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# Is Primary Prevention of Breast Cancer Possible?

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**Abstract**

The epidemiology and knowledge on risk factors for breast cancer, both endogenous and exogenous, is reviewed. It is concluded that primary prevention of breast cancer is possible, but that due to the long natural history of breast cancer, avoidance of risk factors should start early in life. Among the most important risk factors to avoid are alcohol, nulliparity, obesity in post-menopausal women, physical inactivity, tobacco smoking, and an unhealthy diet. It is estimated that if all risk factors for breast cancer could be avoided, the incidence of breast cancer in the West would eventually fall by over 50%.

## INTRODUCTION

Breast cancer is not a modern disease, as many indications of breast cancer in women depicted in the art of former times indicate. But now breast cancer is the commonest cancer in women in the world. In 2012 an estimated 1.68 million new cases were diagnosed in the world [1]. Breast cancer is rare in men. In most countries, breast cancer occurs in over 100 times as many women as in men. Breast cancer is associated with relative affluence, and is commoner in high-income than developing countries. In North America currently breast cancer occurs in about one in nine women, in other Western countries in about one in ten to fourteen. This means that as women age they gradually accumulate this degree of risk, reaching the one in nine level when they survive to their eighties. For younger women, the risk reaches 20 per 1000 by age 50 in North America, a risk of one in 50.

In developed countries the risk of breast cancer increases steadily throughout life, but even when it becomes most common in women in their eighties in the highest risk white population of North America, breast cancer occurs in only about 20 women per 1000 over the ensuing five year period. In Japan and in many other Asian and in developing countries, incidence remains level from about the age of 45 [1]. It is anticipated that as young women age in Japan, their risk could become more similar to that in North America and Europe.The range of mortality rates is much less because of the more favorable survival of breast cancer in developed regions. The highest mortality rates are in Northern Europe and Northern Africa. Breast cancer ranks as the fifth cause of death from cancer overall in the world (458 000 deaths), but it is still the most frequent cause of cancer death in women in developing countries (269 000 deaths, 12.7% of total) and nearly all developed regions, where the estimated 189 000 deaths is almost equal to the estimated number of deaths from lung cancer (188 000 deaths), though death rates from lung cancer now exceed those from breast cancer in Canada and the USA [1]. Breast cancer is increasing in incidence in all countries of the world, both in the developed countries, and in countries that are moving along the path of development. In most developing countries breast cancer is not the commonest cancer in women, that place is taken by cancer of the uterine cervix. But as countries make the economic transition to relative wealth, almost invariably they make the epidemiologic transition to a country where breast cancer is more common than cervix cancer. Increasing awareness of the importance of breast cancer, with the promotion of earlier and better diagnosis, was probably responsible for some of the increases in breast cancer in many western countries in recent decades. More recently, use of screening mammography and hormone replacement therapy have also contributed to the rising rates of breast cancer experienced in most western countries. Screening brings forward the time of diagnosis of breast cancer, and may bring to light cancers that might never have been detected in the lifetimes of some women [2]. This increases the incidence of breast cancer at the ages screening is occurring, that is especially over the age of 50, but in the United States from the age of 40. This we call over diagnosis, cancers that would never have become apparent were it not for screening. This needs to be bourn in mind in interpreting trends in the incidence of breast cancer, countries that introduced mammography screening showed major increases in the incidence of breast cancer, but this should be interpreted as an artifact of screening, not an indication that the risk of breast cancer is increasing. Deaths from breast cancer have been increasing in many countries. Those countries with lower rates in the 1950s (e.g. Japan and Finland) showed consistent increases in mortality, though for Finland the increase ceased around 1990, and a small fall occurred thereafter. Canada and the United States showed almost stable mortality until 1990 when a substantial fall began. Denmark and especially the UK showed important increases, but from 1990 a substantial fall has occurred, at the same rate as for Canada and the USA.

Sweden showed stability, then a slow fall from about 1970 [1]. Interpretation of these trends is difficult. Most of the increases in mortality are reflections of the increase in incidence. Most of the recent decreases in mortality are probably due to improvements in the outcome of therapy for breast cancer, a reflection of the gains achieved through adjuvant chemotherapy and hormonal therapy in clinical trials applied in the general population [3]. Some consider part of the recent falls in Canada, the UK and the United States as due to the success of mammography screening. However, the mammography screening programs in Canada began too recently to explain the mortality reduction, while the slow fall in Sweden suggests that the extensive screening there may not have had much impact, while the later adoption of adjuvant treatment in that country than in Canada and the United States may explain the lesser reduction in breast cancer mortality [4]. Breast cancers usually take a long time to develop. It has been estimated that the "doubling time" of breast cancers, the time it takes for cancers to double in size, is on average about 90 days [5]. This is relatively slow growth compared to many other cancers. This means that the time before a cancer becomes detectable can be several years, and for many cancers, the time from initial commencement to diagnosis with symptoms as long as 10 or more years. Breast cancer, therefore, compared to many other cancers, has a long natural history.

## Causes of Breast Cancer

**Reproductive Behavior:** Breast cancer largely only occurs in women who have, or have had, functioning ovaries for most of their lifetime. Breast cancer in males largely only occurs in those who for some reason have had far greater exposure to female than male hormones, for example male transsexuals who take estrogens. If, in a woman, ovarian function is lost early in life, breast cancer will not occur. If a woman has her ovaries removed, or their function destroyed by radiation or high doses of chemotherapy given as treatment for other forms of cancer by age 40, her risk of breast cancer is reduced about threefold, and much more if the loss of ovarian function occurred before age 30 [6]. The earliest reproductive factor to affect the risk of breast cancer is age at menarche. Women whose menarche occurred before the age of 12 have a risk of breast cancer about 50% greater than those whose menarche occurred over the age of 14. The age menarche is established is related to nutrition, the poorer a girl's nutritional status, the later her age of menarche [7]. The average age at menarche is much older in developing countries than in the West, this accounts for some of the international differences in incidence of breast cancer. Age at menarche has been declining in the West, and is beginning to decline in some Asian countries also. The latest reproductive risk factor to operate in life is age at menopause. Women with an age at menopause over the age of 50 have about 50% greater risk of breast cancer than women with menopause under the age of 50. Age at menopause is later in the West than in developing countries, and has been getting later in the West this last century. Again it seems to be nutritionally related, and accounts for some of the international differences in breast cancer and the rising incidence of breast cancer in the West. The direct relationship between age at menarche and menopause with duration of ovarian activity is easy to understand. Somewhat more difficult are two other risk factors related to reproductive behavior, parity and age at first birth.Two centuries ago in Italy it was recognized that nuns (nulliparous women) had about twice the risk of breast cancer compared to women who had had children [8]. The protective effect of parity is quite strong, women who have had four or more children have about half the risk of breast cancer than those who have had none [9]. There is also a strong effect of age at first birth. Women who have their first birth over the age of 30 have about three times the risk of breast cancer as women who have their first birth under the age of 20. Indeed women who have their first birth over the age of 35 have greater risk of breast cancer than women who have no children at all [6]. There is a strong relationship between age at first birth and number of children, in that women who have many children tend to start having children earlier in their life than women who have few.

Breast feeding is protective for breast cancer [10]. The effect is particularly seen in premenopausal women, and in women with prolonged lactation (more than 5 months). Indeed, if a woman delays her first birth beyond the age of 30, but ensures that the child is breast fed for at least 5 months, the increase in risk of breast cancer caused by her delayed first birth is nullified [11]. There is rather a complex relationship between pregnancy itself and risk of breast cancer. Women who have just completed a pregnancy are initially at higher risk of breast cancer than women who were not pregnant at the same age but who had the same number of previous children, or no previous children [12]. This early effect of a completed pregnancy in increasing risk may account for the fact that women whose first pregnancy is over the age of 35 have a higher risk of breast cancer than women who have never had children. However, this effect of pregnancy in increasing the risk of breast cancer (probably because of high estrogen levels during the last trimester of pregnancy) is soon replaced by the protective effects of pregnancy and lactation. The effect of late age at first birth on increasing the risk of breast cancer is almost certainly not entirely due to hormone effects. It would seem that breast cells become less susceptible to the cancer-causing effects of chemicals and radiation after they have fully matured with the first completed pregnancy [13]. The longer the time period between menarche and first completed pregnancy the longer they have had to encounter cancer-causing substances. Delay in the maturation of breast cells, therefore, increases the time they are susceptible to the onset of the cancer-causing process and increases the risk of breast cancer developing later. Women with intact ovaries have three times the risk of breast cancer than women whose ovaries have been removed. If a prepubertal girl were to have her ovaries removed, she would have hardly any risk of breast cancer at all. If the ovaries are removed before the age of 40, or receive irradiation such that they cease to function, there is at least a one third reduction in the risk of breast cancer. But if the ovaries are removed after the menopause, there is hardly any effect on the risk of breast cancer [14]. There has been controversy over whether induced abortion increases the risk of breast cancer. Although some studies were contradictory, a collaborative re-analysis of a number of studies found no effect on breast cancer risk of induced abortions [15].

**Exogenous hormones:** Women who took oral contraceptives for at least five years 20 or more years ago to delay first pregnancy or space pregnancies have about a 50% increase in risk of breast

cancer [16]. Because of the age of these women, the increase in risk appears to have begun in their 30s and to continue at least through their forties. An additional group of women, who took oral contraceptives when they were in their forties, appear to have been at increased risk of breast cancer while they took oral contraceptives. Most of the preparations of oral contraceptives used 20 years ago had a higher dose of estrogens than usual recently. It is uncertain whether low dose estrogen preparations will have the same effect in increasing breast cancer risk as the older preparations. It is also uncertain whether women who took high estrogen dose preparations will show the same increase in breast cancer risk as they enter their fifties and sixties. Studies of the effect of the injectable contraceptive, medroxy progesterone acetate (Provera), indicate that this preparation, free of estrogen, increases breast cancer risk by a similar extent as for oral contraceptives, with an effect that begins immediately after the first injection [17]. The mechanism of this effect is uncertain.

Non-contraceptive estrogens are now accepted as increasing the risk of breast cancer [18], especially when estrogen is combined with progestin [19]. This effect is detectable after about a five year period of use, and largely affects women in their sixties. The increase in risk is of the order of 25-50%, and this persists while the estrogens are being taken, but appears to cease within about five years after their use has stopped [20]. Use of estrogen alone appears to initially reduce the risk of breast cancer, but this effect did not persist with long term follow-up [21]. There is evidence that the types of breast cancers found in women taking non-contraceptive estrogens have a better outcome than those not taking estrogens, being likely to be estrogen receptor positive.

**Alcohol:** A large number of studies have shown increasing breast cancer risk with increasing alcohol consumption, the risk increased by 20-50% by one glass of wine a day [22]. The type of alcohol consumed does not seem to be important, though in most studies the majority of alcohol consumed was wine. This alcohol effect appears to be independent of diet, as it is of other breast cancer risk factors [23], and seems to be a direct effect of alcohol metabolites in increasing cancer development.

**Tobacco smoking:** Smoking is now recognized as increasing the risk of breast cancer, especially prolonged smoking that begins in the period before first pregnancy [24]. The increased risk from active smoking is paralleled by increased risk of passive smoking especially in pre-menopausal women [25]. Tobacco smoking seems to have a greater effect in increasing the risk of breast cancer in those who are genetically susceptible to the disease [24]. More recent studies have strengthened the evidence on the risks of both active and passive smoking [26].

**Ionizing Radiation:** Ionizing radiation is an established cause of breast cancer, demonstrated particularly in follow-up studies of women who received radiation as a result of the atomic bomb explosions in Hiroshima and Nagasaki, [27] and the follow up of women who were exposed to high levels of radiation to the chest during treatment of tuberculosis in the pre-chemotherapy era [13]. Both these sets of studies have demonstrated that the prepubertal breast is susceptible to the effects of ionizing radiation, and that susceptibility lasts until about the age of first completed birth. Thereafter risk falls substantially, so that women who receive irradiation to their breasts in the late thirties or forties have only a fraction of the risk of breast cancer compared to women irradiated earlier in life. This has made it possible to determine that the risk to women from radiation from mammography given after the age of 40 is extremely low [28]. Radiation given to the pelvis, that damages the ovaries, will reduce the risk of breast cancer. This is because of the inhibitory effect on estrogen production.

**Diet and nutrition:** Nearly every study investigating diet and breast cancer has found that excess caloric intake is associated with increased breast cancer risk [29]. It is uncertain whether the nature of the energy containing foods is important, and particularly whether high intakes of fat, the most energy concentrated nutrient, is the prime culprit. Some of the early animal studies that suggested a role of dietary fat consumption in increasing the risk of mammary cancer were followed by human studies that suggested the same relationship [30]. However, in Mediterranean countries, where the intake of fats is quite high, though largely of olive oil, a monounsaturated fat, breast cancer risk tended to be lower than in countries where the dominant fat consumed was of animal origin, usually saturated fats [31] . Most studies that have attempted to find an energy-independent role of fat in increasing breast cancer risk have largely been negative, but one was positive in pre-menopausal women [32] and one in post-menopausal women. [33]. This suggests that if the energy content of the diet was reduced, and particularly if the intake of saturated fats was reduced, breast cancer risk would fall. It is generally recognized that increases in fruit and vegetable consumption should be encouraged to reduce the risk of cancer. However, a pooled analysis did not find a protective effect of fruit and vegetable consumption on the risk of breast cancer [34]. Nevertheless, one study found a protective effect of high cereal fiber consumption [35] and a second large pooled analysis of a number of studies found that fruit and vegetable consumption was protective of estrogen-negative breast cancers [36]. Height has been found to be associated with breast cancer risk in several studies, with the tallest women being at higher risk of breast cancer [37,38]. Height, although largely related to genetic composition, is also related to adequate nutrition in childhood. It seems clear that nutritionally deprived women are at lower breast cancer risk. This may not be the entire explanation, however. For a woman to be tall, she has to continue growth through puberty, even after her periods have become established at menarche, as age at menarche is nutritionally related. The effect of height is probably a complex relationship between continued production of growth hormone by the pituitary and production by the same endocrine organ of gonadotrophic hormones that increase the production of estrogens. Obesity is clearly related to over nutrition, and in its turn is found to be associated with breast cancer [39]. Obese postmenopausal women have been found to produce estrogens within adipose tissue, and perhaps not surprisingly, obese postmenopausal women are at higher risk of breast cancer than women who have maintained a normal weight for their height. In pre-menopausal women, obesity is not associated with increased breast cancer risk, perhaps because the amount of estrogen produced by the adipose tissue in such women is relatively small compared to that produced by the ovaries themselves. However, premenopausal women who are

extremely obese have suppressed ovarian function, and they have a reduced risk of breast cancer compared to women of normal weight [39].

**Physical activity:** Some years ago it was recognized that female athletes often developed anovular menstrual cycles, that is, their hormonal status was sufficiently affected by their activity that they did not ovulate. Whatever the mechanism for this effect, it is perhaps not surprising, from what we know about inhibition of ovarian activity and risk of breast cancer, that it was later demonstrated that female college athletes had a reduced risk of breast cancer [40]. What was more surprising is that studies of women who would not normally be regarded as athletes have found that those whose lifestyle involves at least moderate physical activity, including gardening, walking, etc., have a lower risk of breast cancer than sedentary women. Of course, women who are more active are likely to eat better, or perhaps more important, achieve a balance in their caloric intake with caloric output in activity, and tend to avoid obesity. Whichever of these factors is dominant, it seems clear that physically active and nutritionally healthy women have a lower risk of breast cancer than their less healthy counterparts [39].

**Organochlorines:** A group of chemical substances that has attracted attention are the organochlorines. These have entered our environment largely from the use of DDT and other chlorine-containing pesticides and herbicides [41]. These substances tend to cumulate in the environment, and get into our food chain. They are of particular interest with regard to breast cancer because some of them, or their metabolic products, have weak estrogenic activity, and they are therefore termed xenoestrogens. In the general environment, there is good evidence that these compounds are associated with adverse effects on the fertility cycles of some animal species, having affected the thickness of eggshells of some birds associated with polluted lakes and rivers, and affected male fertility by reducing spermatogenesis. Several studies have attempted to determine whether there was an association between the levels of such substances in body fat (they are lipophilic, or fat-seeking) and breast cancer, and some early studies suggested there was. Most recent studies of the level of these substances in the blood of women with breast cancer compared to those without have not shown an association, [42] though there is some dispute about their interpretation and whether the study of levels of organochlorines in blood is optimal compared to studies in breast fat. Indeed one study of organochlorines in breast fat in Canada has shown an association with breast cancer risk [43].

**Radiofrequency fields:** Non-ionizing radiation from extremely low frequency electric and magnetic fields (EMF) has been suspected as increasing the risk of breast cancer [44]. Further, there have been case reports that suggest that young women who keep cell phones in their bras have an increased risk of breast cancer, [45] the radiofrequency field exposure caused by cell phones being probable human carcinogens [46].

**Shift work:** There is evidence that women exposed to shift work at night, e.g. nurses, have increased risk of breast cancer. This appears to be at least in part because of disruption in melatonin production by the pituitary. An IARC working group concluded that there is limited evidence in humans for the carcinogenicity of shift work that involves night work, while there is sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night). The working group concluded that shift work that involves circadian disruption is probably carcinogenic to humans (IARC Group 2A) [47].

**Genetics:** For many years it has been recognized that breast cancer tends to occur more in some families than others, and that when breast cancer did appear in some of these "high risk" families, it often seemed to occur at a younger age, even in their 30s and occasionally 20s, and that in such families, breast cancer seemed to occur more often in both breasts. In such families investigators noted that the tendency to develop breast cancer could be transmitted by fathers as well as mothers, and sometimes other cancers were more frequent also, especially ovarian cancer. No more than 5% of the breast cancers that occurred had such strong family relationships, though there were some other families, with less strong associations with breast cancer, where the disease did seem to be more common than usual [48]. It is now known that in extremely high-risk families for breast cancer, specific genes have mutated. The two genes that are now recognized as being responsible for most heritable breast cancer are BRCA 1 and BRCA 2. BRCA 1 increases the risk of both breast cancer and ovarian cancer, BRCA 2 largely breast cancer. Women who are carriers of BRCA 1 have up to an 80% lifetime risk of breast cancer, with over half developing breast cancer by age 50, and about a 40% lifetime risk of ovarian cancer. Women who are carriers of BRCA 2 have up to a 60% lifetime risk of breast cancer. Data for multiple common susceptibility alleles for breast cancer may be combined to identify women at different levels of breast cancer risk [49].

## Application of knowledge of the causes of breast cancer to Prevention

From the studies reviewed above, the most important factors that can be influenced that can reduce breast cancer risk are those associated with lifestyle, especially alcohol use, diet and physical activity and smoking. Women who adhere to dietary guidelines have a lower risk of breast cancer than those who do not [50]. There are strong suspicions that the diet of girls and young women is as or more important than diet in adult life in reducing the risk of breast cancer. Girls and women of all ages should be encouraged to be physically active, to consume a diet with calorie content that matches their calorie output in terms of activity, to avoid excess fat consumption and where possible to substitute unsaturated fats for saturated and to eat plenty of fresh fruits and vegetables as well as maintaining a normal weight. Providing such a lifestyle begins sufficiently early in life, such women will have at least half the risk of breast cancer as their less health conscious colleagues, and will benefit by the reduction of other cancers as well. The benefits of such a comprehensive approach are not restricted to the development of breast cancer [51]. Obese women with breast cancer have a poorer survival than non-obese women and women who had a lower fat diet before breast cancer diagnosis had better survival than those with a higher pre-diagnosis fat intake [52-54]. Therefore a healthy diet combined with physical activity and avoidance of

obesity will benefit women who have been diagnosed with breast cancer. Modification of reproductive behavior is more difficult, though it seems clear that young women should be aware that if they postpone their first birth to beyond the age of 25, they will increase their risk of breast cancer, but they can reduce that risk if they breast-feed their infant for at least 5 months. Tests for BRCA1 and 2 are available, but should only be used when there is reason to believe that there is a high risk of breast cancer in a woman's family. Their greatest value is to show that women in high-risk families who have not yet developed breast cancer are not gene carriers. Those found to be gene carriers have to take a series of difficult decisions. Do they want to rely on regular screening tests to find cancers early, recognizing that there can be no guarantee that the tests will find a cancer in a treatable stage? Are they prepared to undergo bilateral mastectomy with subsequent breast reconstruction, and for BRCA 1 carriers, bilateral oophorectomies, with subsequent estrogen replacement therapy? Even bilateral oophorectomies will not abolish the risk of developing ovarian cancer, as ovarian-like tissue with increased cancer risk can sometimes occur elsewhere in the abdominal cavity. There is evidence that women at increased risk of breast cancer will benefit by taking tamoxifen, but with the disadvantage of an increased risk of endometrial cancer [55,56]. Other hormonal agents are therefore being investigated, though so far, none seem as effective as tamoxifen in reducing breast cancer risk.

## CONCLUSION

In spite of an enormous number of studies, we are still not in the position to determine precisely why breast cancer occurs in every woman diagnosed with the disease. Indeed, many women who develop breast cancer seem to do so in spite of the absence of many or all of the risk factors discussed above. However, most of the causes of breast cancer tend to operate relatively early in life. The lifestyle of young girls influences their future lifetime risk of breast cancer. Their activity and dietary lifestyle may be especially critical in this regard.

It is possible to make some estimates of the proportion of breast cancer caused by the various risk factors discussed in this paper. Poor diet and over-nutrition resulting in obesity contribute about 30%, as does late age at first birth, while lack of physical activity will contribute about 25%. Lack of breast-feeding and high alcohol consumption each contribute about 10%, while use of exogenous estrogens (e.g. hormone replacement therapy) and genetics 5%. Radiation may contribute another 1%. The figures are based on data from the Western world, and their effects overlap, but they are becoming applicable in some of the developing countries as well.

## REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer. 2013.
2. Miller AB. Conundrums in screening for cancer. Int J Cancer. 2010; 126: 1039-1046.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 365:1687-1717.
4. Bleyer A, Baines C, Miller AB. Impact of screening mammography on breast cancer mortality. Int J Cancer. 2016; 138: 2003-2012.
5. Lin RS, Plevritis SK. Comparing the benefits of screening for breast cancer and lung cancer using a novel natural history model. Cancer Causes Control. 2012; 23: 175-185.
6. MacMahon B. Epidemiology and the causes of breast cancer. Int J Cancer. 2006; 118: 2373-2378.
7. De Waard F, Thijssen JH. Hormonal aspects in the causation of human breast cancer: Epidemiological hypotheses reviewed, with special reference to nutritional status and first pregnancy. J Steroid Biochem & Mol Biol. 2005; 97: 451-458.
8. Ramazzini B. 1700. De morbis artificum diatribe (Diseases of workers). Translated by WC Wright. New York: Hafner. 1964.
9. Miller AB, Barclay TH, Choi NW, Grace MG, Wall C, Plante M , et al. A study of cancer, parity and age at first pregnancy. J Chronic Dis. 1980; 33: 595-605.
10. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002; 360: 187-195.
11. Chang-Claude J, Eby N, Kiechle M, Bastert G, Becher H. Breastfeeding and breast cancer risk by age 50 among women in Germany. Cancer Causes Control. 2000; 11: 687-695.
12. Bruzzi P, Negri E, La Vecchia C, Decarli A, Palli D, Parazzini F , et al. Short term increase in risk of breast cancer after full term pregnancy. BMJ. 1988; 297: 1096-1098.
13. Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, et al. Mortality from breast cancer after radiation during fluoroscopic examination in patients being treated for tuberculosis. New Engl J Med. 1989; 321: 1285-1289.
14. Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, et al. Long-term Mortality Associated with Oophorectomy versus Ovarian Conservation in the Nurses' Health Study. Obstet Gynecol. 2013; 121: 709-716.
15. Beral V, Bull D, Doll R, Peto R, Reeves G. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries. Lancet 2004; 363: 1007-1016.
16. Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W , et al. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev. 2010; 19: 2496-2502.
17. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE, et al. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res. 2012; 72: 2028-2035.
18. Bakken K, Fournier A, Lund E, Waaseth M, Dumeaux V, Clavel-Chapelon F, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2011; 128: 144-156.
19. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288: 321-333.
20. Collaborative Group on Hormonal Factors in Breast Cancer. Breast

cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet. 1997; 350: 1047-1059.

21. Chlebowski RT, Rohan TE, Manson JE, Aragaki AK, Kaunitz A, Stefanick ML et al. Breast Cancer after use of estrogen plus progestin and estrogen alone: Analyses of data from 2 Women's Health Initiative Randomized Clinical Trials. JAMA Oncol. 2015; 1: 296-305.

22. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, et al. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. British Journal of Cancer 2002; 87:1234-1245.

23. Rohan TE, Jain M, Howe GR, Miller AB. Alcohol consumption and risk of breast cancer: a cohort study. Cancer Causes Control. 2000; 11: 239-247.

24. Johnson KC, Miller AB, Collishaw NE, Palmer JR, Hammond SK, Salmon AG, et al. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). Tobacco Control. 2011; 20: 2.

25. Miller MD, Marty MA, Broadwin R, Johnson KC, Salmon AG, Winder B , et al. The association between exposure to environmental tobacco smoke and breast cancer: a review by the California Environmental Protection Agency. Prev Med. 2007; 44: 93-106.

26. Macacu A, Autier P, Boniol M , Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat. 2015; 154: 213-224.

27. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. JAMA. 1995; 274: 402-407.

28. Howe GR, Sherman GJ, Semenciw RM, Miller AB. Estimated benefits and risks of screening for breast cancer. Can Med Assoc J. 1981; 124: 399-403.

29. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes and Control. 1990; 1: 81-97.

30. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR , et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer. 2001; 92: 767-774.

31. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med. 2015; 4: 1933-1947.

32. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Energy balance and breast cancer risk: a prospective cohort study. Breast Cancer Res Treat. 2006; 97: 97-106.

33. Sue LY, Schairer C, Ma X, Williams C, Chang SC, Miller AB, et al. Energy Intake and Risk of Postmenopausal Breast Cancer: An Expanded Analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) Cohort. Cancer Epidemiol Biomarkers Prev. 2009; 18: 2842-2850.

34. Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA , et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA. 2001; 285: 769-776.

35. Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB, et al. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. Cancer Causes Control. 1993; 4: 29-37.

36. Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, van den Brandt PA , et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst. 2013; 105: 219-236.

37. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR , et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000; 152: 514-527.

38. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer. 2013; 132: 1125-1132.

39. IARC Handbooks on Cancer Prevention Volume 6, Weight control and physical activity. Lyon, IARC Press, 2002.

40. Wyshak G, Frisch RE. Breast cancer among former college athletes compared to non-athletes: a 15-year follow-up. Br J Cancer. 2000; 82: 726-30.

41. Committee on Environmental Epidemiology, and Commission on Life Sciences, National Research Council. Environmental Epidemiology. Volume 2. Use of the Gray Literature and Other Data in Environmental Epidemiology. Washington, DC, National Academy Press.1997.

42. Gammon MD, Wolff MS, Neugut A, Eng SM, Teitelbaum SL, Britton JA , et al. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. Cancer Epidemiol Biomarkers Prev. 2002; 11: 686-697.

43. Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA, et al. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epid Biom Prev. 2000; 9: 55-63.

44. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monogr Eval Carcinog Risks Hum. 2002; 80: 1-395.

45. West JG, Kapoor NS, Liao S, Chen JW, Bailey L, Nagourney RA, et al. Multifocal Breast Cancer in Young Women with Prolonged Contact between Their Breasts and Their Cellular Phones. Case Rep Med. 2013; 2013: 5 Pages.

46. Morgan LL, Miller AB, Sasco A, Davis DL. Mobile phone radiation causes brain tumors and should be classified as a probable human carcinogen (2A) (Review). Int J Oncology. 2015; 46: 1865-1871.

47. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. IARC Monogr Eval Carcinog Risks Hum. 2010; 98: 9-764.

48. Collaborative group on hormonal factors in breast cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet. 2001; 358: 1389-1399.

49. Mavaddat N, Pharoah PD, Michailidou K, Tyrer J, Brook MN, Bolla MK , et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015; 8; 107.

50. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. Int J Cancer. 2014; 135: 2444-2452.

51. Newman SC, Miller AB, Howe GR. A study of the effect of weight and dietary fat on breast cancer survival time. Am J Epidemiol. 1986; 123: 767-774.

52. Jain M, Miller AB, To T. Premorbid diet and the prognosis of women with breast cancer. J Natl Cancer Inst. 1994; 86: 1390-1397.

53. Jain M, Miller AB. Pre-morbid body size and the prognosis of women with breast cancer. Int J Cancer. 1994; 59: 363-368.

54. Jain MG, Miller AB, Rohan TE, Rehm JT, Bondy SJ, Ashley MJ, et al. Body mass index and mortality in women: Follow-up of the Canadian National Breast Screening Study cohort. Int J Obes. 2005; 29: 792-797.

55. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, et al. Tamoxifen for prevention of breast cancer: extended long- term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015; 16: 67-75.

56. Mocellin S, Pilati P, Briarava M, Nitti D. Breast Cancer Chemoprevention: A Network Meta-Analysis of Randomized Controlled Trials. J Natl Cancer Inst. 2015; 18; 108.

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