Risk Factors for Breast Cancer

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RISK Factors

Breast cancer is the most common cancer in females in the United States and the second most common cause of cancer death in women

- Half of breast cancers can be explained by known risk factors - reproductive factors and proliferative breast disease.
- Additional 10% are associated with family history and genetics.
- Risk may be **modified** by demographic, lifestyle, and environmental factors.

Cancer Incidence

Females		
Breast	297,790	31%
Lung & bronchus	120,790	13%
Colon & rectum	71,160	8%
Uterine corpus	66,200	7%
Melanoma of the skin	39,490	4%
Non-Hodgkin lymphoma	35,670	4%
Thyroid	31,180	3%
Pancreas	30,920	3%
Kidney & renal pelvis	29,440	3%
Leukemia	23,940	3%
All Sites	**948,000**	**100%**

Cancer Deaths

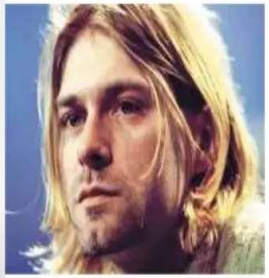
Females		
Lung & bronchus	59,910	21%
Breast	43,170	15%
Colon & rectum	24,080	8%
Pancreas	23,930	8%
Ovary	13,270	5%
Uterine corpus	13,030	5%
Liver & intrahepatic bile duct	10,380	4%
Leukemia	9,810	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,970	3%
All Sites	**287,740**	**100%**

Increasing Age

- The risk of breast cancer increases with older age.
- As per SEER database, the probability of a woman developing breast cancer in the United States between 2013 and 2015:
  - Birth to age 49 – 2.1% (1 in 49 women)
  - Age 50 to 59 – 2.4% (1 in 42 women)
  - Age 60 to 69 – 3.5% (1 in 28 women)
  - Age 70 and older – 7.0% (1 in 14 women)
- Birth to death/Lifetime risk – 12.9% (1 in 8 women)

Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7. Epub 2021 Jan 12

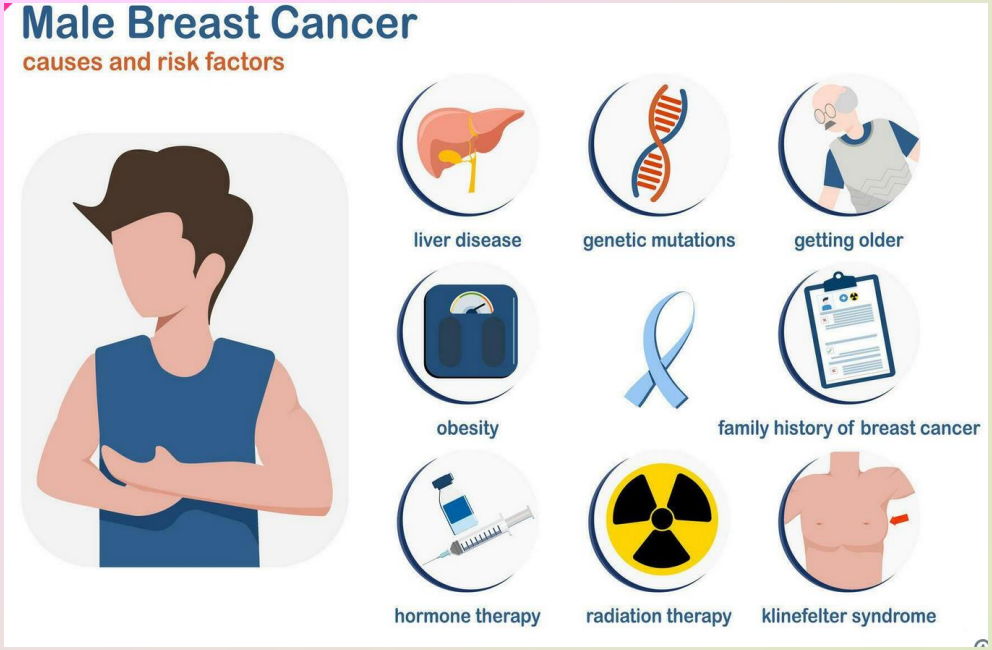
Avoiding Old Age and Cancer…only solution die young!



Anne Frank	15
Ritchie Valens	17
Joan of Arc	19
Buddy Holly	22
River Phoenix	23
James Dean	24
Tupac Shakur	25
Kurt Cobain	27
Jim Morrison	27
Amy Winehouse	27
Janis Joplin	27
Jimi Hendrix	27
John Belushi	33
Mozart	35
Marilyn Monroe	36
George Gershwin	38
Chopin	39

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



Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7. Epub 2021 Jan 12

Race/Ethnicity

- In the US, the highest breast cancer risk occurs among White women
- Many of the racial differences in breast cancer rates are attributable to factors associated with lifestyle.
- Newly diagnosed breast cancer (per 100,000 women) was 124 for White and 122 for Black women
- Black women:
  - More regional or advanced disease (46 vs 36%)
  - 41% higher breast cancer-specific mortality rate (30 versus 21 deaths per 100,000 women).
  - More common at younger age - less than 40 years old
  - More triple-negative breast cancers

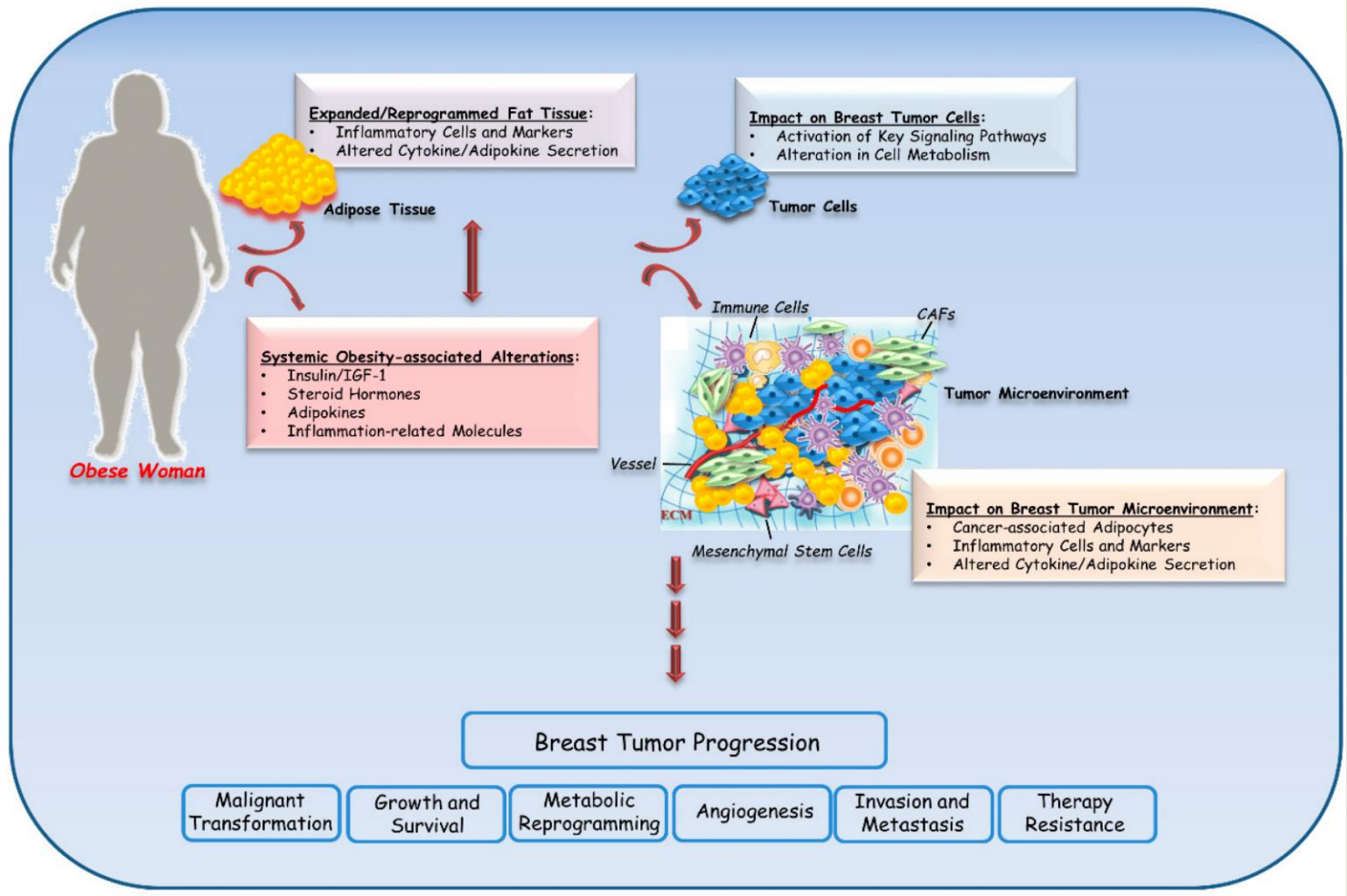
Patterns and Trends in Age-Specific Black-White Differences in Breast Cancer Incidence and Mortality - United States, 1999-2014. MMWR Morb Mortal Wkly Rep. 2016;65(40):1093. Epub 2016 Oct 14.
Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295(21):2492.

Weight and Body Fat in Postmenopausal Women

- A higher BMI (≥30 kg/m2) and/or perimenopausal weight gain have been consistently associated with a higher risk of breast cancer among postmenopausal women
- May be mediated by higher estrogen levels resulting from the peripheral conversion of estrogen precursors (from adipose tissue) to estrogen
- Hyperinsulinemia may also contribute to the obesity-breast cancer relationship because a high BMI is associated with higher insulin levels

Body Fatness and Cancer--Viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794.
Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009;101(1):48. Epub 2008 Dec 30.

Weight and Body Fat in Postmenopausal Women



Excess adiposity is associated with key local and systemic changes, such as altered secretion of cytokines, adipokines, growth factors, and inflammatory molecules. The complex interplay among all of these alterations may contribute to breast cancer progression by both directly impacting the phenotype of cancer epithelial cells and indirectly affecting the behavior of the tumor microenvironment.

Weight and Body Fat in Premenopausal Women

- An increased BMI is associated with a lower risk of breast cancer in premenopausal women, particularly in early adulthood
- Age 18-24 years: BMI >35 has 4.2-fold decreased risk of breast cancer compared to BMI <17
- The explanation of this finding remains unclear.

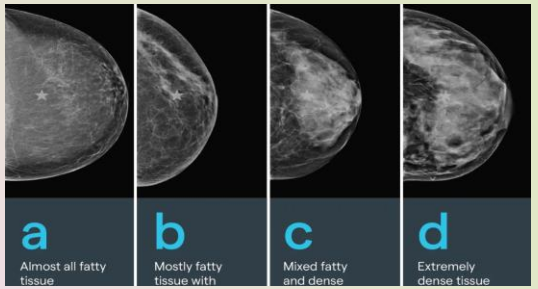
Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. JAMA Oncol. 2018;4(11):e181771. Epub 2018 Nov 8.

Tall Stature

- Increased height is associated with a higher risk of breast cancer in both pre and postmenopausal women
- In one study, women who were >69 inches tall were 20% more likely to develop breast cancer than those <63 inches tall
- The mechanism underlying this association is unknown but may reflect the influence of nutritional exposures during childhood and puberty

Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000;152(6):514.

Dense Breast Tissue



- The density of breast tissue reflects the relative amount of glandular and connective tissue (parenchyma) to adipose tissue
- 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
- Breast density does not appear to be associated with a specific breast cancer subtype or with higher breast cancer mortality
- Breast density is a largely inherited trait, other factors can influence density- Estrogen level?.
  - Lower density has been associated with higher levels of physical activity and with a low-fat diet
- ER antagonist Tamoxifen decreases breast density

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

- 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)

Endogenous Estrogen and Hormone Therapy

- **Higher endogenous estrogen** levels are associated with higher breast cancer risk (particularly hormone receptor-positive disease) in both postmenopausal and premenopausal women.

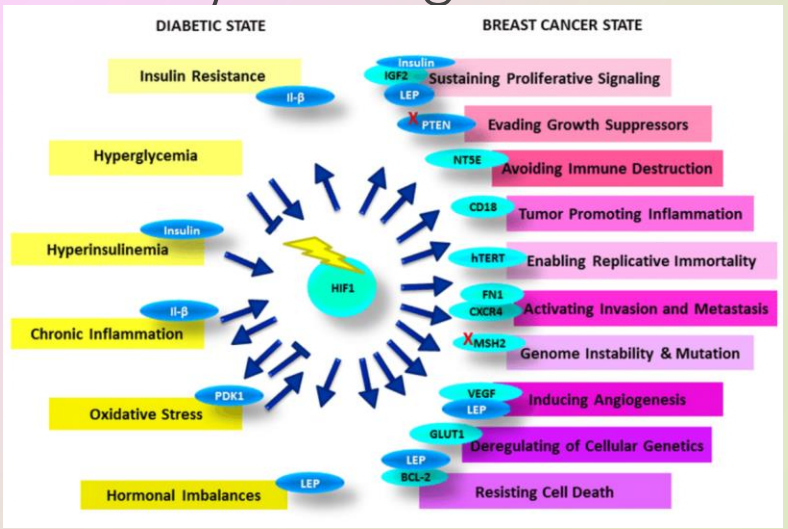
- **Combined estrogen/progesterone**
  - replacement in women with intact uteri has been shown to increase risk of subsequent ER-positive breast cancer.
  - However, in women with prior hysterectomy, single-agent estrogen replacement has not been associated with increased risk of breast cancer (and is actually associated with reduced risks).

- Breast cancer risk is temporarily increased with current or recent use of combined **oral contraceptives**, but this association disappeared within 2-5 years of discontinuation.

Endogenous Estrogen and Hormone therapy

- Elevated **androgen** (ie, Testosterone) levels have been associated with an increased risk of postmenopausal and premenopausal breast cancer

- 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), and higher all-cancer-specific mortality



Reproductive Factors

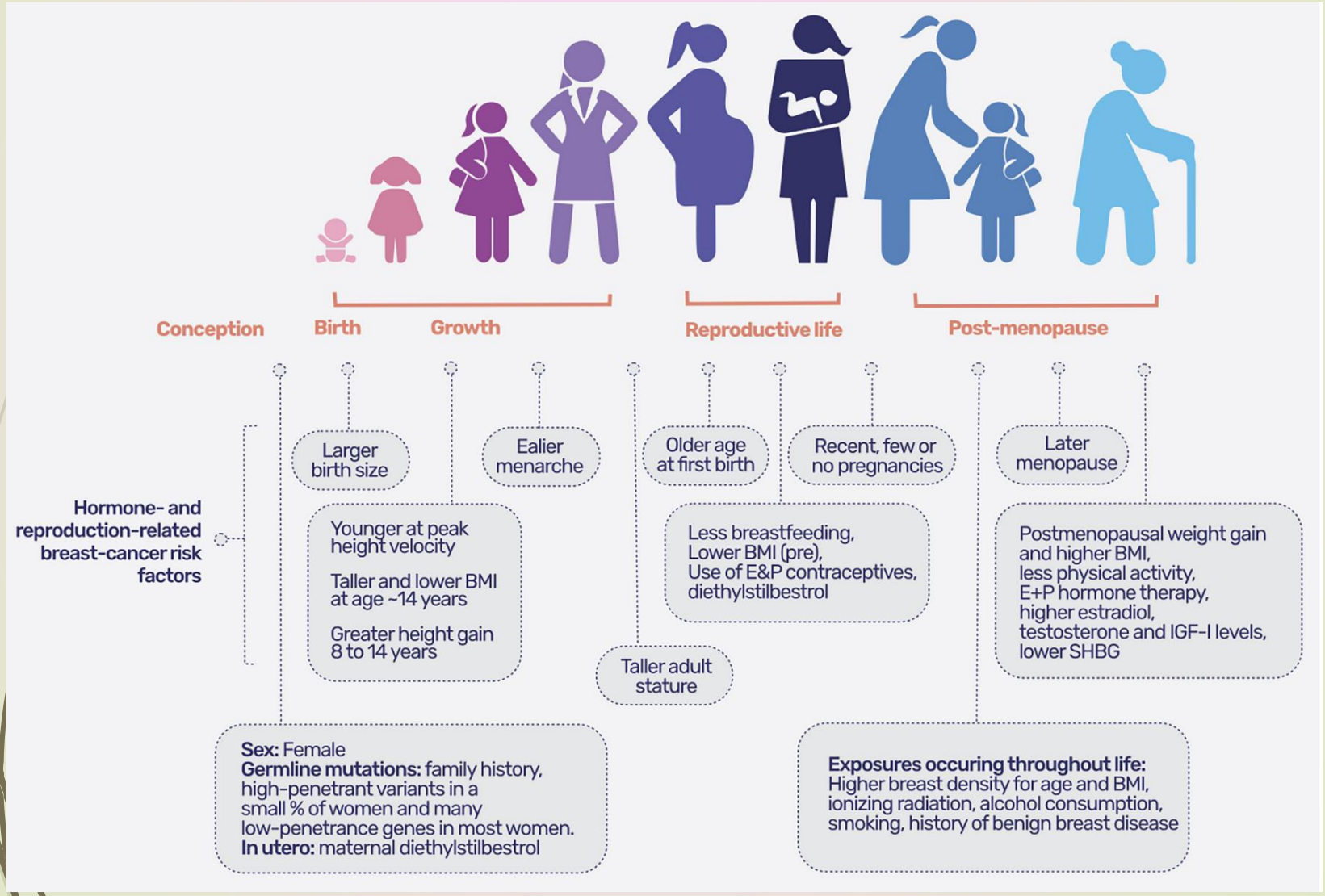
- Early age at menarche (<15 years age) is associated with a higher breast cancer risk.
- Later age at menopause is associated with higher breast cancer risk.
- Nulliparous women are at higher risk for breast cancer compared with parous women (RR from 1.2 to 1.7).
- Although parous women have an increased risk for developing breast cancer within the first few years of delivery relative to nulliparous women, parity confers a protective effect decades after delivery.
- **Multiparity**- some studies suggest a decreased risk with increasing number of pregnancies

Reproductive Factors

- 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.
  - a woman with a first full-term birth at **age 35** = nulliparous

- **In vitro fertilization** does **not** appear to be associated with breast cancer risks

Reproductive Factors



Personal and Family 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.

- The risk associated with a positive **family** history of breast cancer is strongly affected by the number of female first-degree relatives with cancer, and the age when they were diagnosed.

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

Alcohol Use

- There is consistent evidence that breast cancer risk is higher for individuals consuming both low (<1 drink per day) to high (≥3 drinks per day) levels of alcohol compared with abstainers

- Biologic **mechanisms:**
  - increased circulating estrogens and androgens,
  - enhancement of mammary gland susceptibility to carcinogenesis,
  - increased mammary carcinogen DNA damage,
  - greater potential for invasiveness of breast cancer cells

- Association with alcohol consumption and luminal A and HER2-amplified breast cancer


ALCOHOL AND BREAST CANCER RISK
Of 1,000 women in the UK
who each drink...
No alcohol
116 diagnosed with breast cancer in their lifetime
Up to 3 units a day
5 EXTRA CASES
121 diagnosed with breast cancer in their lifetime
3 to 6 units a day
27 EXTRA CASES
143 diagnosed with breast cancer in their lifetime
More than 6 units a day
70 EXTRA CASES
186 diagnosed with breast cancer in their lifetime
Source: CRUK estimates, May 2017, based on Bagnardi et al 2015 breast cancer risk, CRUK 2012 UK lifetime risk estimates, and Health Survey for England 2015 maximum alcohol units consumed on heaviest drinking day in past week.
LET'S BEAT CANCER SOONER
cruk.org
CANCER RESEARCH UK

Alcohol Use

- Breast cancer cases attributed to alcohol intake. In the US, the population attributable risk is estimated to be 2%. In Italy, where alcohol intake is higher, alcohol has been estimated to account for 11% of breast cancer cases

- An additive risk for the combination of postmenopausal hormone therapy and alcohol intake was reported in the Nurses' Health Study

- **Folic acid** intake may attenuate the effect of alcohol consumption on breast cancer. Observational data suggest that females who consume alcohol should also take a daily multivitamin fortified with folic acid. It is uncertain if supplemental folate intake is necessary in the United States, where grain is fortified with folic acid.

Cigarette Smoking

- Multiple studies suggest there is a modestly increased risk of breast cancer in smokers

- The relationship between cigarette smoking and breast cancer is complicated; as many as **50%** of women who smoke also consume alcohol, a known breast cancer risk factor

- Studies regarding passive smoking and breast cancer risk have been inconclusive, but evidence for an increase in risk with passive smoking is emerging

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.
- 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.
- After age **45**, risk is attenuated

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.

Breastfeeding

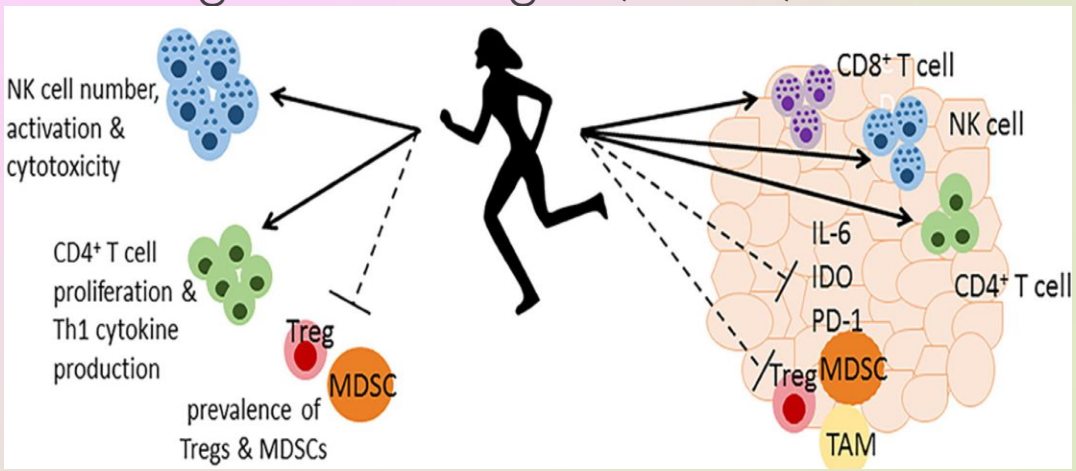
- A protective effect of breastfeeding has been shown in multiple studies, the magnitude of which depends on,
  - the duration of breastfeeding and
  - the confounding factor of parity
- Every 12 months of breastfeeding, there is a 4.3% reduction in the relative risk (RR) of breast cancer
- A postulated 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

- 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

- Increased physical activity may reduce breast cancer risk through hormonal influences such as reducing serum estrogens, insulin, and insulin growth factor-1 levels



Weight Loss in Postmenopausal Women

- While not seen in all studies, weight loss in postmenopausal women may reduce breast cancer risk

- Among prospective studies, the Nurse's Health Study assessed weight change since menopause among approx 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)

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.

- This pattern has been associated with reducing deaths following breast cancer diagnosis, with potential mediating mechanisms including reducing metabolic syndrome components and estradiol

Fat intake

- In a 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

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.
- 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 the Nurses' Health Study, the association of alternate Mediterranean Diet score (aMed) with breast cancer risk was examined. 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.

Fruits and Vegetables

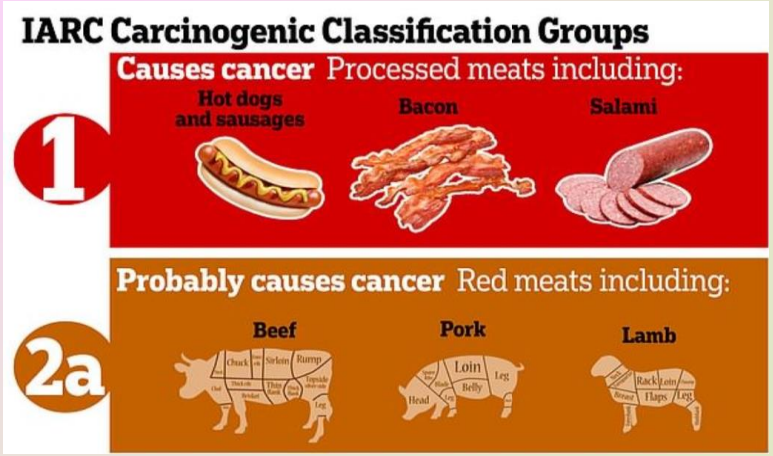
- Data regarding the contribution of fruits and vegetables on breast cancer risk are **inconclusive**, with some evidence suggesting no effect and other studies suggesting a lower breast cancer risk in women with higher fruit and vegetable intakes

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.

Meat Intake

- 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
- The suggested relationship has been based on iron content, estrogen use as a supplement for cattle, and mutagens created by cooking.



Fiber Intake

- In a meta-analysis of 24 epidemiologic studies, dietary fiber intake was associated with a 12% 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% relative risk reduction in breast cancer. However, randomized trials are necessary to confirm this finding

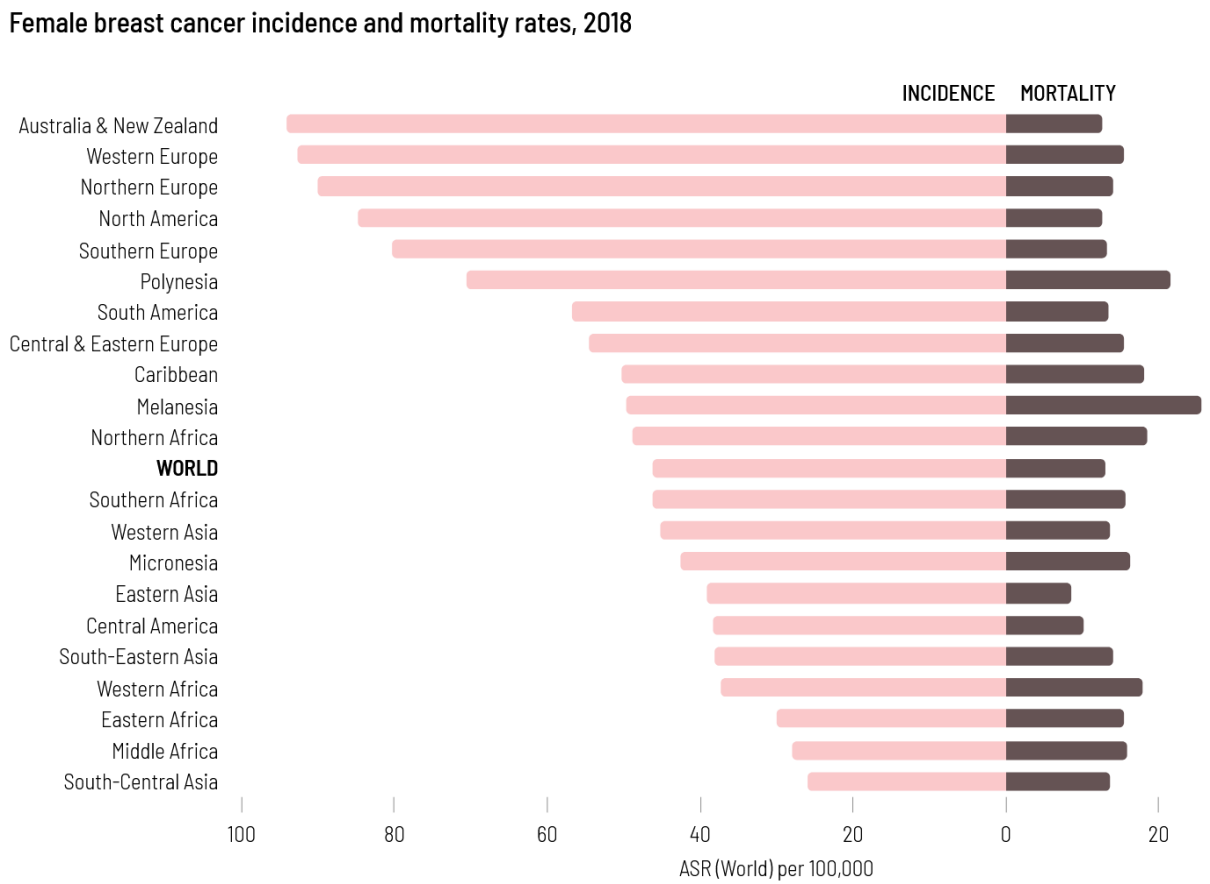
Geographic Residence

- Breast cancer incidence rates
  - highest in North America, Australia/New Zealand, and in western and northern Europe
  - lowest in Asia and sub-Saharan 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 reproductive patterns such as fewer pregnancies and later age at first birth).

- 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. In general, incidence rates of breast cancer are greater in second-generation migrants and increase further in third- and fourth-generation migrants.

Geographic Residence



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**.

- Diagnostic radiation increase risk in patients with BRCA1/2 mutation

Calcium/Vitamin D

- 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, however randomized trials of vitamin D supplementation have **not** shown a protective effect

- In 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

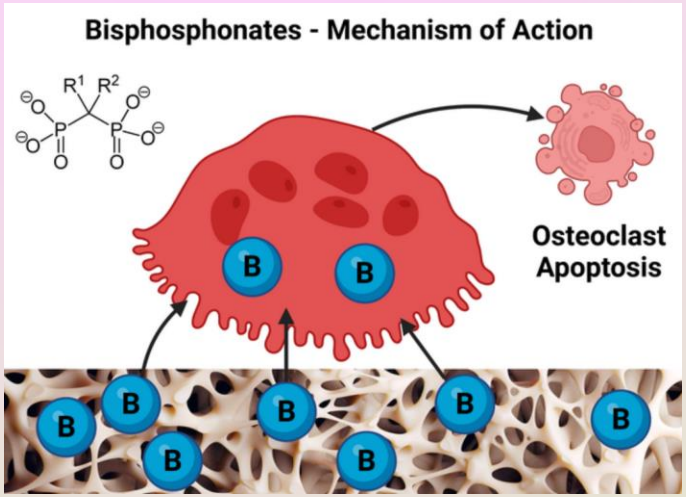
NSAIDs/Acetaminophen

- 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% (OR 0.82, 95% CI 0.77-0.88), with similar findings for aspirin, acetaminophen, cyclooxygenase-2 inhibitors, and, to a lesser extent, ibuprofen
- 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

Bisphosphonates

- Although some studies have shown a decreased risk of breast cancer with bisphosphonates by approximately one-third, other studies, including a large observational cohort of over 64,000 postmenopausal women followed for approximately seven years, have not seen an association.

- 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.



Phthalates

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

- They have been reported to have hormonal effects, but the effect on breast cancer risk is still **unclear**

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.
- 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

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 although evidence is mixed

- This association may be related to nocturnal light exposure, which results in the suppression of nocturnal melatonin production by the pineal gland. 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

Abortion

- Both a large pooled analysis and population-based cohort studies do **not** support an association between abortion (induced or spontaneous) and breast cancer risk

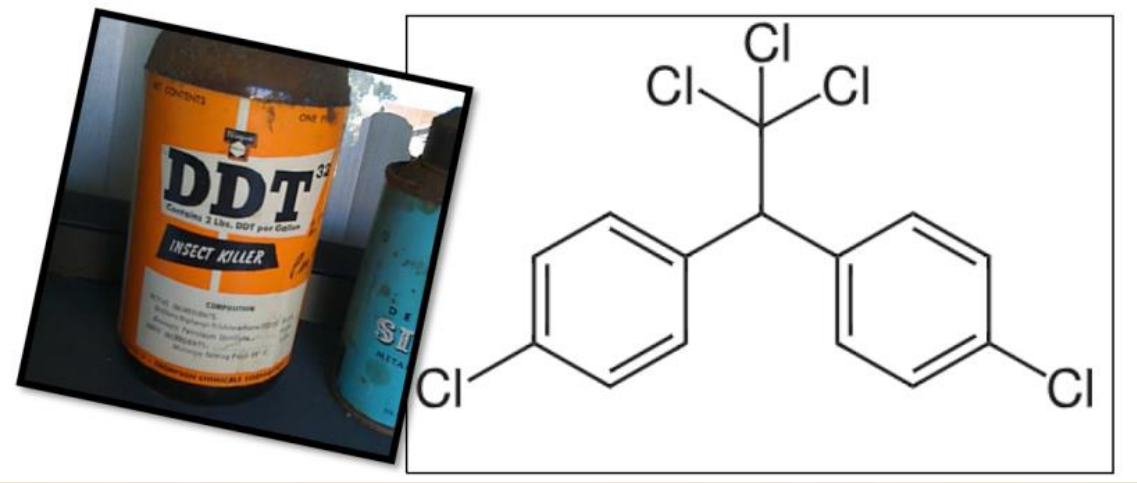
Tubal Ligation

- 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)

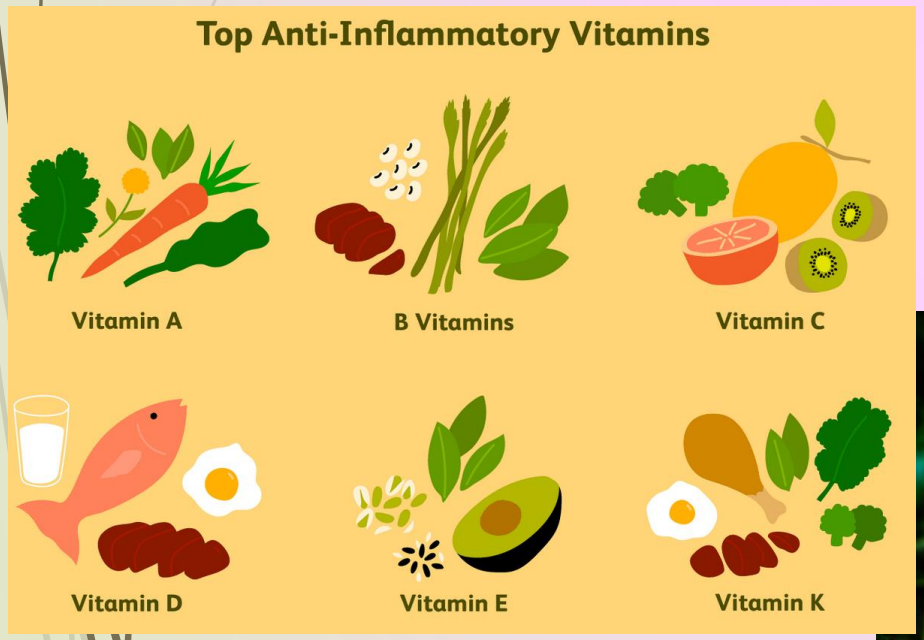
Chemicals

- 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



Antioxidants

- There is **no** evidence for an effect of intake of vitamin A, E, or C or beta-carotene on breast cancer risk



Caffeine Intake

- A number of studies have **failed** to show any association between caffeine intake and breast cancer risk

Other Risk Factors

- 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

Key Websites for Cancer Prevention and Screening

- NCI Prevention Site: cancer.gov/about-cancer/causes-prevention
- NCI Specific Cancers: www.cancer.gov/types
- Cancer Statistics: seer.cancer.gov/
- Screening Guidelines: epss.ahrq.gov/PDA/index.jsp
- National Comprehensive Cancer Network (NCCN): www.nccn.org
- UpToDate: Uptodate.com
- CDC Cancer Risk Graphs: gis.cdc.gov/Cancer/USCS/DataViz.html
- Office of Disease Prevention and Health Promotion: https://health.gov/

BREAST CANCER RISK?

Questions/Comments