Medicina (Kaunas) 2010;46(12):867-73

Environmental factors and breast cancer

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Key words: *organochlorines; metals; ionizing radiation; electromagnetic fields; breast cancer.*

Summary. *This review summarizes the results of studies on the effects of environment on breast cancer risk. As known risk factors such as reproductive life, inheritance, and socioeconomic status are estimated to explain only about half of the breast cancer cases, it has been thought that environmental factors could also be related to the risk of this disease. It is known that ionizing radiation is an environmental risk factor increasing the risk of breast cancer. The data of experimental studies show that some organochlorines could be associated with breast cancer risk although the data from epidemiological studies are not consistent due to the difficulties to assess exposure and other risk factors. Recent experimental studies show that cadmium is an environmental factor that mimics the effects of estradiol in estrogen-responsive breast cancer cell lines while solar radiation possibly decreases the risk due to protective effect of vitamin D. The data on the effect of electromagnetic fields are not consistent. Although evidence about the effect of environmental factors on the risk of breast cancer is not convincing, some of these factors together with inheritance, reproductive life, and age at exposure could be associated with an increased risk of the disease.*

Introduction

Breast cancer remains the leading cause of cancer deaths among women in Europe with still increasing mortality rates due to aging population (130 000 in 2004 and 132 000 in 2006). In 2006, the age-standardized incidence rates of breast cancer were 26 and 25.8 per 100 000 women in Europe and Lithuania, respectively (1).

The strongest determinants of breast cancer risk are female gender, age, and country of birth. The conventional risk factors of breast cancer are related to reproductive life (early age at menarche, nulliparity, late age at the first full-term pregnancy, late age at lactation, short lactation, late menopause) and inheritance (mutations in BRCA1 and BRCA2 genes). The use of exogenous estrogens, radiation exposure, alcohol consumption, higher educational level and socioeconomic status are also well-known risk factors for the disease (2). Most of these factors are associated with cumulative exposure to estrogens (3).

Epidemiological studies have established that the conventional risk factors of breast cancer (excluding exogenous estrogen use, radiation, and alcohol consumption) explain up to 50% of the breast cancer cases in the United States (4). Another 1% of breast cancers in the country may be attributed to diagnostic radiotherapy (5). The growing incidence of breast cancer, some geographical variation of the disease, and inability to explain the causes of breast cancer suggested the environmental factors playing some role in the etiology of breast cancer (3). In the late 1990s, some authors concluded that more than 60% of breast cancer had an environmental etiology (6). Hence, breast cancer is likely to be caused by complex interactions among genetic, endocrine, and environmental factors.

There exists evidence that estrogen is an important determinant of breast cancer risk. However, to date, the data from experimental studies and studies on the associations of breast cancer risk and polymorphisms in genes encoding enzymes involved in estrogen synthesis and metabolism are not consistent.

Experimental studies support the hypothesis that oxidative metabolites of estrogens have genotoxic, mutagenic, transforming, and carcinogenic potential and thus could cause the initiation or progression of carcinogenesis in humans. However, no studies have found that estrogen metabolites are related to human breast cancer (7). Still, estrogen levels in breast tissue of postmenopausal women were 10 to 50 times the levels in blood (8), and the concentrations of estradiol were greater in malignant than nonmalignant tissues, which possibly hints to aromatase activity in breast tissue (9). Besides this, the activity of oxidative pathways in human breast tissue has been demonstrated by levels of estrogen metab-

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olites and conjugates ranging from 3 to 13 pmol per gram of tissue detected in human breast tissue (10). Therefore, it is necessary to determine estrogen-quinone adenine and guanine adducts and oxidative DNA damage in human breast tissue to provide clear evidence for estrogen genotoxicity that could contribute to the initiation or progression of the breast cancer (7).

The classic two-step model of chemical carcinogenesis in animals that may apply in breast cancer development asserts that chemical carcinogens convert normal cells into genetically changed cells or precancerous cells (initiation), and the latter ones can be converted to cancerous cells (progression) after exposure to epigenetic factors, such as estrogens. Thus, nonestrogenic environmental carcinogens (physical, chemical, an biological), which may cause genetic alterations, may play an important role in the development of breast cancer (11).

This review summarizes the findings from the studies on effects of environment on breast cancer risk.

Organochlorines

Organochlorines, classic examples of persistent organic pollutants, have been of worldwide concern owing to their persistence, bioaccumulative ability, and potential negative impacts on humans and animals. Organochlorine pesticides and polychlorinated biphenyls (PCBs) are ubiquitous contaminants and are detected quite far from the pollutant source. Organochlorine pesticides, including dichlorodiphenyltrichloroethane (DDT) and PCBs, were widely used for insect control in forestry, agriculture, and building protection. However, dioxins and furans continue to be inadvertently formed during the chemical and thermal processes (12).

The use of DDT and PCBs in developed countries as well as in Lithuania has been banned for more than 20 years. In 2002, the government of Lithuania has signed the Stockholm Convention on Persistent Organic Pollutants aiming to decrease and finally to stop the production and use of persistent organic pollutants and their release to environment. However, opportunities for exposures continue as DDT and other organochlorines are still widely used in developing countries. The major source of organochlorines in humans is food (12–14).

Organochlorines are strongly lipophilic and resistant to biotransformation. Some of more persistent organochlorines have half-lives of up to several decades in human tissue (13). DDT and PCBs residues are found in adipose tissue, breast adipose tissue, blood, and milk (14). It has been suggested that blood serum reflects the present body burden of a range of organochlorines to the same extent as adipose tissue; thus, serum may be collected instead of adipose tissue to gather similar information. These measurements are a combination of both recent exposures and past exposures, which have metabolized slowly and still may persist (15).

Extensive evidence exists from animal studies on carcinogenicity of DDT and PCBs. The International Agency for Research on Cancer has classified DDT and other chlorinated pesticides as carcinogens in animals (14). Since some organochlorine compounds act as estrogen agonists or antagonists within in vitro and experimental animal systems, a possible association between breast cancer risk and organochlorine exposure has been hypothesized (16).

The data of epidemiological surveys assessing relationship between organochlorines and breast cancer risk are not consistent. Some epidemiological studies identified a positive association between breast cancer risk and adipose or blood levels of the organochlorine pesticide DDT, PCBs, and/or their metabolite, dichlorodiphenyldichloroethylene (DDE) (17, 18). It has been reported that exposure to DDT early in life may increase the risk of breast cancer (19). However, some more recent surveys have not supported this association (20, 21).

Laboratory technicians, leather and fur processors, glass-manufacturing workers occupationally exposed to different organochlorines are thought to be at increased risk of breast cancer (22). Some authors reported the risk of breast cancer associated with self-reported use of residential pesticides (odds ratio, 1.39; 95% confidence interval, 1.15–1.68) (23). Modestly elevated risk of breast cancer was found among women residing closest to areas of pesticide application (24). Lawn and garden pesticide use was associated with breast cancer risk, but there was no dose-response relationship. Little or no association was found for nuisance-pest pesticides, insect repellants, or products to control lice or fleas and ticks on pets (23).

A major drawback of epidemiological studies on human exposure is that individuals are not exposed to a single factor but rather to a combination of substances, and thus the assessment of exposure to a particular substance could be complicated. The inconsistency of results could also be explained by some methodological differences and issues, i.e., single measurements of organochlorines or their metabolites in different biological media at different time from exposure, adjusting or not for possible confounders, and individual susceptibility. Wolff et al. (25) concluded that in environmental epidemiology, based on knowledge of body mass index over time, models for more distant or more recent exposure could be devised to improve the precision of organochlorine compound biomarkers.

Although the findings of epidemiological studies are not consistent, and these studies have not

provided convincing evidence of an association between organochlorines and PCBs with breast cancer, these compounds are rated as "possible" and "probable" human carcinogens, respectively, by the International Agency for Research on Cancer. Therefore, further research is necessary to get a deeper insight into this issue.

Metals

Experimental studies with the human breast cancer cell line MCF-7 showed the ability of divalent metals – cadmium, copper, cobalt, nickel, lead, mercury, tin, and chromium – to activate estrogen receptor α (ER-α) and stimulate cell proliferation. Some amino acids have been identified as potential interaction sites, suggesting that divalent metals and metal anions activate the receptor through formation of a complex within the hormone-binding domain of the receptor (26, 27).

More research has been conducted on the relationship between cadmium and breast cancer. There is evidence that cadmium is able to interact with estrogen receptor, thereby preventing 17β-estradiol from binding the receptor. It has been found that functionally cadmium acts like steroidal estrogen in breast cancer cells because of its ability to form a high-affinity complex with the hormone-binding domain of ER-α (26, 28). Cadmium had also potent estrogen-like activity in vivo. Exposure to cadmium promoted growth and development of the mammary glands, increased uterine wet weight, and induced hormone-regulated genes in ovariectomized animals. In the mammary gland, cadmium promoted an increase in the formation of the side branches and alveolar buds and the induction of casein, whey acidic protein, PgR, and C3 (29). However, other researchers hypothesize that the interaction of cadmium with the estrogen receptor (ER) occurs only after activation of the receptor by a ligand, which impedes transformation of ER to a DNA-binding form. Then it reduces the interaction of activated ER with DNA and subsequent transcriptional activity. The researchers suggest that the putative site of cadmium action could be the DNA-binding domain within the C-terminal domain of ER and does not result in activation of the receptor by cadmium (30).

One epidemiological study reported that women with creatinine-adjusted urine cadmium level of more than 0.58 μg/g had twice the breast cancer risk of those with cadmium level less than 0.26 μg/g (31). It has been found a significant difference between cadmium concentration in malignant breast tumor and healthy breast tissue (32, 33, 34). High concentrations of cadmium (3.2–86.9 μg/g) were found in the breast tissue samples from patients with breast cancer by Antila et al. (35), but the mean cadmium level did not differ from that in healthy controls. We assume that the difference was not found because cadmium was analyzed in the tissue as close to malignant tissue as possible but not in the malignant tissue itself.

Ionizing radiation

Ionizing radiation is a well-established mammary carcinogen (36). Increased breast cancer risk has been shown following acute radiation exposure from the atomic bombings in Japan (37) and following high cumulative doses associated with the treatment of some diseases and multiple diagnostic radiographic examinations (38, 39). Radiotherapy for breast cancer contributed to the development of contralateral breast cancer among women who underwent irradiation at a relatively young age (<35 years) and especially among those with a family history of breast cancer (40).

There is evidence on a linear dose-response relationship between radiation and breast cancer (41). It has been documented that the risk of breast cancer increases with the increasing radiation dose up to at least 40 Gy (42). Some authors argue against existence of a low-dose threshold on the order of 1 to 3 cGy for radiation exposure contributing to breast carcinogenesis (39). The risk of breast cancer was significantly higher in female radiologic technologists who experienced daily low-dose radiation exposures during several years that potentially resulted in appreciable cumulative exposure. The increased risk was defined for total years worked before 1940, but not later (43). Mohan et al. reported that women exposed to occupational radiation before 1950 were at higher risk of breast cancer (44). The subsequent decline in risk was consistent with the dramatic reduction of recommended radiation exposure limits, decreasing occupational radiation exposures, and improvements in radiation technology (43, 44). Still, no increased risk of breast cancer mortality was found among the technologists who daily performed or assisted with fluoroscopically guided interventional procedures (45).

The breast cancer is the most common solid tumor among a large number of long-term survivors of Hodgkin's lymphoma. The cumulative incidence of breast cancer increases with young age at initial treatment, radiation dose, radiation therapy field size, and time from treatment and reaches 25% to 30% in a woman aged 55 years who was treated for Hodgkin's lymphoma at the age of 25. This increased risk of breast cancer appears approximately 10 years after primary therapy and persists beyond 25 years of follow-up (46). A multicenter study conducted to estimate the relative risk of breast cancer in terms of radiation dose to site of breast cancer, cumulative dose of alkylating agent chemotherapy, and other risk factors revealed that a radiation dose

of ⩾4 Gy to the breast was associated with a 3.2-fold higher risk of breast cancer compared with the risk in women who received lower doses to the breast without alkylating agents. The risk of breast cancer increased up to 8 times with a dose of more than 40 Gy (P<0.001 for trend). Breast cancers related to excess radiotherapy occurred for >25 years after exposure, with a statistically significant trend (P=0.03) with radiation dose still evident (42, 47, 48). However, a combined analysis of data from eight cohorts confirmed the decline in risk at the highest dose levels. It is thought to be related partly to killing of cells rather than transformation (35). Radiotherapy combined with alkylating agents conferred a non-significant 1.4-fold risk of breast cancer, whereas treatment with alkylating agent chemotherapy alone was related to a 40% reduction in risk. A 50% decrease in breast cancer risk was also observed following a dose of ⩾5 Gy to the ovaries. Reductions in risk were in accordance with the proportion of women who experienced treatment-related menopause. The occurrence of menopause before the age of 40 years was associated with a significant decrease in breast cancer risk compared with women who remained premenopausal (42, 47, 48).

Some findings suggest a similarity in risks for acute and fractionated high-dose-rate exposures with much smaller effects from low-dose-rate protracted exposures (41). Fractionated exposures for therapeutic radiation were similar to a single exposure of the same total dose in their ability to induce breast cancer (35, 49). The increased risk of breast cancer remained a lifelong concern in females treated during the childhood with currently reduced radiotherapy doses and for infants receiving multiple chest computer tomographies (49, 50).

The results supporting the linearity of the radiation dose response and breast cancer highlighted the importance of age and age at exposure on the risk of breast cancer that was greater for those treated before the age of 20 years (36, 51). Some authors concluded that the carcinogenic effect of therapeutic or accidental radiation was highest when the exposure occurred during the childhood while the exposure after the age of 40 years imparted low or minimal risk (49). Other characteristics that may influence the magnitude of dose-specific risk included age at the first full-term birth, parity, and possibly a history of benign breast disease, exposure to radiation during the pregnancy, and genetic factors (36).

Electromagnetic fields

The hypothesis that long-term exposure to relatively weak electromagnetic fields in the power frequency range of 50–60 Hz could increase the risk of breast cancer is based on the assumption that magnetic field exposure suppresses nocturnal melatonin production and that melatonin is a protective factor against breast cancer, possibly by affecting the level of estrogen (52). Experimental studies support the relationship between melatonin and breast cancer. Studies on human breast cancer cell lines have shown that melatonin modulates several estrogen-dependent regulatory proteins, suppresses the activity of the estrogen receptor gene, and arrests the metastatic capacity of cells (53). Some epidemiological studies observed a positive association between 6-sulfatoxymelatonin, a major melatonin metabolite, and the risk of breast cancer in premenopausal and postmenopausal women. However, there was some evidence that this might be driven by the influence of subclinical disease on melatonin levels, with a possible inverse association among premenopausal women diagnosed further from recruitment (54). Nevertheless, some authors did not find evidence that the level of melatonin was strongly associated with the risk of breast cancer (55).

Some epidemiological studies have indicated a slightly increased risk for breast cancer among postmenopausal women exposed occupationally to extremely low-frequency magnetic fields (56). Kliukiene et al. (57) have shown an association between exposure to magnetic fields and the risk of breast cancer and more important role for residential exposure than for occupational exposure, in particular during the last 5 years before diagnosis. A meta-analysis of epidemiologic studies concluded that exposures to electromagnetic fields were associated with a marginal increase in the risk of breast cancer (58). However, the epidemiological data on the magnetic field exposure and breast cancer were not consistent (59, 60).

The lack of consistency in results from different studies could be due to some methodological issues related to the assessment of electromagnetic field exposure and evaluation of confounding factors for breast cancer. There is doubt whether the differing indices of exposure may be considered as valid indicators of real exposure (58).

Solar radiation

The breast cancer mortality and incidence rates have been found to be inversely associated with the increasing levels of total average sunlight energy (61). Knight et al. reported reduced breast cancer risks associated with increasing sun exposure from ages 10 to 19 years, weaker associations from ages 20 to 29 years, and no association for ages 45 to 54 years. The reduced risk was also associated with the use of cod liver oil and increasing milk consumption (62). A high sun exposure index reduced the risk of advanced breast cancer among women with light constitutive skin pigmentation (odds ratio, 0.53; 95% confidence interval, 0.31–0.91) (63). A

protective effect of ultraviolet B on the risk of breast cancer was independent of fertility rate, proportion of the population overweight, alcohol intake, animal energy intake, and other covariates (64).

It has been suggested that the relationship between breast cancer and sunlight could be partly explained by vitamin D that is hypothesized to lower the risk of breast cancer by inhibiting cell proliferation via the nuclear vitamin D receptor (65, 66). A pooled analysis aimed to assess the dose-response association between serum 25(OH)D and risk of breast cancer showed that the intake of 2000 IU/day of vitamin D_3 and when possible very moderate exposure to sunlight could raise serum 25(OH)D to 52 ng/mL, a level associated with a 50% reduction in the incidence of breast cancer, according to observational studies (67). Data on the variation in survival from breast cancer by season showed the highest survival for summer and autumn diagnosis, corresponding to maximal calcidiol levels. This suggests that sun exposure may improve outcome from breast cancer (68, 69). However, the data on the risk of breast cancer in relation to sunlight are not consistent (70).

Thus, in spite of some epidemiological studies supporting a protective sunlight effect in women, the relationship between vitamin D and the risk of breast cancer remains unclear and needs further research to clarify the utility of assessing vitamin D through a diet and sunlight exposure taking into account the potential modifying effects and individual susceptibility.

Concluding remarks

The data obtained from different experimental and epidemiological studies show that the breast cancer is probably caused by complex interactions among genetic, endocrine, and environmental factors. Although the influence of environmental factors on the risk of breast cancer is not convincing, some of these factors together with inheritance, reproductive life, and age at exposure could be related to an increased risk of breast cancer. Which environmental factors are a cause of breast cancer may be answered by future studies that would include more detailed assessment of exposure to different environmental factors, effect biomarkers, and individual susceptibility.

Aplinkos veiksniai ir krūties vėžys

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Raktažodžiai: organiniai chloro junginiai, metalai, jonizuojamoji radiacija, elektromagnetiniai laukai, krūties vėžys.

Santrauka. Straipsnyje apžvelgiami užsienio ir Lietuvos mokslininkų atlikti tyrinėjimai, kuriais siekta išsiaiškinti aplinkos veiksnių keliamą riziką susirgti krūties vėžiu. Kadangi tik pusę krūties vėžio atvejų priežasčių paaiškina su reprodukciniu moters ciklu susiję veiksniai, paveldėtas polinkis susirgti šia liga, socialiniai ir ekonominiai veiksniai, manoma, kad aplinkos veiksniai taip pat turi įtaką šios ligos pasireiškimui. Jonizuojamoji radiacija yra aplinkos veiksnys, didinantis riziką susirgti krūties vėžiu. Eksperimentiniai tyrimai rodo, jog kai kurie organiniai chloro junginiai sukelia krūties vėžį, tačiau epidemiologinių tyrimų duomenys, dėl sunkumų išmatuojant ekspoziciją bei vertinant kitus rizikos veiksnius, nėra vienareikšmiai. Naujausi eksperimentiniai tyrimai rodo, jog kadmis veikia kaip estrogenai, sukeldamas šiems hormonams būdingą poveikį. Tačiau saulės poveikyje gali sumažėti rizika susirgti krūties vėžiu, nes pasigaminęs vitaminas D turi apsauginį poveikį. Duomenys apie elektromagnetinių laukų sąsajas su krūties vėžiu nėra vienareikšmiai. Nors daugelio aplinkos veiksnių keliama rizika nėra galutinai įrodyta, tyrimai rodo, kad šie veiksniai kartu su paveldėtu polinkiu susirgti krūties vėžiu, reprodukcinio moters ciklo savitumais bei amžiumi, kada patirtas žalingo veiksnio poveikis, gali turėti įtakos krūties vėžio pasireiškimui.

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Received 15 September 2009, accepted 7 December 2010
Straipsnis gautas 2009 09 15, priimtas 2010 12 07