RESEARCH COMMUNICATION

Role of Xenoestrogens and Endogenous Sources of Estrogens on the Occurrence of Premenopausal Breast Cancer in Iran

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Abstract

Breast cancer affects Iranian women one decade younger than their counterparts in other countries and the underlying risk factors have remained controversial. The aryl hydrocarbon receptor (AhR) mediates endocrine disruptive activities of polyaromatic hydrocarbons (PAHs) and dioxins, which may compromise ovarian functions of women in polluted environments. This study focused on tissue expression levels of AhR and associations with exposure to chemicals with estrogen-like activities (xenoestrogens) and other reproductive factors in premenopausal breast cancer patients. Fifty cases who underwent surgery from June 2009 to June 2010 were matched with 100 controls by age and hospital records. AhR overexpression was detected in 87% of epithelial cells of young breast cancer patients. Living near factories generating PAHs and dioxins was considered as a major risk factor in premenopausal breast cancer (p=0.001, OR=4.8). History of idiopathic infertility was identified as a second significant risk factor (p=0.002, OR=3.50), which could be affected by endogenous estrogen levels. Long term (>5 yrs) consumption of oral contraceptive pills was identified as the third most important risk factor (p=0.006, OR=2.27). Adiposity and abnormal weight gain after 18 years were considered as two major background factors, which may contribute to the levels of endogenous estrogens. Direct and indirect exposure to cigarette smoke (p=0.005, OR=1.43) was considered as a weak risk factor without association with AhR levels. It seems that AhR overexpression is affected by exposure to xenoestrogens and by adiposity. Early occurrence of breast cancer in Iran may be a result of interactions between hormonal and environmental factors.

Key words: Breast cancer - adiposity - AhR - xenoestrogens - endogenous estrogens

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Introduction

Although the probability of breast cancer incidence increases with the age (Bray et al., 2004), breast cancer could occur in young women before their menopause (Zhang and Wang, 2010). In Iran, the breast cancer problem seems more serious because it affects Iranian women at least one decade younger than their counterparts in developed countries (Kolahdoozan et al., 2010; Zhang and Wang, 2010). The underlying risk factors could be related to hormonal and environmental factors (Bidgoli et al., 2010b). Considerable number of epidemiologic evidence shows the role of premenopausal exposure to exogenous sex steroid hormonal resources in the development of female breast cancer.

The steroid hormones have been classified as a group 1 human carcinogen by international agency for research on cancer (Cogliano et al., 2005; IARC, 2007). Among hormonal risk factors in breast cancer, the role of polycystic ovary syndrome has been suggested (Soran et al., 2005) in its occurrence, which may contribute to the altered levels of estrogens and other sex steroid hormones in young patients.

Endocrine disrupting chemicals (EDCs) are natural or synthetic compounds that interfere with normal functions of endocrine systems. Many EDCs with estrogenic activities, i.e., xenoestrogens, are resistant to biodegradation, due to their structural stability, and persist in the environment (Dickerson et al., 2007). There is increasing concern about EDCs that are able to mimic hormones and interact with hormone transport proteins. As EDCs potentially disrupt hormone metabolic pathways, they can mimic functions of endogenous hormones and, in some cases, completely block the functions. A substantial number of environmental pollutants, such as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons (PAHs), phthalates, bisphenol A, pesticides, alkylphenols and heavy metals (arsenic, cadmium, lead, mercury), have been shown to disrupt endocrine functions and may cause breast

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cancer (Balabanic et al., 2011). The aryl hydrocarbon receptor (AhR) mediates the toxicity of EDCs with xenoestrogenic activities (Van der et al., 2009). Roles of AhR in incidence of benign and malignant breast tumors (Bidgoli et al., 2011) and reproductive disorders (Bidgoli et al., 2010a) have been described recently by us. AhR overexpression has been found in estrogen receptor (ER) α-negative human breast tumors and its overexpression is positively correlated with the expression of other genes (Vogel et al., 2011). Lower levels of ERalpha and progesterone receptor were suggested in breast cancer tissues of premenopausal patients compared to the levels in those of postmenopausal patients (Bidgoli et al., 2010b; Vogel et al., 2011). This is consistent with the hypothesis that long term exposure to endogenous or exogenous estrogenic resources down regulates the tissue levels of ER and progesterone receptor.

This study aimed to examine roles of long term exposure to xenoestrogens in early incidence of breast cancer in Iran. In addition, this study investigated relationships among reproductive factors, adiposity and endogenous levels of estrogens.

Materials and Methods

Population study

A case-control study was carried out among 50 newly diagnosed breast cancer patients and 100 normal controls in Tehran from 2009 to 2010. Cancers were identified from both self-reports registration and pathological reports. Exclusion criteria for cases and controls were menopausal evidence, evidence of pregnancy and recent lactation. Menopausal status at the time of recruitment was defined according to information on ovariectomy, hysterectomy, menstruation status (still menstruating, number of menses over the past 12 months). Women were considered postmenopausal if they had undergone a bilateral ovariectomy or if their menses had stopped 12 months or more (unless due to hysterectomy) ago. Women who were still menstruating by using exogenous hormones and women with no information on the number of menses over the past 12 months were excluded from this study. The control group was matched with cases for age ± 5 years.

Identification of reproductive variables

Demographical variables were obtained from specific questionnaire items: A Delivery related factors including mother's and grandmother's age, father and grandfather's age, mother's weight and birth weight at delivery; B, Menstruation related factors including age, weight and height at menstruation, irregular menstruation, amenorrhea and dysmenorrheal; C, Marriage related factors including marital status, age at marriage, age at first intercourse and frequency of intercourses per week.

Identification of hormonal disorders

Information on hormone use was obtained from specific questionnaire items. They covered questions on ever and current use of oral contraceptive pills (OCPs), the brand names, age at start and total duration of the use. Other methods of contraception were recorded including use of intrauterine device, tubectomy and use of progestins. Pregnancy related factors including number of full-term pregnancies, age and maximum weight gain at each pregnancy, months of breast feeding at each delivery, history of abortion induction were recorded. History of infertility covered questions on years of infertility, i.e., more than 2 years without birth controlling methods, use of ovulation stimulating drugs, hormone therapy or history of in vitro fertilization. Patients were asked their gynecological disorders including ovarian cysts, uterine firoadenoma, irregular menstruation, hyrsutism and other disorders.

Identification of background factors

Exact weight and height of cases and controls as well as their weight changes from menstruation to maturation, from pregnancy to breast feeding until present were recorded by pretested questionnaires. Body mass index (BMI) was calculated and compared between cases and controls.

Identification of environmental resources of AhR ligands

Exact living and working addresses of cases and controls were recorded and matched with the map of factories generating PAHs and dioxins. A complete list of factories that release toxicants with hormone-like effects was made before starting the study. The women who lived within 4 km from the pollutant factories were considered as high risk people.

Other lifestyle factors

Personal history of endocrine disorders, pattern of physical activity, occupations, smoking (active versus passive), alcohol consumption, using any drug, radiation exposure, weight gain after age 18 were recorded by pretested specific questionnaire. Dietary factors of exposure will be discussed separately.

Immunohistochemical studies

Out of 50 cases, 30 parrafinized blocks were selected for pathological and immunohistochemical studies. As previously described (Arbabi Bidgoli S et al., 2011, dew axed and rehydrated tissue sections were subjected to antigen retrieval using microwave oven and boiling citrate buffer (pH=6.0). Endogenous peroxidase activity and nonspecific binding sites were blocked by incubating sections with 0.3% hydrogen peroxide in methanol for 30 min. and 3% bovine serum albumin for 60 min, successively. Sections were then incubated 30 min at room temperature with AhR mouse monoclonal antibody (clone PRT9, abcam) that recognizes the cytoplasmic expression of human AhR in breast tissues. The results were visualized using the envision system (Dakocytomation) based on the manufacturer's

instruction with necessary modifications. Sections were also counterstained with Meyer's haematoxyline. The ideal staining conditions were established in our preliminary experiments. Method of scoring has been recently described (Bidgoli et al., 2011).

Statistical methods

Values were expressed as percent per population or as the mean±standard deviation. To assess associations between expression of AhR and clinicopathological data, the nonparametric chi square test was used. Relative risks and odds ratios were calculated by the Cochran-Mantel-Haenszel statistics using SPSS 16 and the odds ratios were reported for this case control retrospective study. When the odds ratio in cases was >1, if the probability values was <0.05 and when the 5% confidence interval of the true odds ratio was greater than 1, then we interpreted it as significant risk factor. When the odds ratio in controls was <1, if the probability values was <0.05 and when the 5% confidence interval of the true odds ratio was less than 1, then we interpreted it as protective factor significant.

Results

Clinicopathological features of patients

The mean age of patients whose tissues were immunohistochemically analysed (n=30) was 38.7±4.905 years. In these cases 50% (n=15) of tumors were located in right side and mean size was 3.23±2.25 cm. Most of tumors (87%/n=26) showed poorly differentiated nuclear grade and calcification but necrosis was observed in 63% (n=19) of them. Moreover most of them (76.7%/n=23) had lymphatic invasion, 33.3% (10) undifferentiated, 36.7% (11) poorly differentiated, 6.7% (2) moderately differentiated and 23.3% (7) well differentiated.

AhR levels in premenopausal breast cancer patients

AhR overexpression was detected in 87% of epithelial cells of breast cancer patients. Surprisingly, 70% of tissues showed strong staining of AhR and 16% showed moderate staining. The expression levels of AhR were not associated with clinicopathological parameters.

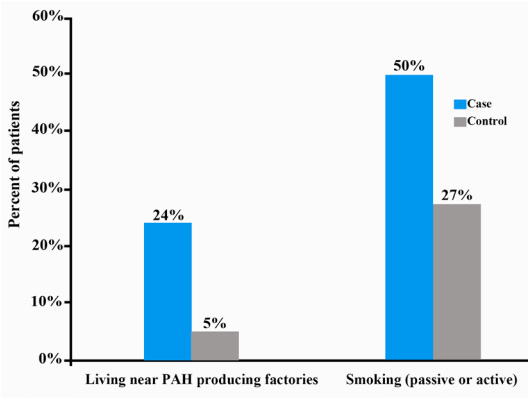

Figure 1. Comparison of PAH Exposure between Cases and Controls

Table 1. Comparison of Reproductive and BMI Factors between Cases and Controls

Characteristics	Cases	Controls	P-value
Age	38.7±4.9	37.2±5.6	NS
Delivery factors			
Mother's age at delivery	24.4±7.0	26.5±6.8	NS
Father's age at delivery	31.8±6.7	33.9±8.4	NS
Birth weight >4 kg	4 (8%)	11 (11%)	NS
Menstruation related factors			
Age at menarche	12.7 (1.43)	13.2 (1.49)	NS
Overweight at menarche	7 (14%)	18 (18%)	NS
Irregular menstruation	16 (32%)	32 (32%)	NS
Marriage related factors			
Marital status (married)	44 (88%)	92 (92%)	NS
Age at marriage	21.6±5.4	22.9±4.1	NS
Pregnancy related factors			
Nulliparity	9 (18%)	11 (11%)	NS
Age at first pregnancy	22.7±5.0	25.0±4.2	NS
History of abortion	12 (24%)	16 (16%)	NS
Infertility	8 (16%)	2 (2%)	0.002*
Breastfeeding factors			
Lack of Breastfeeding	9 (18%)	11 (11%)	NS
Breastfeeding <1 year	7 (14%)	19 (19%)	NS
Breastfeeding 1-2 yr	5 (10%)	19 (19%)	NS
Breastfeeding over 2 yr	29 (58%)	51 (51%)	NS
Style of OCP consumption			
No taking	21 (42%)	51 (51%)	NS
Under 1 year	10 (20%)	28 (28%)	
1-3 years	6 (12%)	9 (9%)	
3-5 years	4 (8%)	8 (8%)	
5-10 years	9 (18%)	4 (4%)	0.006*
>10 years	0 (0%)	0 (0%)	NS
Age at first OCP	23.9±6.0	22.9±3.8	NS
History of Reproductive Disorders			
Ovarian cyst	24 (48%)	32 (32%)	NS
History of malignant breast disease in first degree family	5 (10%)	12 (12%)	NS
History of benign breast disease in first degree family	9 (18%)	12 (12%)	NS
History of other malignant disease in first degree family	25 (50%)	41 (41%)	NS
Height	162 ±6.7	162 ±5.5	NS
Body Mass Index			
≤ 24.9 kg/m²	21 (42%)	60 (60%)	NS
≥ 25 kg/m²	29 (58%)	40 (40%)	0.028*
= 25-29.9	18 (36%)	32 (32%)	NS
≥ 30 kg/m²	11 (22%)	8 (8%)	
Weight gain after 18			
No change	3(6%)	16 (16%)	NS
< 10 kg	8 (16%)	26 (26%)	
10-20 kg	21 (42%)	42 (42%)	
>20 kg	18 (36%)	16 (16%)	0.034*

Reproductive risk factors in premenopausal breast cancer

Risk factors in premenopausal breast cancer were evaluated in several categories by comparing with normal groups (see Table 1). Reproductive variables were categorized to 8 major groups, which include 1) delivery related factors, 2) menstruation related factors, 3) marriage related factors, 4) pregnancy related factors, 5) breastfeeding factors, 6) OCP consumption and 7) history of hormonal dysfunctions e.g. ovarian cysts and

hyrsutism. The last factor could be affected by exposure to EDCs. Out of various reproductive factors, history of idiopathic infertility was identified as a significant risk factor in premenopausal breast cancer (p=0.002, OR=3.50, ratio 8:1). Sixteen % of breast cancer patients showed history of idiopathic infertility whereas the same incidence was 2% in normal group. History of long term (5-10 yrs) OCP consumption was detected as another important risk factor in premenopausal breast cancer (p=0.006, OR=2.27, ratio 9:2). Other factors didn't associate with increased risk of premenopausal breast cancer. Linear regression model didn't show any association between AhR expression levels and the reproductive factors.

Adiposity and premenopausal breast cancer

Table 2 compares the background factors between cases and controls. The average weight of breast cancer patients before the diagnosis was significantly higher than that of controls (69.88±12.54 versus 64.29±10.45, p=0.008, OR=5.58, CI 95% 1.49-9.68). Adiposity (BMI ≥ 25 kg/m^2) could be considered as an important risk factor of premenopausal breast cancer (Table 2). In fact 58% of cases were over weighted before the early breast cancer incidence whereas the same situation was detected in 40% of controls (p=0.028, OR=1.45). The pattern of weight gain was another important risk factor that means 36% of cases showed history of >20 kg weight gain after 18 years old whereas the same situation was detected in 16% of controls (p=0.034, OR=2 (1.03-3.86). Linear regression analysis showed that the level of AhR was significantly higher (p=0.006) in adipose patients compared to non-adipose patients.

PAHs exposure and premenopausal breast cancer

Exposure to PAHs and dioxins were examined by recording the living and working addresses. Out of 50 cases 24% were exposed to EDCs whereas the same situation were detected in 5% of controls (p=0.001, OR =4.80) (Figure 1). Passive or active exposure to cigarette smokes were weakly associated with increased risk of premenopausal breast cancer (p=0.005, OR=1.43). Linear regression analysis showed that the expression levels of AhR were significantly higher (p=0.006) in patients living close to factories generating PAHs than those living far from the factories.

Discussion

PAHs are potent mammary carcinogens in rodents, but their effect on female breast cancer development seems to be controversial (Gammon et al., 2002). Although a nested case-control study in postmenopausal Shanghai women provided no evidence of association between PAHs exposure and increased risk of breast cancer (Lee et al., 2010), recent studies have showed a dual action for PAHs on the breast, with different effects in pre and postmenopausal women. PAHs exposure may increase the risk of breast cancer in premenopausal women (Band et al., 2002) whereas increased risk of postmenopausal breast cancer was seen in women with higher urinary excretion of both estrogens and androgens (Onland-Moret et al., 2003). This study has revealed the role of environmental PAHs exposure as the most important risk factor in premenopausal breast cancer. In addition it indicates that endogenous sources of estrogen are the second most important risk factor in the incidence of this malignancy.

Some comparisons on the production levels of PAHs compounds between Iran, i.e., 1.3 kg toxicity equivalency quantity (TEQ)/year, and fifteen industrialized countries in the range of 0.1–4.0 kg TEQ/ year showed that Iran has elevated levels of these toxic compounds in the environment (Azari MR et al., 2011). The contribution of PAHs on the incidence of other types of cancer in Iran has been reported previously (Kamangar et al., 2005). Although the breast cancer patients were mostly non-smokers, 24% were heavily exposed to other PAHs resources according to records of their working and living addresses. In contrast, 5% of controls were exposed to PAHs resources other than cigarette smokes (p=0.001, OR=4.80). AhR overexpression was detected in 87% of epithelial cells of young breast cancer patients. The AhR binds with high affinity to PAHs, but also binds with lower affinity to structurally diverse exogenous and endogenous chemicals. In fact AhR agonists induce ERalpha-dependent transactivation. These compounds also induce binding of AhR and ERalpha to the CYP1A1 and pS2 gene promoters, which is consistent with their activities as both selective AhR modulators and selective ER modulators (Liu et al., 2006). Human epidemiological studies and experimental animal data have strongly suggested that xenobiotics with estrogenic properties may increase the incidence of breast cancer. In recent 15 years, many studies have reported positive correlations between levels of xenoestrogenic compounds in blood or peritumoral adipose tissues and breast cancer risk (Salehi et al., 2008). Overexpression of activated AhR in premenopausal breast cancer patients in this study may emphasize the possible role of xenoestrogenic compounds as AhR ligands in this phenomenon. The role of nutritional sources of PAHs and xenostrogens will be discussed in other studies.

To our knowledge risk factors of breast cancer could be classified into four broad categories: 1) genetic/ familial 2) reproductive/hormonal, 3) lifestyle, and 4) environmental (Fenichel and Brucker-Davis, 2008; Chen et al., 2009). Except for the first group of risk factors, which was excluded from this study by detection of BRCA1 and BRCA2 mutation, the rest three groups of risk factors were evaluated in this study. From the published literature, established risk factors of postmenopausal breast cancer include aging, later age at first full-term pregnancy, lack of full-term pregnancy, postmenopausal obesity, and genetic factors. However, these known risk factors cannot account for the premenopausal

breast cancer. Of various reproductive factors, we found history of idiopathic infertility as an important risk factor (p=0.002, OR=3.50) (Table 2), which may indirectly emphasize the role of endocrine disruptors and xenoestrogens in this regard (Brisken, 2008). The exact association between idiopathic infertility and increased risk of breast cancer should be examined in larger human population studies, which should also need to consider combined effects of exposures and vulnerable groups such as those with higher levels of exposure to assess gene-environment interactions.

Obesity has been suggested as another risk factor for breast cancer in postmenopausal women and overweight women are more likely to have poor outcomes (Sung et al., 2011). We showed higher body weights in cases than controls (69.88±12.54 kg versus 64.29±10.45 kg, p=0.008, OR=5.58, CI 95%, 1.49-9.68) (Table 2). The pattern of weight gain was also another important risk factor in premenopausal breast cancer patients. Thirty six% of cases showed history of abnormal (>20 kg) weight gain after 18 whereas the same situation was detected in 16% of controls (p=0.034, OR=2(1.03-3.86). There is accumulating evidence which indicate that endogenous estrogens, e.g. 17β-estradiol (E2), and environmental estrogenic EDCs are involved in the regulation of body weight and obesity (Berstad et al., 2010). Higher levels of AhR were detected in the breast tissues of overweight cases (p=0.006), which showed the indirect role of xenoestrogens in obesity and breast cancer. It is reported that estrogens regulates the body weight and energy metabolism in the brain in a way similar to that of the leptin, the hormone that regulates energy metabolism in the brain. During menopause, women tend to gain body fat. The increase in adiposity is likely due to the decline in endogenous estrogens (Wu et al., 2009). On the other hand, estrogen therapy has positive effects on carbohydrate and lipid metabolism in overweight-obese younger postmenopausal women (Chiam et al., 2009; Habanova et al., 2010). The controversial role of estrogen on premenopausal breast cancer should be further studied more exactly by focusing on the role of leptin and other adiponectines as responsible proteins.

The other important risk factor in early occurrence of breast cancer was OCP consumption according to the results of present study (p=0.006, OR=2.27) . Although one recent study showed that OCP and hormone replacement therapy decrease the breast cancer onset in Slovakia (Chen et al., 2009), they didn't consider this situation as a significant risk factor in early breast cancer. OCP consumption could be considered as an important risk factor in premenopausal breast cancer in Iranians who are overweight and expose to xenoestrgens by their living or working places and may suffer from idiopathic infertility. These findings suggest that endogenous female hormonal factors as well as xenoestrogens and adiposity play significant roles in the development of premenopuasal breast cancer in Iranian women.

References

Azari MR, Falak F, Masoudinejad MR (2011). Assessment of dioxin-like compounds released from Iranian industries and municipalities. *Tanaffos*, **6**, 59-64.

Balabanic D, Rupnik M, Klemencic AK (2011). Negative impact of endocrine-disrupting compounds on human reproductive health. *Reprod Fertil Dev*, **23**, 403-16.

Band PR, Le ND, Fang R, et al (2002). Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet*, **360**, 1044-9.

Berstad P, Coates RJ, Bernstein L, et al (2010). A case-control study of body mass index and breast cancer risk in white and African-American women. *Cancer Epidemiol Biomarkers Prev*, **19**, 1532-44.

Bidgoli HH, Bogg L, Hasselberg M (2011). Pre-hospital trauma care resources for road traffic injuries in a middle-income country--a province based study on need and access in Iran. *Injury*, **42**, 879-84.

Bidgoli SA, Ahmadi R, Zavarhei MD (2010b). Role of hormonal and environmental factors on early incidence of breast cancer in Iran. *Sci Total Environ*, **408**, 4056-61.

Bidgoli H, Zamani A, Taherzadeh MJ (2010a). Effect of carboxymethylation conditions on the water-binding capacity of chitosan-based superabsorbents. *Carbohydr Res*, **345**, 2683-9.

Bray F, McCarron P, Parkin DM (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Res*, **6**, 229-39.

Brisken C (2008). Endocrine disruptors and breast cancer. *Chimia*, **62**, 406-9.

Chen JQ, Brown TR, Russo J (2009). Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. *Biochim Biophys Acta*, **1793**, 1128-43.

Chiam K, Tilley WD, Butler LM, et al (2009). The dynamic and static modification of the epigenome by hormones: a role in the developmental origin of hormone related cancers. *Biochim Biophys Acta*, **1795**, 104-9.

Cogliano V, Grosse Y, Baan R, et al (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol*, **6**, 552-3.

Fenichel P, Brucker-Davis F (2008). Environmental endocrine disruptors and breast cancer: new risk factors? *Gynecol Obstet Fertil*, **36**, 969-77.

Gammon MD, Santella RM, Neugut AI et al (2002). Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. *Cancer Epidemiol Biomarkers Prev*, **11**, 677-85.

Habanova M, Svikruhova J, Slavikova E (2010). Hormonal contraceptives and their relationship to breast cancer. *Klin Onkol*, **23**, 428-32.

IARC (2007) Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy.'IARC,

Kamangar F, Strickland PT, Pourshams A, et al (2005). High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. *Anticancer Res*, **25**, 425-8.

Kolahdoozan S, Sadjadi A, Radmard AR, et al (2010). Five common cancers in Iran. *Arch Iran Med*, **13**, 143-6.

Lee KH, Shu XO, Gao YT, et al (2010). Breast cancer and urinary biomarkers of polycyclic aromatic hydrocarbon

and oxidative stress in the Shanghai Women's Health Study. *Cancer Epidemiol.Biomarkers Prev*, **19**, 877-83.
Liu S, Abdelrahim M, Khan S, et al (2006). Aryl hydrocarbon receptor agonists directly activate estrogen receptor alpha in MCF-7 breast cancer cells. *Biol Chem*, **387**, 1209-13.
Onland-Moret NC, Kaaks R, van Noord PA, et al (2003). Urinary endogenous sex hormone levels and the risk of postmenopausal breast cancer. *Br J Cancer*, **88**, 1394-9.
Salehi F, Turner MC, Phillips KP, et al (2008). Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors. *J Toxicol Environ.Health B Crit Rev*, **11**, 276-300.
Soran A, Talbott EO, Zborowski JV, et al (2005). The prevalence of benign breast disease in women with polycystic ovary syndrome: a review of a 12-year follow-up. *Int J Clin Pract*, **59**, 795-7.
Sung MK, Yeon JY, Park SY, et al (2011). Obesity-induced metabolic stresses in breast and colon cancer. *Ann NY Acad Sci*, **1229**, 61-8.
Van der HE, Bechoux N, Muller M, et al (2009). Food flavonoid aryl hydrocarbon receptor-mediated agonistic/antagonistic/synergic activities in human and rat reporter gene assays. *Anal Chim Acta*, **637**, 337-45.
Vogel CF, Li W, Wu D, et al (2011). Interaction of aryl hydrocarbon receptor and NF-kappaB subunit RelB in breast cancer is associated with interleukin-8 overexpression. *Arch Biochem Biophys*, **512**, 78-86.
Wu MH, Chou YC, Chou WY, et al (2009). Circulating levels of leptin, adiposity and breast cancer risk. *Br J Cancer*, **100**, 578-82.
Zhang JJ, Wang M (2010). Latent class joint model of ovarian function suppression and DFS for premenopausal breast cancer patients. *Stat Med*, **29**, 2310-24.