

# Sunlight, Nutrition And Health Research Center

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## Breast cancer – risk and risk reduction factors

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### Abstract

Breast cancer strikes over 200,000 women per year in the U.S. Diet and lifestyle account for most of the population risk for breast cancer. Using a model that compared many countries in terms of breast cancer mortality and dietary intakes, it was found that countries with the highest consumption of animal products and alcohol and the lowest consumption of fish had five times the risk of breast cancer compared to those countries with intakes at the other ends of the spectrum. While a proper diet and exercise can reduce the risk of breast cancer, an additional way to reduce the risk is to get plenty of vitamin D. A recent analysis of the geographic variation of breast cancer mortality rates in the U.S. shows the highest rates in the northeast and urban areas, and lowest rates in the south and rural areas. According to this analysis, breast cancer risk could be cut in half by sufficient vitamin D levels. Dietary sources of vitamin D are insufficient to supply enough vitamin D to be effective in reducing the risk of colon cancer. Thus, one should try to get adequate vitamin D from the Sun, artificial UVB exposure, or supplements. It is the goal of this essay to present a summary of the latest information on the risk and risk reduction factors for breast cancer so that readers can make changes to reduce their risk of developing this disease. However, the reader is advised to do more study before changing diet and/or lifestyle based on what is presented here.

### Introduction

Breast cancer is, perhaps, the most feared cancer. It is common, often strikes in mid-life, can be deadly, and can profoundly affect a woman's opinion of herself and her body. In 2004, it is estimated that 216,000 women will discover they have breast cancer and 40,000 will die from it [Jemal et al., 2004]. In this critical review, we focus on current data regarding the effect of nutrition and lifestyle, on the risk of developing breast cancer. A health lifestyle, consisting of a healthy diet, physical activity, and avoidance of stimulants, is recommended from childhood throughout life [Gerber et al., 2003].

The two obvious risk factors for breast cancer are being female and advancing age. However, there are a number of risk and risk reduction factors for breast cancer other than the obvious ones. The primary risk factors at the population level are those that increase the circulating levels of hormones that encourage cell growth, such as estrogen, progesterin, insulin, and insulin-like growth factor-I

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Position of health organizations and agencies in Australia, Canada, New Zealand, the United Kingdom, and the United States, and the World Health Organization, on UV radiation and vitamin D

(IGF-I). The primary risk reduction factors are those that limit these growth signals and encourage cell differentiation and death, especially for cells that are developing in the wrong way. These factors include antioxidants and anti-carcinogens and vitamin D.

### **Dietary factors and breast cancer**

Thus, diet plays a very important role in breast cancer risk. The ecologic approach, which considers populations defined geographically, has always found that animal products, especially animal fat, are a very important risk factor for breast cancer [Armstrong and Doll, 1975; Rose et al., 1986; Sasaki et al., 1993; Caygill et al., 1996; Hebert and Rosen, 1996; Grant, 2002a] (see Figure 1). These studies also generally find that fish consumption is a risk reduction factor for breast cancer [Kaizer et al., 1989; Sasaki et al., 1993; Caygill et al., 1996; Hebert and Rosen, 1996; Grant, 2002a]. The fat and fish links have been confirmed in some case-control [Favero et al., 1998; Shannon et al., 2003] and cohort [Cho et al., 2003] studies. Red meat is an important risk factor [Hermann et al., 2002; Cho et al., 2003]. Animal products have not been found to be risk factors in cohort studies [Missmer et al., 2002], but this may be due to the fact that participants in cohort studies tend to have similar diets. In the ecologic approach, countries may differ by 10-fold in the fraction of energy derived from animal products, (e.g., 4.3% in Korea, 34% in the U.S., and 42% in Finland in 1970). In single-country cohort studies, the variation is usually less than a factor of two.

Vegetable products in general seem to confer some protection against breast cancer, perhaps by replacing animal products in the diet [Grant, 2002a]. High consumption of fruits and vegetables was found to be associated with half the usual risk for breast cancer in a study conducted in New York State [Freudenheim et al., 1996]. The same study found no risk reduction for vitamin supplements. A case-control study in Italy found that raw vegetables were associated with reduced risk of breast cancer [Favero et al., 1998]. A study in Shanghai found that certain fruits and vegetables were associated with a lower rate of breast cancer [Malin et al., 2003].

There is evidence that sugar and a high glycemic index (e.g., diets high in sugar, potatoes, and refined grains) are risk factors for breast cancer [Favero et al., 1998; Augustin et al., 2001; Potischman et al., 2002]. A related study found that higher circulating levels of glucose are associated with increased risk of breast cancer [Muti et al., 2002].

High alcohol consumption has been correlated with breast cancer in several studies. Increased estrogen and androgen levels in women consuming alcohol appear to be important mechanisms underlying the association [Singletary and Gapstur, 2001].

### **Other factors and breast cancer**

Overweight and obesity are associated with increased risk of breast cancer due to increased levels of circulating insulin and estrogen [Stoll, 1998, 2002]. The mammary gland is sensitive to the level of circulating estrogens [La Guardia and Giammanco, 2001]. A combined case-control and cohort study found that breast cancer risk increased with increasing body mass index (BMI), and this increased risk was substantially reduced by adjustment for serum estrogen concentrations. Adjusting for free estradiol reduced the risk ratio for breast cancer associated with a 5 kg/m<sup>2</sup> increase in BMI from 1.19 (95% CI = 1.05 to 1.34) to 1.02 (95% CI = 0.89 to 1.17) [Key et al., 2003]. Thus, the increased

risk of breast cancer with increased weight seems to be associated with increased levels of circulating estrogen.

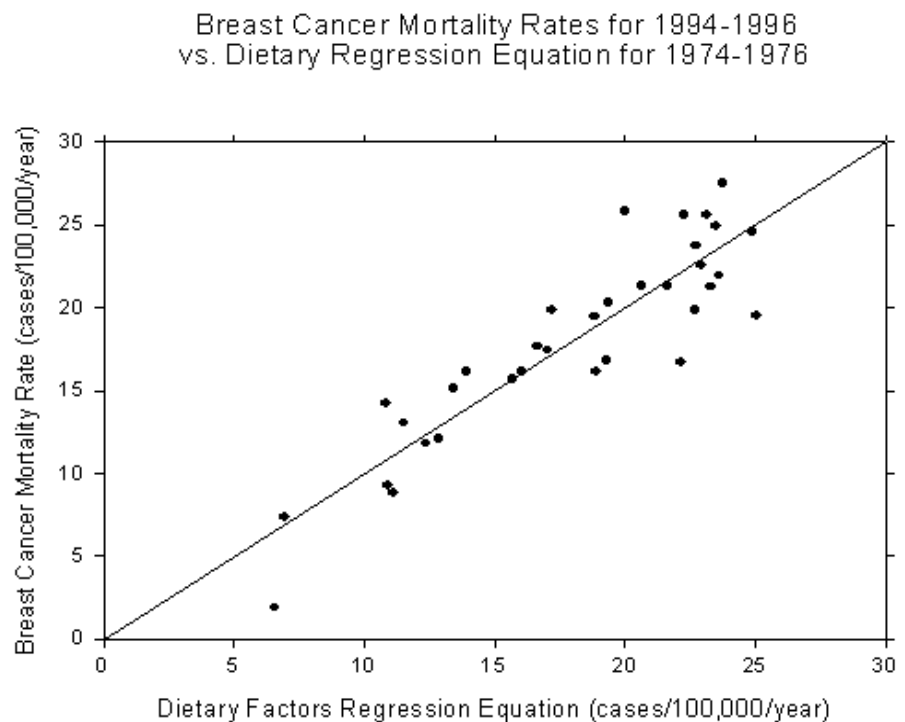


Figure 1. Breast cancer mortality rates for 1994-1996 vs. dietary factors for the same period. Animal product energy divided by total energy and alcohol were important risk factors, while fish was an important risk reduction factor [Grant, 2002a].

The hormone IGF-I also appears to play an important role in breast cancer. Epidemiological studies found an association between elevated blood levels of IGF-I and an increased risk for breast cancer. IGF-I is the major mediator of growth hormone (GH) action. On the cellular level, IGF-I enhances cell proliferation and inhibits cell death. Further, IGFs are also involved in blood vessel sprouting, an important process in cancer progression. These characteristics are the basis for their involvement in maintenance and progression of cancer. The functions of IGF-I are mainly mediated through the type-I IGF-receptor [Furstenberger et al., 2003]. In addition, there is a tight link between the growth regulatory pathways of IGFs and estrogens in estrogen-receptor (OR)-positive breast cancer cells. Animal studies indicate a role of IGF-I and its receptor in breast cancer development [Helle, 2004].

Certain nutrition and lifestyle factors may promote breast cancer indirectly by stimulating cells (alcohol, hormone therapy after menopause), inhibiting DNA-repair mechanisms (lack of vitamins), affecting estrogen metabolism (phytoestrogens), or enhancing tumor growth. Some substances may act directly as carcinogens. For example, aromatic hydrocarbons in tobacco or increased polycyclic aromatic hydrocarbons in scorched meat are known carcinogens. Smoking has a modest association with breast cancer risk [Reynolds et al., 2004].

Genetics plays a role in breast cancer development. In particular, women with mutations in known breast cancer-associated genes (e.g., BRCA1) are at very high risk [Ellison et al., 1995; Fentiman, 2001]. However, genetics explains only about 5% of breast cancer deaths in the U.S. Individual differences in the effects of nutritional factors on mammary cells could be caused by genetic differences.

### **Vitamin D, ultraviolet radiation and breast cancer**

So, what about vitamin D? Inspection of the Atlas of Cancer Mortality data [Devesa et al., 1999] for white females for the periods 1950-69 and 1970-94 shows large variations in breast cancer rates within the U.S. For the period 1970-94, the highest rates are in New Jersey and New York (29-33 deaths/100,000/year), while the lowest rates are in the southeastern states and Utah (16-21 deaths/100,000/year). Utah, with the clean-living lifestyle of the Mormons, is easy to understand. However, some gradually varying factor must exist to explain the general geographic variation. It can be assumed that the American diet is nearly the same throughout the country [Grant, 2002b; Grant, submitted]. This assumption is supported by a nutrition survey (1977-78) in which it was determined that the micro- and macro-nutrient intake was similar to within 10-20% for the 4 major regions of the U.S. [Nutrition Monitoring Div., 1985]. The work of the Garlands provided the key to understanding the geographic variation of breast cancer mortality rates in the U.S. They proposed that variations in solar ultraviolet-B (UVB) radiation (290-320 nm) and the resulting production of vitamin D could explain the observed geographical variation [Garland and Garland, 1980; Garland et al., 1990]. Their studies used UVB data obtained from the Total Ozone Mapping Spectrometer for July 1992 [Herman et al., 1999] to approximate vitamin D production. UVB can be used by cholesterol in the skin to produce vitamin D, and Americans derive much of their vitamin D from sunlight [Holick, 2004].

A recent study has shown a clear association between vitamin D intake and breast cancer (see Table 1). A number of other factors were also included such as alcohol, Hispanic heritage, lung cancer (an index of the health effects of smoking), poverty level, and living in an urban area [Grant, submitted].

**Table 1.** Regression results for breast cancer mortality rates, 1970-94, for white and American females in the 48 contiguous states plus DC; for black Americans, only 40 states plus DC had sufficient numbers of deaths for inclusion in the analysis.

<b>Race</b>	<b>Adjusted r<sup>2</sup>, F, *</b>	<b>1<sup>st</sup> Term (t, p)</b>	<b>2<sup>nd</sup> Term (t, p)</b>	<b>3<sup>rd</sup> Term (t, p)</b>	<b>4<sup>th</sup> Term (t, p)</b>
White	0.81, 51	UVB -10, *	Urban 6.2, *	Alcohol 3.7, *	Poverty -1.0, 0.35
Black	0.64, 25, *	LungCanF 4.2, *	UVB -3.4, 0.001	Urban 2.2, 0.031	

\* p<0.001; t is the Students t-test; the fraction of the variance explained by each factor approximately given by the product of the adjusted r<sup>2</sup> times t<sup>2</sup> divided by the sum of t<sup>2</sup> for all factors.

This same study revealed that urbanization is an important risk factor for -breast cancer and several other cancers. Note that urbanization is the second most important risk factor when solar UVB radiation is the primary risk reduction factor, but never when lung cancer is the most important risk factor. Urbanization is also not consistently associated with any other factor. However, urbanization was correlated with lung cancer for both males and females in the period 1950-69. Lung cancer rates were much lower in this period than in the later period, and pollution emissions from factories and vehicles were much less controlled than in the later period. Thus, air pollution could have played a role in the etiology of lung cancer in this period. However, in general, it is hypothesized that urban residence reduces a person's exposure to solar UVB compared to living in a rural region, and this is the reason that urban residence may increase breast cancer risk. In a review of rates for 26 types of cancer in a number of countries, it was found that rates for 23 types were higher in urban areas than in rural areas [Doll, 1991]. Urbanization was associated with slightly increased risk of cancer in the Netherlands and attributed to lifestyle [Schouten et al., 1996].

Breast Cancer Mortality Rates, White Females, 1970-94  
vs. Regressions Based on Alcohol and UVB Radiation  
and With and Without Urban Residence

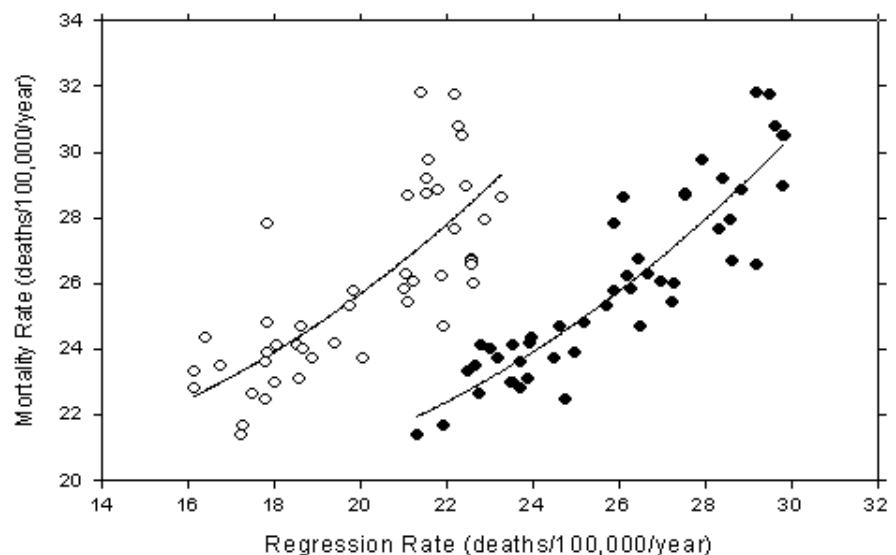


Figure 2. Breast cancer mortality rates for white females in the U.S., 1970-94, vs. a regression model based on alcohol and urban residence as risk factors and UVB radiation as a risk reduction factor. The dots are the full result, while the circles assume that the degree of urbanization is zero [Grant, submitted].

Table 2 summarizes the important risk and risk reduction factors for breast cancer. The factors most likely combine multiplicatively. In other words, one's risk of developing breast cancer would be the product of one's risk for each factor, unless the factors have some overlap. For example, a positive family history of breast cancer could be due to genetic or environmental factors, so if the genetic and environmental factors are known, they should be used, rather than the factor for family history. In fact, one paper explored the synergistic interaction between dietary factors, finding that a high fiber, high fermented milk product diet was associated with a large reduction in breast cancer risk [Van 't

Veer et al., 1991]. A study in Moscow was able to show that animal products were associated with high risk for breast cancer, while vegetable products were protective [Zaridze et al., 1991]. Mezzetti et al. [1998] came to similar conclusions in a multi-factorial study in Italy.

**Table 2.** Risk and risk reduction factors for breast cancer, associated mechanisms, and estimates of the degree of risk or risk reduction.

Factor	Mechanism	Hazard Ratio (HR) Odds Ratio (OR) Risk Ratio (RR)*	Reference
Risk		(higher number means greater risk)	
Genetics – not heterozygous for BRCA1		RR <200, age <40 years  (affects 5% of those with breast cancer)	Easton et al., 1995  Fentiman, 2001 Begg, 2002
– not heterozygous for BRCA1		RR <15, age 60-69 years	Easton et al., 1995  Begg, 2002
Female	Estrogen, progestin	RR = 150 vs male	Jemal et al., 2004
Positive family history	Environmental and genetic similarities	RR = 1.5-3.6, depending on how closely related	Pharoah et al., 1997
Pesticides	Carcinogenic	OR = 2.8 for living within a mile of a hazardous waste site	Bounias, 2003 O'Leary et al., 2004
Animal products, especially animal fat	Increased estrogen, insulin, IGF-I	RR = 2.5	Armstrong and Doll, 1975  Grant, 2002a
Increased weight	Increased estrogen, insulin, IGF-I	RR = 1.6  BMI >31 kg/m <sup>2</sup> vs ≤ 20 kg/m <sup>2</sup> ;  HRT non-users	Huang et al., 1997
		RR = 2.5  BMI >31.1 kg/m <sup>2</sup> vs ≤ 22.6 kg/m <sup>2</sup> ;  HRT non-users	Murimoto et al., 2002
Age		RR = 1.5 per 10 years of age, >40 yr	WHO, 1998 Ries et al., 2000
Dioxins	delayed proliferation and differentiation of the mammary gland, elongation	HR = 2.1 for X10 increase	Warner et al., 2002  Birnbaum, Fenton, 2003

	of the window of sensitivity to potential carcinogens		
Smoking	Free radicals, carcinogens	OR = 2.0 RR = 2.1 HR = 1.3	Pryor, 1997  Lash, Aschengrau, 1999;  Muscat et al., 2003; Reynolds et al., 2004
Urban residence	Reduced UVB, vitamin D	RR = 1.5	Grant, submitted
Alcohol	Increased estrogen and androgen levels		Singletary and Gapstur, 2001
Alcohol	Acetaldehyde, low folate	RR = 1.4	Sellers et al., 2002
Alcohol		RR = 1.1 per 10 g of alcohol/day (1 drink)	Ellison et al., 2001  Tjonneland et al., 2003
High glycemic index	hyperinsulinemia/ insulin resistance	OR = 1.3-1.4	Augustin et al., 2001  Potischman et al., 2002
Hormone replacement therapy	Estrogen, progestin	RR = 1.3 with estrogen; 1.4 with estrogen+progestin	Hulka, 1997
Early menarche	Estrogen, progestin	RR = 1.3 for <12 years vs. 15 years	Brinton et al., 1988
Delay in childbearing	Increased estrogen, progestin	OR = 1.13 per 5-year delay in 1 <sup>st</sup> child	Lambe et al., 1996
Risk reduction		(lower number means less risk)	
Diet: high fiber intake and high intake of fermented milk	Low fat?	OR = 0.48	Van 't Veer et al., 1991
Vegetables	Synergistic effect of components?	OR = 0.48	Freudenheim et al., 1996
Vitamin C, alpha-tocopheral, folic acid, beta-carotene, lutein + zeaxanthin	Antioxidants, anti-carcogins	OR = 0.47-0.55	Freudenheim et al., 1996
Tamoxifen	chemopreventive agent in women with a high risk of breast cancer,	RR ~0.5  for invasive breast cancer; side	Brekelmans, 2003  Rastogi and

	including carriers of a BRCA2 mutation, but is probably not effective in BRCA1	effects associated with its use (endometrial cancer, thromboembolism)	Vogel, 2003
Vitamin D	Attenuation of growth signals, increased cell differentiation, reduction of angiogenesis	RR = 0.5 (product of UVB irradiance times urban-rural difference)	van den Bemd GJ and Chang, 2002; Grant, submitted
Exercise	Reduces BMI, insulin resistance	RR = 0.6-0.7 for 3-4 hours of exercise/wk	McTiernan, 2003
Calcium	?	R = 0.69 >800 mg/day versus <or=200 mg/day	Shin et al., 2002
Ultraviolet B radiation	Vitamin D production	RR = 0.7 for southern states vs. northeastern states	Grant, 2002a, Grant, submitted
Rural vs. urban residence	Vitamin D production	RR = 0.7	Grant, submitted
Fish	n-3 oils, vitamin D  generation of prostaglandins which lower cell proliferation potential	OR = 0.88 for >3.5 servings/wk	Weisburger, 1985, 1997, 2000  Grant, 2002a  Terry et al., 2002
Parity (number of children)	Reduced estrogen, progestin	OR = 0.90 per live birth	Lambe et al., 1996

\* Odds ratio (OR) – a ratio of cross products of the probability of developing the disease by cases and controls who are/are not exposed to the suspected agent. If a is the number of cases (those with the disease) exposed, b is the number of controls (those without the disease) exposed, c is the number of cases not exposed, and d is the number of controls not exposed, the odds ratio is  $(a \times d)/(b \times c)$ . This measure generally applies to retrospective or case-control studies.

Hazard ratio (HR) – a comparative measure of the strength of the relationship of an exposure, intervention, or treatment and an outcome over a defined time for a study group divided into exposure and control groups.

Risk ratio (RR) – the ratio of the probability of developing the disease for those in the highest category of exposure to the agent divided by the probability for those in the lowest category of exposure. This measure generally applies to prospective or cohort studies.

The ecologic study by Grant [2002a] also looked at combinations of factors in breast cancer (Table 1). Since many of the risk and risk reduction factors are highly correlated, it is often difficult to separate them out. Using multiple linear regression analyses is a good way to determine the interaction of the factors. However, one has to be careful in such work. For example, the degree of

urbanization gives only a small contribution to the regression equation, but when the regression equation is replotted setting the degree of urbanization to zero, it is apparent that living in an urban region makes a major contribution to breast cancer risk (Figure 2).

### **Conclusions**

While these results are the findings of observational studies and are likely to hold true, they have not necessarily been accepted or endorsed by the health community. In the future, there will likely be carefully controlled double blind cross over studies to test for a causal relationship. Some observational studies, such as that finding that women who used hormone replacement therapy (HRT) after menopause, generally had better health habits, which was overlooked in the earlier studies. However, it was realized in more recent studies that the risk factors for various diseases such as breast cancer from HRT outweighed any long-term health advantages [Chlebowski et al., 2003; Rossouw et al., 2003; Wassertheil-Smoller et al., 2003], although HRT is still used by women trying to reduce menopausal symptoms. Therefore, anyone considering changing his or her diet or lifestyle in order to reduce the risk of breast cancer, or any disease, should read the referenced papers as well as others that can be found. Note that it can take decades for the health system to fully accept and endorse new findings regarding lifestyle. The American health care system is much more interested in secondary prevention (examinations and prescription drugs) and tertiary treatments (surgery and chemotherapy) than with primary prevention approaches (diet and lifestyle). Thus, it is wise for people to be proactive in protecting their own health and wellbeing.

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