low bone mineral density may reflect a lower-estrogen environment, so the decreased risk observed with bisphosphonates in some studies may reflect a population that is at lower risk of getting breast cancer. (See 'Bone mineral density' above.)

The protective effect of bisphosphonates in the adjuvant setting of women diagnosed with breast cancer is an ongoing area of research. (See "Use of osteoclast inhibitors in early breast cancer".)

Phthalates — Phthalates are chemicals found in medical supplies, food containers, cosmetics, toys, and medications, particularly those with suspended-release formulations

[153,154]. They have been reported to have hormonal effects [155], but the effect on breast cancer risk is still unclear. For example, in a nested case-control study of postmenopausal participants in the prospective WHI, there was no association between urinary metabolites of phthalates and breast cancer incidence [156]. However, in a nationwide Danish cohort study of women at risk for cancer, high levels of phthalate exposure from medications (≥10,000 cumulative mg, calculated from prescriptions filled) was associated with an approximately twofold increase in the rate of ER-positive breast cancer (but not ER-negative breast cancer) [157]. The association was stronger among premenopausal women. At this point, more conclusive data are needed to determine whether high-level exposure, as through long-term use of phthalate-containing medications, is a breast cancer risk factor.

Infertility — The association between infertility and breast cancer risk is controversial. Several epidemiologic studies suggest that infertility due to anovulatory disorders decreases the risk of breast cancer [63,158,159]. However, other studies have observed either no association or a slight increase in risk associated with infertility after adjusting for prior pregnancy history and age at first delivery [158,160].

Night-shift work — Night-shift work is recognized by the International Agency for Research on Cancer and the World Health Organization as a probable carcinogen [161], although evidence is mixed [161-164]. This association may be related to nocturnal light exposure, which results in the suppression of nocturnal melatonin production by the pineal gland [165]. Evidence to support this comes from the finding that low levels of 6-sulfatoxymelatonin (the major melatonin metabolite) are associated with an increased risk of breast cancer [165,166]. (See "Pharmacotherapy for insomnia in adults", section on 'Melatonin'.)

FACTORS THAT DO NOT INFLUENCE BREAST CANCER RISK

Abortion — Both a large pooled analysis [167] and population-based cohort studies [168-172] do not support an association between abortion (induced or spontaneous) and breast cancer risk. The effect of age of first full-term birth is discussed above. (See 'Increasing age at first full-term pregnancy' above.)

Chemicals — Organochlorines include polychlorinated biphenyls, dioxins, and organochlorine pesticides such as dichlorodiphenyltrichloroethane. These compounds are weak estrogens, highly lipophilic, and capable of persisting in body tissues for years. However, an association with breast cancer has not been demonstrated [173,174].

Antioxidants — There is no evidence for an effect of intake of vitamin A, E, or C or beta-carotene on breast cancer risk [175,176].

Tubal ligation — Early observational studies reported inconsistent results on the association between tubal ligation and breast cancer risk. A meta-analysis of 77,249 postmenopausal, cancer-free women found no association between tubal ligation and breast cancer risk (odds ratio 0.97, 95% CI 0.84-1.09) [177].

Caffeine — A number of studies have failed to show any association between caffeine intake and breast cancer risk [178,179]. (See "Benefits and risks of caffeine and caffeinated beverages".)

Other — Well-done epidemiologic studies have failed to find any association between cosmetic breast implants, electromagnetic fields, electric blankets, and hair dyes and breast cancer risk [174,180].

For women undergoing in vitro fertilization, there does not appear to be an increased long-term risk of breast cancer. This is discussed in detail elsewhere. (See "Assisted reproductive technology: Pregnancy and maternal outcomes", section on 'Breast cancer'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Factors that affect breast cancer risk in women (Beyond the Basics)")

SUMMARY

- **Non-modifiable risk factors for breast cancer** – Non-modifiable factors associated with higher breast cancer risk include increasing age, female sex, white race, family history, certain genetic alterations, breast atypia, and dense breast tissue. (See 'Factors associated with greater breast cancer risk' above.)

- **Reproductive risk factors –** Reproductive factors that increase breast cancer risk include early menarche, later age at the time of first pregnancy (>35 years old), absence of breastfeeding, and nulliparity. (See 'Reproductive factors' above.)

- **Modifiable risk factors**

  - For postmenopausal women, obesity is associated with a higher breast cancer risk, which is ameliorated by weight loss. However, a higher body mass index has been associated with a lower risk of breast cancer in premenopausal women. (See 'Weight and body fat in postmenopausal women' above.)

  - Combined estrogen/progesterone menopausal hormone therapy in women with intact uteri has been clearly shown to increase risk of subsequent estrogen receptor-positive breast cancer. However, in women with prior hysterectomy, single-agent estrogen replacement has not been associated with increased risk of breast cancer (and is actually associated with reduced risks). (See "Menopausal hormone therapy and the risk of breast cancer".)

  - Alcohol use and current smoking are associated with a higher risks of breast cancer. (See 'Alcohol use and smoking' above.)

  - A low-fat dietary pattern, which includes increase in fruits, vegetables, and grains, may reduce risk of death from breast cancer in postmenopausal women. (See 'Other dietary factors' above and 'Low-fat dietary pattern in postmenopausal women' above.)

  - Regular, moderate physical activity may provide modest protection against breast cancer. (See 'Physical activity' above.)

- **Factors that do not influence breast cancer risk –** A number of other variables, including abortion, caffeine intake, in vitro fertilization, cosmetic breast implants, and hair dyes are not associated with increased risks of breast cancer. (See 'Factors that do not influence breast cancer risk' above.)

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Conflict of interest policy

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