MINI-REVIEW

Effects of Reproductive Factors on Risk of Breast Cancer: A Literature Review

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Abstract

Breast cancer is the leading women's cancer worldwide. However, there are geographical considerable differences with high rates of disease in North America and North Europe and relatively low rates in Africa and Asia. This article reviews the effects of reproductive factors on risk of breast cancer : early menarche, nulliparity or late age at first birth, late menopause, as well as hormonal factors. Knowing risk factors of breast cancer could significantly contribute to an improved prevention of this cancer. Furthermore, this review aimed to highlight potentially controversial conditions in the Asian countries compared to other parts of the world which could in the future improve early prevention of breast cancer in Asian women.

Key words: Breast cancer - reproductive factors - risk factors - hormones

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Introduction

The association between pregnancy and breast cancer risk has been reported in some studies (Russo and Russo 1990; Russo et al., 1999). However, contradictory results have also been reported (Sivaraman, 1998; Grubbs et al., 1985). According to the process of carcinogenesis, undifferentiated mammary gland cells might be initiated by carcinogens and after promotion give raise to a breast tumor several years later (Ponten et al., 1990). The mammary gland epithelium could reach full differentiation at the first full-term pregnancy and differentiated cells do not divide or proliferate under normal conditions and are less susceptible to the effects of carcinogens. In other words the earlier the first full-term pregnancy is associated to the earlier the mammary gland cells differentiation (Ponten et al., 1990).

On the other hand, the first full-term pregnancy changes long-term hormonal levels including decreased prolactin, higher sex hormone-binding globulin (SHBG), and lower estrogen (Goldman and Hatch, 2000). These changes may provide further protection against breast cancer. Meanwhile, a transient increase in the risk of breast cancer after childbirth has been reported (Chie et al., 2000). Women who have a first birth at 30 years or older have a significantly high risk of breast cancer compared with those below 25 years old (Nagata et al., 1995; Tamakoshi, et al., 2005). Women who did not have a first birth until age 30 might already have had cells that had undergone early stages of malignant transformation, and pregnancy could have stimulated the growth of these mutated cells. However, the association of age at first delivery with breast cancer risk was strengthened only among postmenopausal women in the Tamakoshi's study. This fact is inconsistent with the results of the studies conducted in Western countries reporting that late age at first full-term pregnancy had a greater effect on the risk of breast cancer diagnosis at early age or before menopause (Clavel-Chapelon et al., 2002; Tryggvadottir et al., 2002). Further investigation is necessary to determine whether these findings are a result of the lack of reproductive information, such as the final term of pregnancy, the number of abortions and breast feeding, or are linked to the hormonal milieu or lifestyle, or are merely attributable to chance.

Methodology

Four databases were used for the literature search which were Medline, Pub Med, Science Direct, and Black Well Synergy. The search terms were "reproductive factors", "risk factors" and "breast cancer". Over 50 articles published between 1990-2006 were reviewed which included systematic reviews, quasi experimental reports, surveys and qualitative studies. The inclusion criteria were effects of reproductive factors on the risk of breast cancer. The reproductive risk factors categorized into four main areas: pregnancy factors, menstrual factors, hormonal factors, and protective effects of lactation.

Pregnancy Factors

Parity

Two of the earliest known and most reproductive factors related to breast cancer are decrease the risk of

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breast cancer with increase parity, and increase the risk with single marital status. According to an early study by Macmahon et al (1993) the protective effect of parity was due to protective effect of young age at first birth. Adversely, in a recent study done by Tamakoshi et al (2005) multiparity was associated with a decreased risk of breast cancer independent of the effect of age at first delivery, although these two variables were inversely correlated (correlation of coefficient r = -0.27, p<0.001). This result is consistent with the possibility that cellular differentiation of the mammary gland initiated by the first birth might mask or overcome the short-term promoting effect of subsequent pregnancy for multiparous women. Every new pregnancy might differentiate the remaining undifferentiated cells, which are caused by inconsistency in the process of differentiation (Ponten et al., 1990). Other investigators reported that the protective effect of pregnancy on breast cancer may be due to two beneficial consequences of completed pregnancy. Firstly, prolactin levels are substantially lower in multiparous than in nuliparus women. Secondly, multiparous women have lower levels of circulating estradiol and higher level of bioavailable or free estradiol (Innes and Byers, 1999; Goldman and Hatch, 2000; Lee et al., 2004).

According to Nagata's study (1995) in Japan, nuliparous women have higher risk of breast cancer than women with first birth before age 25 (odds ratio OR=1.56, 95%, CI:1.27-1.91). Aversely, another study in Japan by Tamakoshi, et al. (2005) reported that the risk of breast cancer for parous women compared with nulliparous was near unity (RR= 0.95; 95% CI: 0.38–2.32), However, among parous women, the relative risk decreased by the number of parity. With reference to those with one delivery relative risk of breast cancer was 0.78 (0.42– 1.44) for two deliveries, 0.68 (95%, CI: 0.36–1.31) for three, and 0.31 (95%, CI:0.13–0.76) for four and more delivery. There was a significant declining trend between the number of parity and the risk of breast cancer (p-value<0.01). They also showed that only among parous women, there was a borderline significant increase in the risk of breast cancer with rising age at first delivery, with the highest risk occurring in women who had their first delivery at age 35 or older (RR = 2.12, 95%, CI: 0.72-6.21, p=0.05). (Tamakoshi et al., 2005)

Alternatively, parity could be a surrogate for other exposures relevant to breast cancer risk. Physical activity associated with large families has been suggested as such an exposure (John et al., 2003; Mctiernan et al., 2003; Lee et al., 2004). Tamakoshi et al (2004) found that the women with more children were likely to take more time to exercise. However, the protective effect of multiparity was unchanged after adjustment for physical activity, smoking, alcohol intake, and diet. The independent protective effect of multiparty on the risk of breast cancer observed may be due to some unidentified factors such as social or psychological factors. More researches are needed to investigate the effect of large family on the lifestyle, risk of cancer or other chronic diseases.

Age at First Delivery

Women who have a late first full term pregnancy (after age of 35 years) are at an elevated risk of breast cancer, compared with women with first birth before age 25. A meta-analysis of eight case-control studies in Japan reported that late age at first delivery and early age at menarche were significantly associated with risk of breast cancer. They also found that parity is one of the independent risk factors of breast cancer (Nagata et al., 1995). In contrast, Tamakoshi et al (2005) observed a positive association of age at first delivery with breast cancer risk among menopausal women. Women who had their first delivery at age 35 or older had three times more likely risk of breast cancer than younger women (RR=3.33, 95%, CI: 1.07-10.3, p=0.02). Meanwhile, no association of age at first delivery with breast cancer was observed among the premenopausal women (Tamakoshi et al., 2005).

Abortion

A number of studies have examined the risk of breast cancer associated with spontaneous and induced abortion. Although there has been some controversy in the past about the relationship between abortion and breast cancer risk. A collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries described the inconsistent finding across studies and difficulties in evaluation these associations. They concluded that beast cancer risk did not appear to be associated with an increased number of either spontaneous or induced abortions (Collaborative Group on Hormonal Factors in Breast Cancer, 2004). While numerous studies have suggested that abortion may moderately increase the risk of breast cancer (Brind et al. ,1996; Wingo et al. 1997; Zografos et al., 2004), the nature of these studies makes the accuracy of their results questionable. Case-control studies rely on the reporting of past behavior, and when it comes to a sensitive topic like abortion, this can have a significant impact on the precision of the information gathered. The cases in these studies the women with breast cancer may be much more likely to provide complete information about their abortion history than the controls the women without breast cancer. Such differences in the completeness of reporting can compromise the accuracy of the study results. Cohort studies are more likely to provide accurate results on the topic of abortion because they tend to gather sensitive information before women are diagnosed with breast cancer.

Menstrual Factors

Age at Menarche

Modest elevation in breast cancer risk is associated with early age of menarche (Russo and Russo, 2000). Also observations suggest that regular ovulatory menstrual cycle increase a woman's risk of breast cancer (Magnusson et al., 1999; Goldman and Hatch, 2000). Breast cancer risk could be more than two times greater among women whose menstrual cycles become regular within one year of their first menstrual period than among women with a five years or longer delay in the onset of regular cycle (De Stavola et al., 2004). It has been hypothesized that early menarche induces an early proliferation of mammary gland cells

through early exposure to high hormonal levels (Harrison et al., 1999). However, there was no association between age at menarche and breast cancer risk in the Japan Collaborative Cohort Study (Tamakoshi et al., 2005). Inconsistent findings may be a result of the difference of age at menarche as well as the study areas and subjects.

Age at Menopause

According to epidemiological studies, late age at menopause is known to be a risk factor for breast cancer (Goldman at Hatch, 2000; Oran et al., 2004; Zografos et al., 2004). Women who reach menopause at a late age are more likely to have a higher risk of breast cancer, although no consistent trend is observed (Goldman and Hatch, 2000). The higher breast cancer risk in women with a late menopause is most likely explained by both the longer duration and higher level of exposure to estrogen and progesterone experienced by these women. They also may experience a larger number of anovulatory cycles resulting in a lack of cyclic progesterone. The effect of hormonal milieu on breast cancer during anovulatory cycle is less clear. Artificial menopause by bilateral oophorectomy also markedly reduces breast cancer risk and the effect is greater than that natural menopause (Goldman and Hatch, 2000; Zografos et al., 2004). Differences between effect of natural and artificial menopause on risk of breast cancer can be explained by the fact that ovarian function does not stop at the time of menopause among women with intact ovaries, but declines over period of a few months or year.

On the other part, the menstrual and reproductive events might affect breast cancer risk differently in pre- and postmenopausal women. In a meta analysis study in Japan, the odds ratio of risk of breast cancer for two categories of parity, number of births of 2 or more compared to one birth, were 0.74 (95%, CI:0.49-1.13) and 0.61 (95%, CI:0.38-0.98), respectively for pre-menopausal women; and it was 0.94 (95%, CI:0.55-1.60), and 0.84 (95%, CI:048-1.46), respectively, for postmenopausal women. High parity was more strongly associated with risk in premenopausal women, although the difference between pre- and postmenopausal women was not statistically significant (Nagata et al., 1995).

Hormonal Factors

Endogenous Estrogens

Since the 1960s, numerous studies have been conducted on the influence of hormones on breast cancer risk. Estrogens, female hormones, have been measured in various body fluids, urine, blood, and more recently breast tissue. Estrogens in the body exist in several forms, estradiol, estrone and estriol being the three main ones. Differences in levels of these hormones exist from country to country and probably it have been linked to different risks of breast cancer (Goldman and Hatch, 2000). Other studies confirmed the effects of age at menarche or pregnancy history (Magnusson et al., 1999; Russo and Russo, 2000). The hypothesis behind the effects on breast cancer risk of reproductive events relates to hormonal influences, in particular estrogens. Their role is crucial not only in cancer initiation and promotion (Russo and Russo, 1998), but could also possibly be used for prevention (Russo and Russo, 2000). Hormones and reproductive life closely interact not only in the occurrence of disease but also in the development of the mammary gland and the susceptibility to carcinogenesis (Russo and Russo, 1999).

Women with high levels of estrogens, in particular free estrogens, not linked to the sex-hormone-binding globulin, have long been recognized as being at a high risk of cancer development (Goldman and Hatch, 2000). This demonstrates that even in the absence of exogenous hormones, risk of cancer is influenced by the endogenous hormonal milieu. In fact, future cancer risk is in part also determined by conditions of exposure in uterus. A study done by Michels et al (1999) showed high birth weight as a risk factor for cancer and in particular for breast cancer. Similarly, another study concluded that among twins, the risk of breast cancer may be affected by the type of twinning (dizygotic versus monozygotic) and sex of the dizygotic twin (Cerhan et al., 2000).

Hormone Replacement Therapy (HRT)

Hormone replacement therapy has been used by millions of women to relieve menopausal symptoms and to reduce the risk of certain chronic diseases, most often heart disease and osteoporosis (Wrensch, 2003; Zografos et al., 2004). In the mid 1970s it became evident that unopposed estrogen use resulted in an increased risk for endometrial cancer (IARC, 1999). Consequently, a progesterone was added to the estrogens, commonly for 10–14 days of each artificial cycle. A dramatic decline in the incidence of endometrial cancer followed. However, there are evidences on the relationship between postmenopausal hormone therapy and risk of breast cancer from many epidemiological studies. A pooled analysis of the data from 51 epidemiologic studies and a review of data from 15 cohort and 23 case-control studies showed that in the majority of the studies there was a small increase in risk with longer duration of use in current and recent HRT users (International Agency for Research on Cancer IARC, 1999). The results of nine cohort and five case-control studies and the findings of a pooled analysis of the original data indicated that the increased relative risk observed with long-term use of postmenopausal estrogen-progestogen therapy was not different from that for long-term use of estrogens alone (IARC, 1999). A significant increased risk for long-term combined HRT users was found in several recent studies (Ross et al., 2000; Schairer et al., 2000; Wiess et al., 2000; Chen et al., 2002; Newcomb et al., 2002). However, the differences found between different regiments of HRT were not statistically significant (IARC, 1999).

On the other hand, breast cancer tumors found in women on HRT were more localized in nature and more often were less aggressive, being more often well differentiated and less often lymph-node-positive (IARC, 1999). This might explain why most studies that report on death from breast cancer found a lower disease specific mortality rate in HRT users compared to non-users. Breast cancers in HRT users were significantly smaller in size,

better differentiated, and they were less likely to spread to the auxiliary lymph nodes (IARC, 1999). Therefore, there is strong but not conclusive evidence to show that breast cancers arising in HRT users have better prognostic characteristics than those found in non-users. However, the possibility should be considered that HRT users could develop an increased risk for relatively mild breast tumors, while probably not reducing their base-line risk for aggressive tumors, which have a poorer prognosis. Finally, there is the possibility that the phenomenon of a better prognosis of breast cancer in HRT users is due to confounding factors. This could be the case when HRT users have easier access to medical care, have more mammograms, have tumors diagnosed earlier and adhere more frequently to a healthier lifestyle, thereby favorably influencing their prognosis.

Overall, in deciding whether or not to take postmenopausal hormones, women should have in-depth discussions with their physicians about the potential risks and benefits of HRT. Working through these complicated issues with a physician is a key to helping a woman decide if, and for how long, she wants to use postmenopausal hormones. If she decides to take hormones, the National Institutes of Health (NIH), 2004 recommend that they be used only at lowest doses for the shortest possible durations necessary to achieve benefits.

Oral Contraceptive Pills (OCPs)

Millions of women take birth control pills and would like to know how this may affect their risk of breast cancer. More than 10 cohort and 50 case-control studies have assessed the relationship between use of combined oral contraceptives and risk of breast cancer. The evidences suggest a small increase in the relative risk of breast cancer especially among current and recent users. However, it is unrelated to duration of use and type or dose of preparation and may be partly linked to detection bias (IARC, 1999).

Collaborative reanalysis of data on 53, 297 women with breast cancer and 100, 239 women without breast cancer from 54 epidemiological studies found that women were taking birth control pills, their relative risk of breast cancer was 10 to 30 percent (or 1.1-1.3-fold) higher than that of women who had never used birth control pills. Once women stopped taking the pill, however, their risk began to diminish and returned to normal within about 10 years (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). In most of the studies in this analysis, the women were taking older, higher-dose versions of the pill, and so one area under active study is how today's lower-dose pills might affect the risk of breast cancer. The evidence to date hasn't been able to answer this question confidently. Furthermore, data on the effect of injectable progestogen-only contraceptives on breast cancer risk from two case-control studies and a pooled analysis have shown relative risks vary between 1.0 and 1.3, and were not statistically significant (IARC, 1999).

Inconsistence results has been reported by a case-control study which found no association between birth control pills and breast cancer (Marchbanks et al., 2002). The finding of this single study is not compelling enough to change the general conclusions based on all the data to date. In fact, the findings in certain groups of women in this study actually support the conclusion of the combined analysis that birth control pill use slightly elevates breast cancer risk. Although, the increased breast cancer risk associated with pill use can be a little frightening for women, it is important to note that most women on the pill have a low risk of breast cancer to start with because they are typically young and premenopausal. So even with a slight increase in risk, they are still unlikely to develop breast cancer while they are on the pill. Before making any decisions about birth control pills, women should weigh the pros and cons of using them. Though they have some associated risks , birth control pills have a number of advantages as well, including preventing unwanted pregnancies and decreasing a woman's risk of both uterine and ovarian cancers (Van Den Brandt et al., 2002).

Lactation

Studies have shown that lactation protected women against breast cancer development. (Parker et al., 2001; Lee et al., 2004). An explanation for the protection afforded by lactation is that the cumulative number of ovulatory menstrual cycles a woman experiences will be lower among women substantial lactation experience because breast-feeding delays ovulation following a completed pregnancy. Breast-feeding is a potentially modifiable behavior, thus its impact on the reduce risk of breast cancer is extremely important particularly among premenopausal women. Evidence is less certain with regard to the risk of postmenopausal women (Goldman and Hatch, 2000; Parker et al., 2001; Lee et al., 2004; Zografos et al., 2004). Enger et al (1997) also found that the risk of breast cancer among pre- and post menopausal was nearly 35% and 30% , respectively lower among those who breastfed more than 15 months compare to those not breastfed their children. The reasons that why some studies have not observed protective effects of lactation may be due to small proportion of women with sufficient lactation experience. Variation in the time when supplementary feeding is introduced and in frequency and duration of each breastfeeding episode may also contribute to the inconsistent findings.

Collaborative reanalysis of data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease, mothers who breastfed for a total of one year were found to be slightly less likely to develop breast cancer than mothers who had not breastfed; those who breastfed for a total of two years got about twice the benefit of those who breastfed for a total of one year (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Add this reduced risk of breast cancer to the other benefits of breast-feeding such as fewer childhood infections, fewer sick days used to care for an ill child, a quicker return to pre-pregnancy weight and possibly a lower risk of ovarian cancer and there are compelling reasons for women to choose to breast-feed their children if the resources are available and they are capable of doing so.

Conclusions

The study of risk factors, first of all, aims to improve the understanding of possible pathogenic mechanisms of malignant diseases. Secondly, some factors are more or less under the control of the woman (such as age of menopause [induced menopause], nulliparity [due to socioeconomic factors of course and not to biologic], age of the first full-term pregnancy, period of breastfeeding, oral contraceptives, HRT, diet, body weight, and alcohol) and therefore their detection has direct practical effect on cancer prevention.

Breast cancer has already become the most common malignancy among women in Asian countries. The recent increase in beast cancer risk is more pronounced in premenopausal than postmenopausal women. Therefore, it is necessary to further examine the change in reproductive factors, their effect on breast cancer, and the interactive effects between reproductive factors and lifestyle factors such as obesity and fat intake among women particularly most of whom have lived largely Westernized lifestyle since childhood. Given the crucial role of the hormonal pathway in the occurrence and development of tumors, better knowledge of the determinants of endocrine events such as puberty and fertility is needed. Too much is still unknown and yet too little is studied with respect to the etiology of breast cancer, in particular premenopausal disease. Education programs to inform early detection methods for breast cancer, including breast self-exam, mammography, and/or clinical breast exams, should be offered to those who have a high risk of developing breast cancer.

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