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REVIEW

Energetic factors, ovarian steroids and the risk of breast cancer

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In industrial countries, women often have excess metabolic energy due to high food consumption and low physical activity. High lifetime energy availability results in high lifetime levels of ovarian steroid hormones. Oestrogens and progesterone are hypothesized to play a crucial role in the development and prognosis of breast cancer. Epidemiological studies document the importance of physical activity and caloric limitations in reducing breast cancer risk. The risk of breast cancer is much higher in industrial countries than in developing countries, where women are characterized by lower energy intake and higher energy expenditure. It is likely, that the beneficial effects of physical activity and of negative energy balance are mediated by the reduced levels of ovarian steroids. While both weight loss and physical activity may have similar efficacy in suppressing ovarian function and, therefore, in reducing the risk of breast cancer, we suggest that it may be more advantageous for premenstrual women to achieve lifetime reduction in steroid levels by increasing their physical activity, rather than by weight loss due to caloric restriction alone.

Key words: Breast cancer prevention, energy balance, oestrogen, exercise, physical activity, progesterone.

Introduction

In economically developed countries, energy from food is abundant and the need for energy expenditure is limited. In such conditions the ovary operates at its maximal potential. In women who have high energy intake and low energy expenditure menstrual cycles are characterized by high levels of ovarian steroid hormones (Ellison, 1995). In addition, growing up in an environment with virtually unlimited availability of energy leads to an early menarche (Ellison, 1982; Petridou *et al.*, 1996), which increases reproductive lifespan and lifetime steroid production (Apter and Vihko, 1983). Furthermore, modern women have a low number of full-term pregnancies and, on average, breastfeed their children for a short time.

Ovarian steroid hormones, especially oestradiol, have been identified as important factors in the development and prognosis of breast cancer (Henderson *et al.*, 1988; Key and Pike, 1988; Pike *et al.*, 1993). Major lifestyle risk factors for breast cancer, such as early menarcheal age, late menopause, limited number of pregnancies, short duration of breastfeeding (Kelsey, 1993) – all contribute to high lifetime levels of ovarian steroids. In addition, maintaining a positive (or even neutral) energy balance and having low levels of energy expenditure is associated with high ovarian steroid production during the reproductive years (Ellison, 1999).

Consequently, reducing the lifetime oestrogen and progesterone levels might be the most important step in lowering the risk of breast cancer in women. However, changing some of the risk factors, which

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would lead to lower ovarian steroid levels, although theoretically advantageous, may be impossible in practice. For example, lowering the age of menopause would lead to lower lifetime steroid levels, but it would be an unlikely choice for most women. Similarly, manipulating the age of menarche, of first birth or the duration of breastfeeding, although possible, may be too difficult or impractical. In addition, there are also other health aspects, which should not be overlooked when such a manipulation is proposed.

In recent years, epidemiological studies have pointed to the importance of physical activity and negative energy balance for the reduction of breast cancer risk in women (Bernstein *et al.*, 1994; Friedenreich and Rohan, 1995; Thune and Gaard, 1998). Both risk-reducing energetic factors (i.e. physical activity and negative energy balance) probably have similar abilities to decrease breast cancer risk, most likely by reducing the lifetime levels of ovarian steroid hormones (Bernstein and Ross, 1993; Ellison, 1999). However, we propose that physical activity rather than dieting is a more advisable choice when it comes to breast cancer prevention. This is because of the other health aspects of ovarian steroids. Oestrogens are necessary for protection against osteoporosis, cardiovascular diseases and, possibly, Alzheimer's disease (Alden, 1989; Barrett-Conor and Bush, 1991; Nguyen *et al.*, 1995; Spencer *et al.*, 1999). Progesterone may also interact with oestrogen or have an independent effect in providing cardiovascular and bone density benefits (Alden, 1989).

Although attempts to influence characteristics of the life history of a woman (e.g. age of menarche and menopause, timing of the first pregnancy, number of full-term pregnancies) may be difficult in practice, lifetime levels of ovarian steroids can be reduced by altering energy-related factors. The negative energy balance resulting either from low caloric intake, high energy expenditure or a combination of both, leads to menstrual cycles with lower levels of ovarian steroids (Lager and Ellison, 1990; Ellison, 1995; De Souza *et al.*, 1998; Rosetta *et al.*, 1998; Zanker and Swaine, 1998). Moreover, an increase in the levels of energy expenditure reduces levels of ovarian hormones, even in women who remain in a neutral energy balance (Bullen *et al.*, 1985; Ellison and Lager, 1986; Jasienska and Ellison, 1998).

In order to investigate the importance of energetic factors in the risk of breast cancer we present a conceptual framework within which to view some of the rapidly accumulating evidence from several areas of research (Figure 1). Epidemiological data indicate that physical activity and negative energy balance are related to a decrease in breast cancer risk in women. At the same time, clinical and field studies point to physical activity and negative energy balance as factors leading to a reduction in ovarian steroids levels. Ovarian steroids are known to stimulate mitotic activity of breast tissue and to interact with growth hormones, and therefore are thought to increase the rate of breast cancer growth (Ciocca and Fanelli, 1997).

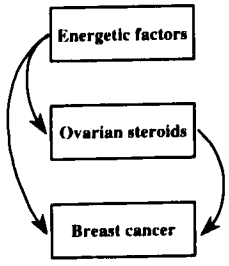

Figure 1. A conceptual flow diagram illustrating the relationships discussed here between energetic factors, ovarian steroids and risk of breast cancer. Epidemiological data point to the influence of energetic factors (physical activity and energy balance) on the risk of breast cancer. Clinical studies document the impact of energetic factors on ovarian steroids production. Ovarian steroids have been implicated in the development of breast cancer.

Relations between energetic factors and breast cancer risk

Studies of breast cancer epidemiology have implicated exercise and diet as lifestyle factors that can affect the risk of the disease. Frisch *et al.* (1985) examined the incidence of breast and reproductive tract cancers in 5398 college alumnae categorized by their participation in organized athletics during college. Those who had been college athletes had a significantly lower risk of breast cancer than did nonathletes after controlling for potential confounding factors. Recent studies of physical activity and breast cancer incidence using case–control studies (Bernstein *et al.*, 1994; Mittendorf *et al.*, 1995; Coogan *et al.*, 1997; Carpenter *et al.*, 1999) and prospective studies (Fraser and Shavlik, 1997; Thune *et al.*, 1997; Rochhill *et al.*, 1999) have also shown that moderate levels of exercise or occupational physical activity in adulthood are associated with reduced cancer risk.

Evidence has also been presented on the relationship between weight and energy intake and breast

cancer risk and the progress of the disease. Newman *et al.* (1986) found in a case–control study that body weight showed a significant positive association with breast cancer mortality, while dietary fat intake did not. In addition, weight gain in adulthood has been observed to increase risk of breast cancer (Ballard-Barbash *et al.*, 1990; Ziegler *et al.*, 1996; Huang *et al.*, 1997). Excess weight particularly increases the risk of breast cancer in postmenopausal women, where it may increase the rate of extragonadal oestrogen production. Height has also been positively associated with breast cancer risk (de Waard, 1975, 1981; de Waard and Trichopoulos, 1988; Tretli, 1989), possibly reflecting chronically high energy intake during growth. De Waard and Trichopoulos (1988) suggest that energy intake as a risk factor for breast cancer may provide a unifying concept in attempts to understand breast cancer epidemiology, while Hocman (1988) extends a similar concept to the epidemiology and prevention of other cancers as well. Recently, in a prospective study Thune and Gaard (1998) reported a strong reduction in breast cancer risk among women with low energy intake, high physical activity and stable body mass index.

Ovarian steroids and breast cancer

Ovarian steroid hormones have been identified as important factors in the development and prognosis of breast cancer (Henderson *et al.*, 1988; Key and Pike, 1988). At the cellular level, both oestradiol and progesterone act to regulate mitosis and cellular proliferation (Soto and Sormenschein, 1987; Clarke and Sutherland, 1990). The close relationship between ovarian function and breast cancer has been apparent since Beatson (1896) reported success in treating premenopausal breast cancer with bilateral oophorectomy. Oestradiol acts as a potent mitogen in target tissues, including end bud and ductal epithelial cells of the breast, actions that are mediated both through oestrogen receptors and through the promotion of polypeptide growth factors (Dickson and Lippman, 1987; Soto and Sormenschein, 1987). Progesterone also stimulates mitotic activity in both normal and neoplastic breast tissue, especially in lobuloalveolar epithelial cells, apparently by accelerating early phases of the cell cycle (Clarke and Sutherland, 1990). For therapeutic purposes, natural and synthetic progestins oppose the mitogenic actions of oestradiol by multiple pathways including the suppression of ovarian oestrogen production through negative feedback on the pituitary, downregulation of oestradiol receptors, and alteration of oestradiol metabolism.

Hormonal therapy has become an important aspect of breast cancer treatment, with the primary aim being a reduction in the mitogenic activity of ovarian steroids. Modes of treatment include the use of synthetic anti-oestrogens, such as tamoxifen, synthetic progestins, aromatase inhibition, GnRH analogues and antiprogestins (Santen *et al.*, 1990; Henderson *et al.*, 1993; Jordan, 1995; Chang, 1998). In postmenopausal women, extragonadal oestrogen produced by the peripheral aromatization of adrenal androgens can constitute a continuing risk factor (Siiteri, 1990; Thomas *et al.*, 1997; Stoll, 1999). In addition, in postmenopausal women endogenous steroid hormones from hormonal replacement therapy are suggested to increase the risk of breast cancer (Colditz, 1998).

Variation in ovarian function and breast cancer risk

Natural variation in ovarian function is implicated as a risk factor for breast cancer in the relationships that are observed between breast cancer incidence and aspects of individual gynaecological and reproductive history (Henderson *et al.*, 1988; Key and Pike, 1988). Nulliparity and late age at first birth are both associated with significantly elevated breast cancer risk, presumably due to the delay or absence of final tissue differentiation in the terminal lobuloalveolar ducts (MacMahon *et al.*, 1970; Kvale and Heuch, 1987). However, all other aspects of reproductive history associated with elevated risk reflect exposure either to an increased number of ovarian cycles or elevated steroid levels within cycles, or both (Figure 2) (see also Casagrande *et al.*, 1979).

Elevated risk is associated with early menarcheal age and with late menopausal age (Henderson *et al.*, 1985; Bruzzi *et al.*, 1988). Several studies have demonstrated that early menarcheal age is associated with a higher incidence of ovulatory cycles and more robust patterns of ovarian steroid secretion well into adulthood, so that not only the number of ovarian cycles but also the steroid levels within cycles are increased for early maturing women (Apter and Vihko, 1983; Venturoli *et al.*, 1987). The total number of pregnancies a woman has had is negatively associated with breast cancer risk, independently of the age at first birth (Pathak *et al.*, 1986; Bruzzi *et al.*, 1988), as is the total amount of time spent

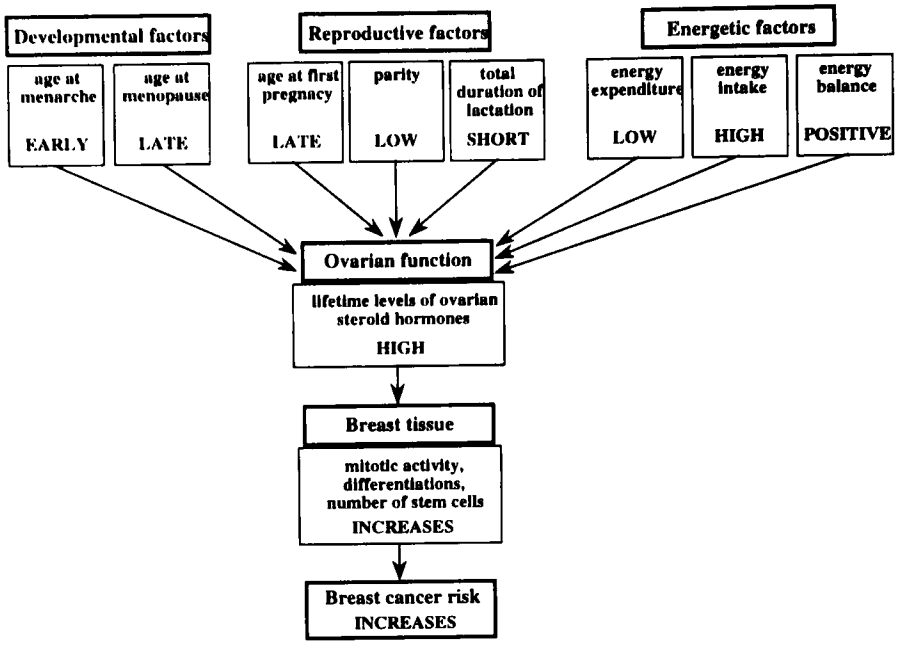

Figure 2. A model of breast cancer epidemiology. Major developmental, reproductive and energetic risk factors contribute to increases in lifetime levels of ovarian steroid hormones. High steroid levels, by influencing various aspects of breast tissue metabolism, may cause an increase in the risk of breast cancer.

lactating (Byers *et al.*, 1985; McTiernan and Thomas, 1986). Because both pregnancy and lactation suppress ovarian function, these associations also contribute to the evidence that natural variation in ovarian function modulates breast cancer risk. Age at menopause and at last full-term pregnancy, independent of age at first pregnancy, have been found to be positively associated with breast cancer risk (Kalache *et al.*, 1993), reflecting the maintenance of ovarian function in late reproductive life.

Energetic factors and ovarian steroids

Natural variation in ovarian function, which appears to modulate breast cancer risk, is itself associated with variation in several 'lifestyle' factors subject to individual behavioural control, including exercise, energy balance and diet. High levels of exercise, severe negative energy balance, and some highly unusual diets are associated with increased incidence of menstrual disturbances and even total amenorrhoea (Prior *et al.*, 1982; Prior, 1985; Broocks *et al.*, 1990; Rosetta, 1993; Rosetta *et al.*, 1998). More moderate levels of variation in these same factors, however, have also been associated with more subtle changes in ovarian function, including the suppression of ovarian steroid levels, without disrupting menstrual patterns (Ellison, 1990; De Souza *et al.*, 1998; Jasienska and Ellison, 1998). The high incidence of menstrual disturbances in female endurance athletes has been well documented (Feicht *et al.*, 1978; Prior, 1985; Rosetta, 1993). Such disruptions appear to be associated with alterations in pituitary gonadotrophin release (Cumming *et al.*, 1985) and can be induced in previously untrained women who are subjected to demanding regimes of aerobic exercise (Bullen *et al.*, 1985).

Yet other indices of ovarian function vary in association with more moderate levels of exercise even when menstrual cycles are regular (Pirke *et al.*, 1989; De Souza *et al.*, 1998). Shangold *et al.* (1979) reported that luteal phase length varied as a linear function of weekly running exercise even at very low weekly distances. Salivary progesterone levels were suppressed in recreational joggers who average less than 24 km a week (Ellison and Lager, 1985, 1986; Bledsoe *et al.*, 1990). Bernstein *et al.* (1987) found that the incidence of anovulatory cycles in adolescent girls showed a dose–response relationship to weekly energy expenditure. Broocks *et al.* (1990) also report suppressed ovarian steroid profiles in women engaged in various forms of recreational exercise.

Negative energy balance, reflected by weight change, appears to have an association with ovarian

function that is independent of exercise or energy expenditure. Vigersky *et al.* (1977) documented disturbances in pituitary gonadotrophins and amenorrhoea associated with 'simple weight loss' of 15% of initial weight. Pirke *et al.* (1985) found that caloric restriction diets in young women are associated with increased incidence of menstrual disturbances and suppressed ovarian steroid profiles. Further study indicated that such diets caused impairment of episodic luteinizing hormone (LH) secretion even in women of normal weight (Pirke *et al.*, 1988). Lager and Ellison (1990) documented lower salivary progesterone profiles in normal weight women losing moderate amounts of weight through calorie restriction dieting. They also found that suppression of ovarian steroid levels was even more pronounced in the cycle following that in which the weight loss occurred. The effects of suppressed ovarian function are apparently potentiated when weight loss occurs in combination with exercise (Bullen *et al.*, 1985), or when it occurs in young women (Schweiger *et al.*, 1989).

Variation in ovarian function in association with variation in energetic factors is not restricted to voluntary exercise or dieting in urban women. Similar variation has been described as resulting from workload or seasonal food shortages in women with more traditional lifestyles. Farm women in rural Poland show profiles of salivary progesterone that vary with the intensity and duration of their manual workloads (Jasienska, 1996a,b; Jasienska and Ellison, 1998). Women in Zaire and Nepal both show seasonally suppressed levels of ovarian steroids associated with changes in workload and energy balance (Ellison *et al.*, 1986; Panter-Brick *et al.*, 1993). In Zaire, this seasonal variation in ovarian function has been implicated in the seasonal pattern of conception that is also observed (Bailey *et al.*, 1992). It has been noted (Ellison *et al.*, 1993) that ovarian responsiveness to energetic factors appears to be a common feature of human reproductive biology designed by natural selection so that female fecundity is modulated in response to important ecological variables. Even when women in rural Poland, Zaire, Nepal, Thailand and Bolivia are in positive energy balance, their mean steroid levels are considerably lower than those in Boston women (Datura *et al.*, 1989; Ellison, 1994). The patterns of variation in salivary progesterone by age in these populations, however, are remarkably parallel (Ellison *et al.*, 1993). The steroid levels characteristic of an urban population like Boston may thus represent an extreme of range of global variation, a fact that may be a result of good energetic conditions during childhood and adolescent growth and development (Ellison, 1994).

Furthermore, evidence suggests that energy expenditure due to participation in sport or occupational work may influence ovarian function independently of negative energy balance. Bullen *et al.* (1985) investigated the effects of an intense physical exercise regime on ovarian function in previously untrained women. While women in one group were losing weight during eight weeks of intense training regime, women randomly assigned to the second group were receiving diet with enough additional calories to maintain their pre-study weight. Even though suppression of ovarian function was more pronounced in the weight-loss group, women who did not lose weight also showed evidence of ovarian suppression.

Ovarian suppression has also been documented in women who were maintaining stable body weight while running on average 20 km per week (Ellison and Lager, 1986). Even though the runners' cycles were of similar length to those of the controls, they were characterized by lower levels and shorter profiles of luteal progesterone.

Ovarian suppression due to high levels of energy expenditure, not associated with the negative energy balance, has also been shown in relation to occupational work (Jasienska, 1996b; Jasienska and Ellison, 1998). Polish farm women had reduced salivary progesterone levels during the months of intense harvest-related activities. These women were in good nutritional status (mean BMI of 24.4 kg/m^2, mean body fat of 27.5%) and did not fall into a state of negative energy balance as a result of increases in workload intensity. Results of these studies suggest that negative energy balance is not a necessary condition for the occurrence of physical activity-induced reproductive suppression in women.

Geographic variation in breast cancer incidence

Breast cancer is the most common cancer in women worldwide (Parkin *et al.*, 1999). Consequently, breast cancer is a major health problem of great interest and concern to physicians and women in general. The age-adjusted incidence of breast cancer varies between countries with a four- to sevenfold higher incidence rates in the US and western European countries than in, for example, Japan (Parkin *et al.*, 1999). Apart from this international variability, the

most interesting findings have come from migrant studies (Haenzel and Kurihara, 1968; Buell, 1973; Ziegler *et al.*, 1996). A study by Ziegler *et al.* (1996) observed that white Californian Americans had the highest incidence rates of breast cancer among three studied groups of women. The Chinese and Japanese women living in California had intermediate rates, while the lowest incidence rates were observed for Chinese and Japanese women living in China and Japan. These differences, also reported by others (Parkin and Iscovich, 1997), cannot be accounted for by variation in genetic factors, since the incidence of breast cancer among Japanese or Chinese immigrants in the US after one or two generations approaches that reported for the general US population. These findings strongly suggest the impact of lifestyle variables on breast cancer risk.

Potential for behavioural intervention

According to most current hypotheses of breast cancer aetiology, ovarian steroids play an important role at every stage of the disease process from the initial transformation of healthy cells to the progress of disease postdiagnosis (Hershcopf and Bradlow, 1987; Henderson *et al.*, 1988; Henderson, 1993; Ciocca and Fanelli, 1997). However, there is a pressing need to identify interventions capable of impeding or preventing the early stages of development of the disease or the disease-prone state. The potential for behavioural intervention to modulate breast cancer risk has been noted by several investigators (Frisch *et al.*, 1985; Bernstein *et al.*, 1987; Bradlow and Michnovicz, 1989). The responsiveness of human ovarian function to variation in lifestyle factors such as physical activity and energy balance suggests that these may be important variables to focus on. The evidence reviewed suggests that moderate variation in these variables, compatible with realistic recommendations and attainable goals for many women, can potentially result in significant changes in ovarian steroid levels. If ovarian function is highly sensitive to these variables, behavioural intervention in this area may have significant practical potential.

Therefore, in attempts to lower lifetime ovarian steroid levels the energetic factors should be taken into consideration. Negative energy balance resulting either from low caloric intake, high energy expenditure or combination of both, leads to menstrual cycles with low levels of ovarian steroids (Ellison, 1990). Evidence shows that when a woman of reproductive age loses weight her steroid levels in the ongoing menstrual cycle, and usually also in the following cycle, are lowered (Lager and Ellison, 1986, 1990). In addition, an increase in the levels of energy expenditure, even when not accompanied by negative energy balance, also causes ovarian suppression (Bullen *et al.*, 1985; Lager and Ellison, 1986, 1990; Jasienska and Ellison, 1998). Therefore, there are two paths of behavioural changes that may be recommended for achieving lifetime decrease in ovarian steroids and possibly the risk of breast cancer. Ovarian steroids levels can be lowered either by weight loss or by increase in physical activity.

It is important to note that ovarian steroids have been associated with several other significant health risks in women besides breast cancer. Ovarian, uterine and cervical cancer risks are elevated in women with high exposure to oestrogen, whether ovarian or exogenous. Oestrogen exposure, on the other hand, appears to be negatively associated with coronary heart disease risk (Barrett-Conor and Bush, 1991) and osteoporosis (Cummings *et al.*, 1985; Alden, 1989; Nguyen *et al.*, 1995; Sowers *et al.*, 1998). Progesterone may also interact with oestrogen in modulating these other health risks. There is evidence, for example, that progesterone may have an independent positive effect on the maintenance of bone mineral density (Prior, 1990).

Therefore, it should be borne in mind that behavioural strategies aiming to reduce ovarian steroids may have potential negative consequences in areas other than breast cancer risk. Many of these, however, may be ameliorated by collateral health benefits or may be easily reversible. The suppression of ovarian oestrogen levels through exercise and calorie restriction may increase the risk of coronary heart disease, but changes in weight and relative body composition expected from the same behaviours are associated with lower coronary heart disease risk. Similarly, lower ovarian steroid levels due to exercise may contribute to the loss of bone mineral density (Nguyen *et al.*, 1995), but exercise regimes may have a counteracting positive effect (Davee *et al.*, 1990; Zhang *et al.*, 1992; Alekel *et al.*, 1995). Recreational running and low weight have been associated with reduced fecundity (Bates *et al.*, 1982; Green *et al.*, 1986, 1988), yet the suppressive effects of exercise and low weight on ovarian function appear to be quite reversible in the short term (Warren, 1990). Furthermore, positive adjustment of fecundity can be achieved by behavioural strategies aimed at increasing body weight and changing energy balance (Bates, 1985).

Conclusions

Evidence from several areas of research strongly suggests that the protective effect of physical activity and negative energy balance on breast cancer risk is mediated via reduced levels of ovarian steroids. Other researchers proposed that changes in life-history characteristics of women should be implemented in order to reduce lifetime levels of oestrogens and progesterone, and therefore reduce the risk of breast cancer (Frisch *et al.*, 1985; Eaton *et al.*, 1994). Although these changes would clearly result in lower lifetime levels of steroids, they are difficult to implement in practice. More practical reduction in ovarian steroids may be achieved through weight loss and increase in physical activity.

We suggest that it may be more advantageous for premenstrual women to achieve lifetime reduction in steroid levels by increasing physical activity rather than by weight loss due to caloric restriction alone. A combination of physical activity with some caloric restriction may also be recommended, especially for women who tend to gain weight or who are significantly overweight. The advantages of using physical activity to reduce steroid levels are related to other health aspects of steroid hormones. While weight loss alone reduces levels of ovarian hormones, exercise not only has similar effects on ovarian function but also, in addition, provides other health benefits.

A new avenue for research would be to determine the most beneficial physical regime leading to reduction of breast cancer risk and, at the same time, reduction in the risk of osteoporosis and cardiovascular diseases. While low ovarian steroid levels are recommended for breast cancer prevention, such low levels may be detrimental for bone or cardiovascular health. Therefore, it needs to be investigated what intensity and type of exercise and physical work is optimal for the total health.

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