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IMPACT OF ENVIRONMENTAL CONTAMINANTS ON BREAST CANCER

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Abstract: Breast cancer is the most frequent cancer in women. It is believed that among the causes of breast cancer, hereditary factors account for only 5-10% of risk and the environmental exposures to environmental contaminants account for an additional 30-50% of risk. This paper summarizes findings related to the risk of breast cancer due to exposure to following environmental contaminants: polycyclic aromatic hydrocarbons, polychlorinated biphenyls and dioxins, organochlorine pesticides, organophosphorous pesticides, bisphenol A, phthalates, parabens, organic solvents, atmospheric pollutants, alkylphenols, metals, ionizing radiation, electromagnetic field and light pollution. Results obtained in *in vitro* experiments with breast cancer cell lines and *in vivo* with model rodents as well as in population based case-control studies are presented and the mode of action of individual environmental contaminants on mammary gland is discussed. Attention is also devoted to the effects of the timing of exposure to environmental contaminants (mainly exposition during development of the mammary gland) on breast cancer risk. Outcomes of professional exposure to some environmental contaminants on breast cancer risk are analysed as well.

Keywords: mammary cancer, chemical carcinogens, ionizing radiation, magnetic fields

Introduction

Cancer is a term used for diseases, in which abnormal cells divide without control and are able to invade other tissues. A neoplasm is a group of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely and can spread to other parts of the body through the blood and lymph systems [1]. There are estimated 3.45 million new cases of cancer (excluding non-melanoma skin cancer) in Europe in 2012; the female breast cancer was estimated in 464,000 cases (13.5% of all cancer cases). The estimated total number of cancer deaths in Europe in 2012 was 1.75 million, of which 56% (976,000) were in men and 44% (779,000) in women, whereby breast cancer estimated deaths were 131,000, *ie* 7.5% [2]. Breast cancer is the leading

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cancer site in women in all countries in Europe and it is also the first cause of death from cancer in women in Europe [2].

It is estimated that about 40% of all cancers in women are hormonally mediated. Both estrogens and androgens play critical roles in the development of breast cancer, which has been confirmed by numerous epidemiologic data on the levels of serum and urine hormones in populations at low and high risk, as well as by case-control and cohort studies. Estrogen carcinogenesis is attributed to receptor-mediated growth and proliferation of breast epithelial cells and to DNA impairment caused by activated estrogen metabolites [3]. The formation of DNA adducts is recognized as the initial step in chemical carcinogenesis [4]. Oxidative catabolism of estrogen, mediated by various cytochrome P450 enzymes, generates reactive free radicals that can cause oxidative damage. The same enzymes of estrogenic metabolic pathways catalyse biological activation of several xenobiotics that may exert their pathological effects through generation of reactive free radicals [5]. Therefore an important role in the development of breast tumours can play the balance between phase I carcinogen activation and phase II detoxification systems [6].

Environmental estrogens can induce tissue-specific, time- and dose-dependent estrogenic or antiestrogenic responses and their effects on the incidence of breast cancer depend on both the levels and the timing of exposure to these compounds, particularly during stages of mammary gland development that are extremely sensitive to hormone levels [7]. Moreover, environmental carcinogens (*eg* organochlorine pesticides and polychlorinated biphenyls) that can be stored in the adipose tissue due to their lipophilic character can be released at convenient dose in the blood circulation and target peripheral tissues to induce carcinogenesis [8].

Although certain occupational chemicals are known to be carcinogenic in humans, it has been difficult to definitively determine the adverse health effects of many environmental pollutants due to their tremendous chemical diversity and the absence of a consistent structural motif [9]. Rudel et al [10] reported that in all, 216 chemicals associated with increases in mammary gland tumours in at least one study, including industrial chemicals, chlorinated solvents, products of combustion, pesticides, dyes, radiation, drinking water disinfection byproducts, pharmaceuticals and hormones, natural products and research chemicals, had been identified.

Risk factors for breast cancer can be classified into four categories: (1) genetic/familial, (2) reproductive/hormonal, (3) lifestyle, and (4) environmental. Established risk factors for breast cancer include older age, later age at first full-term pregnancy, no full-term pregnancies, postmenopausal obesity and genetic factors [11]. Prolonged exposure to estrogens, xenoestrogens, hormone replacement therapy and contraceptives has been recognized as key aetiological factors of human breast cancer [12].

Belpomme et al [13] attributes a more important role to environmental factors in cancer genesis than it is usually agreed, because cancer incidence shows increasing tendency despite a significant decrease of alcohol consumption and tobacco smoking in men; this increasing incidence is observed across all age categories, including children; and there is growing incidence of cancers which are not related to obesity nor to other lifestyle-related factors; on the other hand, the accumulation of many new carcinogenic factors in the environment raised.

In cancer research, odds ratios are most often used in case-control (backward looking) studies to find out if being exposed to a certain substance or other factor increases the risk

of cancer. The odds ratio (OR) is a measure of association between an exposure and an outcome and it represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. The 95% confidence interval (CI) is used to estimate the precision of the OR [14].

Animal studies to evaluate potential chemical carcinogenicity are particularly important for breast cancer because environmental and occupational epidemiologic research is sparse [10]. Rodents are a common model for mammary cancers, partially because the differentiation of the milk ducts in rats has some similarities with human breast development [15].

This review summarizes findings related to the risk of breast cancer due to exposure to following environmental contaminants: polycyclic aromatic hydrocarbons, polychlorinated biphenyls and dioxins, organochlorine pesticides, organophosphorous pesticides, bisphenol A, phthalates, parabens, organic solvents, atmospheric pollutants, alkylphenols, metals, ionizing radiation, electromagnetic field and light pollution.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are common environmental pollutants formed by the incomplete combustion of fossil fuels and wood that are found in high concentrations in coal tar sealants, creosote and asphalt, however PAHs are also produced by traffic, barbecuing, smoking or charring food over a fire; cosmetics made of coal tar contain PAHs as well. Benzo[*a*]pyrene (BaP), one of the PAHs produced when combustion is incomplete, has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen [16] and used as a marker for PAHs in ambient air and food [17]. Benzo[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, dibenzo[*a,h*]anthracene and indeno[1,2,3-*c,d*]pyrene are considered as probable human carcinogens [17]. PAHs emitted by machining, fuel combustion, and other decomposition processes have been identified as mammary carcinogens in animal testing [10].

The two major mechanisms of metabolic activation of a PAH involve formation of radical cations and diol epoxides as ultimate carcinogenic metabolites. These intermediates react with DNA to yield two types of adducts: stable adducts that remain in DNA unless removed by repair and depurinating adducts that are lost from DNA by cleavage of the glycosyl bond between the purine base and deoxyribose. The formation of estrogen-DNA adducts is a critical factor in the etiology of breast cancer, because the ratio of estrogen-DNA adducts to estrogen metabolites and conjugates has repeatedly been found to be significantly higher in women at high risk for breast cancer, compared to women at normal risk [18].

Carcinogenic PAHs are classified into bay and fjord region compounds according to structural differences in the molecule region where enzymatic epoxidation occurs. Dibenzo[*a,l*]pyrene, one of the fjord region compounds, has been demonstrated to be the most carcinogenic PAH [19]. Also benzo[*c*]chrysene possesses both a bay region and a fjord region in the same molecule. It was shown that both bay region and fjord region diol epoxides are formed as intermediates in the metabolism of benzo[*c*]chrysene *in vivo*, however fjord region diol epoxides are more carcinogenic than structurally related bay region diol epoxides [20]. PAH-DNA adducts are detectable in normal and malignant breast tissues and women with reduced DNA repair capacity may be at an increased risk of

developing breast cancer [21, 22], although the association does not appear to be dose dependent and may have a threshold effect [23]. PAH-DNA adducts measured in breast tumour tissue and in normal tissue of white, African-American and Latina women were significantly associated with breast cancer (OR = 4.43, 96% CI 1.09-18.01) after controlling for known breast cancer risk factors and current active and passive smoking as well as dietary PAHs suggesting that genetic damage reflecting individual exposure and susceptibility to PAHs may play a role in breast cancer [24]. However, results from large population-based Long Island Breast Cancer Study focused on a survival analysis among women with newly diagnosed invasive breast cancer between 1996 and 1997 did not provide strong support for an association between detectable PAH-DNA adducts and survival among women with breast cancer, except, perhaps, among those receiving radiation treatment [25]. In a study of the risk of premenopausal breast cancer due to exposure to benzene and PAH, a greater increase in the risk of estrogen receptor (ER)-positive (OR 2.27, 95% CI 1.14-4.54) than ER-negative (OR 1.12, 95% CI 0.47-2.64) breast cancer was estimated [26].

Treatment of breast cancer cell line MCF-7 (acronym of Michigan Cancer Foundation-7) with oil samples containing PAHs as well as BaP produced a significant increase in levels of reactive oxygen species (ROS) suggesting that oil samples with higher concentrations of polycyclic aromatic hydrocarbons may exert adverse effects on human mammary epithelial tissue through induction of oxidative stress [27].

BaP, a mammary carcinogen in rodents, that contributes also to the development of human breast cancer, was found to induce the activation of signal transduction pathways and biological processes involved in the invasion/metastasis process in MDA-MB-231 metastatic human breast cancer cell line [28], and BaP exposure at high concentrations of 1 and 5 $\mu mol \cdot dm^{-3}$ induced significant repression of DNA mismatch repair in ZR75-1 human breast cancer cells [22]. While BaP toxic effects on human breast cancer cell line, MCF-7 cells, were manifested by growth inhibition and apoptosis, toxic effects of fluoranthene were not exerted through apoptosis [29].

In rats treated with the dose of 200 μmol/rat of 6-nitrochrysene (6-NC) both incidence and multiplicity of mammary adenocarcinomas were significantly elevated but at the dose of 100 μmol/rat these outcomes were not significantly different from those of control rats. While control mutants consisted primarily of GC to AT transitions, the 6-NC-induced mutants were comprised of several major classes of mutations with GC to TA, GC to CG, AT to GC and AT to TA as the most prevalent [30].

PAHs may be associated with specific breast tumour p53 mutation subgroups rather than with overall tumour suppressor gene p53 mutations and may also be related to breast cancer through mechanisms other than p53 mutation [31]. Testing of the effects of BaP exposure on cellular growth dynamics and DNA methylation in four breast cancer cell lines confirmed the p53-specific disruption of the cell cycle as well as the disruption of DNA methylation as a consequence of BaP treatment, thus reinforcing the link between environmental exposures, DNA methylation and breast cancer [32].

According to Jeffy et al [33] mammary tumourigenicity of PAHs may be attributable, at least in part, to disruption of BRCA-1 expression by reactive PAH-metabolites, and consequently exposure to PAHs may be a predisposing factor in the etiology of sporadic breast cancer.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are industrial chemicals used in the manufacturing of electrical equipment, heat exchangers, hydraulic systems and several other specialized applications up to the late 1970s. Polychlorinated biphenyls (PCBs) are ubiquitous persistent environmental pollutants that accumulate in body fat and exhibit endocrine-disrupting properties. PCB 101 and its hydroxylated metabolites applied in concentrations $5 \cdot 10^{-9}$, $5 \cdot 10^{-8}$, $5 \cdot 10^{-7}$, $5 \cdot 10^{-6}$ mol · dm^{-3} had no effect on MCF-7 cell proliferation after exposure time 24, 48, 72 and 96 h [34]. On the other hand, from the PCB congeners (118, 138, 153 and 180) tested by Ptak et al [35], PCB 138 and 153 had the highest stimulatory effects on proliferation of MCF-7 cells and the proliferative and anti-apoptotic actions of PCB 138 and 153 were still observed in the presence of 17β-estradiol, while the actions of PCB 118 and 180 were reversed. These results suggest the possibility that PCB 138 and 153 contribute to the action of endogenous 17β-estradiol on cell proliferation and apoptosis in the MCF breast cancer cell line. The relationship between seven PCBs concentrations in serum and breast cancer risk factor was mainly due to serum levels of PCB 153, which were significantly higher in breast cancer women than in disease-free subjects (1.63±1.26 ppb vs. 0.63±0.78 ppb), even after accounting for other potential risk factors [36]. Analysis of archived early postpartum serum samples collected from 1959 to 1967, an average of 17 years before diagnosis (mean diagnosis age 43 years) for 16 PCB congeners in a nested case-control study showed strong breast cancer associations with three congeners. The net association of PCB exposure, estimated by a post-hoc score, was nearly a threefold increase in risk (OR, 75th vs. 25th percentile = 2.8, 95% CI 1.1, 7.1) among women with a higher proportion of PCB 203 in relation to the sum of PCBs 167 and 187 [37]. However, epidemiologic studies concerning exposure to PCB and breast cancer risk have been controversial. Several earlier studies suggested a positive association [38-44], other studies showed no increased breast cancer risk [45-50]. More recent data suggested that the CYP1A1 m2 polymorphisms might add an increased risk to the etiology of breast cancer in women with environmental exposure to PCBs [51]. PCBs enhance the metastatic propensity of breast cancer cells by activating the Rho associated protein kinase (ROCK) signalling that is dependent on ROS induced by PCBs. Inhibition of ROCK may stand for a unique way to restrain metastases in breast cancer upon PCB exposure [52]. The results of Eum et al [53] indicate that *ortho*-substituted PCBs may contribute to tumour metastasis by inducing transendothelial migration of cancer cells through the augmentation of endothelial hyperpermeability and adhesion of cancer cell onto endothelial cells.

Dioxins

Dioxins are a class of chemical contaminants that are formed during combustion processes such as waste incineration, forest fires and backyard trash burning, as well as during some industrial processes such as paper pulp bleaching and herbicide manufacturing. The IARC classified 2,3,7,8-tetrachlorodibenzo[*b*,*e*][1,4]dioxin (TCDD) is a known human carcinogen, based on predominantly male occupational studies of increased mortality from all cancers combined [54]. The environmental toxin TCDD is a high affinity ligand for the aryl hydrocarbon receptor (AhR); it modulates several endocrine pathways

including inhibition of 17β-estradiol-induced responses in mammary gland and in human breast cancer cell lines. TCDD inhibited spontaneous and carcinogen-induced mammary tumour formation and growth in rodent models [55, 56] and age-dependent formation of mammary tumours in female Sprague-Dawley rats [57]. Using a carcinogen induced rat mammary cancer model it was shown that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility for mammary cancer [58]. Exposure during pregnancy severely impaired mice mammary gland differentiation, and severe defects in development, including stunted growth, decreased branching and poor formation of lobular alveolar structures, occurred [59]. Thus, TCDD acts as a developmental toxicant of the mammary gland in rodents which alters multiple endocrine systems resulting in delayed proliferation and differentiation of the mammary gland in the developing breast and an elongation of the window of sensitivity to potential carcinogens. This suggests that causes of endocrine-related cancers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumour detection. Moreover, it was found that high-fat diet increased sensitivity to maternal TCDD exposure, resulting in increased breast cancer incidence, by changing metabolism capability [60]. ROS formation is a significant determinant factor in mediating the induction of oxidative DNA damage and repair in human breast cancer cells exposed to TCDD, and the TCDD-induced oxidative stress and DNA damage may, in part, contribute to TCDD-induced carcinogenesis [61]. In a summary analysis of occupational exposure to TCDD Adami et al [62] reported that the rate ratio of breast cancer for exposed cf unexposed women was 1.08 (CI = 0.68-1.58).

In 1976, an accident in a plant near Seveso, Italy, exposed the local population to TCDD. Breast cancer among females was found to be below expectations in the most contaminated zones [63] and a 15-year mortality study after the "Seveso accident" showed no increase for breast cancer among females exposed to TCDD in comparison with the population of a surrounding non contaminated area [64]. On the other hand, Pesatori et al [65] mentioned an increased risk of breast cancer of females in the most contaminated zone 15 years since the accident (five cases, risk ratio 2.57; 95% CI, 1.07-6.20). Dioxin levels in the archived area that were collected soon after the explosion showed that the hazard ratio for breast cancer associated with the 10-fold increase of TCDD levels in serum was significantly increased to 2.1 (95% confidence interval, 1.0-4.6) [66].

Investigation of the incidence of breast cancer in Midland, Saginaw and Bay Counties, Michigan, USA confirmed that increased breast cancer incidences were spatially associated with soil dioxin contamination and aging was a substantial factor in the development of breast cancer [67].

Organochlorine pesticides

Pesticides are used extensively for pest control and weed destruction. Organochlorines such as 1,1'-(2,2,2-trichloroethane-1,1-diyl)bis(4-chlorobenzene) (DDT) have been used extensively as insecticides. DDT, a halogenated hydrocarbon, was introduced as an insecticide in the 1940s, and in 1972, the United States Environmental Protection Agency (EPA) prohibited this chemical in the USA. DDT and its metabolite 1,1'-(2,2-dichloroethene-1,1-diyl)bis(4-chlorobenzene) (DDE) are lipid soluble compounds that persist in the environment and bioaccumulate in the body in adipose tissue at levels far higher than those in blood and breast milk, and therefore some researcher groups

investigated whether exposure to these pesticides is associated with breast cancer risk in women [42, 68-72].

Some findings suggested that environmental chemical contamination with organochlorine residues may be an important etiologic factor in breast cancer. For example, a 4-fold increase in the relative risk of breast cancer for an elevation of serum DDE concentrations was estimated [42]. Another paper also associated a high serum concentration of DDT with a more than 3-fold increased risk of breast cancer [68], indicating an apparent dose-response relationship. In an area of high environmental exposure in the Michalovce district of eastern Slovakia higher serum levels of DDE (OR = 3.04, 95% CI 0.65-14.3) were positively associated with the risk of breast cancer, while there was no association for DDT (OR = 1.19, 95% CI 0.27-5.23) [69]. Exposure to organochlorines including DDT as a risk factor for breast cancer in the United States, Finland, Mexico and Canada was reported by Wolff & Weston [70]. Exposure to DDT early in life was found to increase breast cancer risk [71], and women with positive breast cancer ER and progesterone receptor who were exposed to a fogger truck that sprayed DDT prior to 1972, had a 44% increased odds compared to other breast cancer subtypes (OR = 1.44; 95% CI 1.08-1.93) [72].

In MCF-7 cell line expressing ER-α, 1-chloro-2-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene (*o*,*p*'-DDT), DDE, and 1,1'-(2,2-dichloroethane-1,1-diyl)bis(4-chlorobenzene) (DDD, 50-1000 nmol · dm^{-3}) were able to decrease cell proliferation and viability while in MDA-MB-231 cell line, negative for ER-α, no evident response was observed. Moreover, in the presence of these compounds the invasive potential of the less invasive cell line MCF-7 had significantly induced, while the more invasive cell line MDA-MB-231 had its invasion potential dramatically reduced [73]. The complex organochlorine mixture containing 15 different components in environmentally relevant proportions increased the proliferation of MCF-7 cells due to its estrogenic potential [74]. According to Aube et al [75] DDE could increase breast cancer progression by opposing the androgen signalling pathway that inhibits growth in hormone-responsive breast cancer cells.

Atrazine (6-chloro-*N*-ethyl-*N*'-(propan-2-yl)-1,3,5-triazine-2,4-diamine) is one of the most widely used herbicides. Chronic studies of atrazine and simazine (6-chloro-*N*,*N*'-diethyl-1,3,5-triazine-2,4-diamine) and their common metabolites showed an elevated incidence of mammary tumours only in female Sprague Dawley (SD) rats, but their potential impact on humans appears to be primarily on reproduction and development and is not related to carcinogenesis [76]. While atrazine was not associated with breast cancer risk [77, 78], dieldrin (3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphtho[2,3-*b*]oxirene) [79] and lindane [(1*R*,2*S*,3*r*,4*R*,5*S*,6*r*)-1,2,3,4,5,6-hexachlorocyclohexane] were [80]. Dieldrin had also a significant adverse effect on overall survival and breast cancer specific survival (risk ration (RR): 2.78, 95% CI, 1.38-5.59 and RR: 2.61, 95% CI, 0.97-7.01) [79]. Examination of atrazine exposure to breast cancer risk for women living in rural areas of Wisconsin provided the odds ratio of breast cancer 1.1 (95% CI 0.9-1.4) for women exposed to atrazine concentrations of 1.0-2.9 ppb. Results from this large population-based study did not suggest an increased risk of breast cancer from adult exposure to atrazine in drinking water [81]. On the other hand, healthy women showed a very different profile of organochlorine pesticide mixtures (the most prevalent mixture of organochlorines was the combination of lindane and endrin [3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphtho[2,3-*b*]oxirene]) than

breast cancer patients (more frequent combination of aldrin [(1*R*,4*S*,4a*S*,5*S*,8*R*,8a*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene], DDE and DDD), suggesting that organochlorine pesticide mixtures could play a relevant role in breast cancer risk [82].

However, unlike the above mentioned findings, the majority of studies did not find association between exposure to organochlorine pesticides and increased incidence of breast cancer. For example, occupational exposure to relatively high levels of DDT/DDE were not associated with an increased incidence of breast cancer [83] and even after 20 years of follow-up, exposure to relatively high concentrations of DDE showed no evidence of contributing to an increased risk of breast cancer [84]. Recent and past exposure to DDT did not play an important role in the etiology of breast cancer not even among women living in a country with a tropical climate in the North of Vietnam where insecticide use for mosquito control is common [85]. Extensive studies focused on the levels of organochlorine pesticides determined in serum did not support the hypothesis that organochlorines increase breast cancer risk [38, 43, 86-90]. An association between adipose tissue levels of organochlorine pesticides (DDT, DDE) and breast cancer risk was also not estimated [91-93]. Similar results, i.e. that DDE does not increase the risk of breast cancer in humans, were obtained also in an extended and updated a meta-analysis of the association between exposure to DDT and the risk of breast cancer [94]. An increased risk of breast cancer among subgroups of women with specific metabolic genotypes due to organochlorine pesticides was also not confirmed [95].

Organophosphorous pesticides

Organophosphorous pesticides have been used extensively to control mosquito plagues. Parathion (*O*,*O*-diethyl *O*-(4-nitrophenyl) phosphorothioate) and malathion (diethyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate) that are extensively used to control a wide range of sucking and chewing pests of field crops, fruits and vegetables have many structural similarities with naturally occurring compounds, and their primary target of action in insects is the nervous system; they inhibit the release of the enzyme acetylcholinesterase at the synaptic junction [15, 96]. In rats parathion and malathion were found to induce changes in the epithelium of mammary gland influencing the process of carcinogenesis and such alterations occurred at the level of nervous system by increasing the cholinergic stimulation. Mammary tumour incidence in the parathion-treated rats was 14.3% and in malathion-treated animals was 24.3%, and treating the animals with atropine (which acts to oppose the cholinergic effects of the organophosphates) allowed the milk ducts to develop more normally and prevented the mammary cancers [15]. Parathion and malathion induced malignant transformation of breast cells through genomic instability altering p53 and c-Ha-ras genes considered pivotal to cancer process [97]. Parathion alone was able to induce malignant transformation of an immortalized human breast epithelial cell line MCF-10F, as indicated by increased cell proliferation, and it was found to be an initiator factor in the transformation process in breast cancer [98]. While high doses of organophosphorus insecticide chlorpyrifos (*O*,*O*-diethyl *O*-(3,5,6-trichloropyridin-2-yl) phosphorothioate) inhibited cell proliferation, low levels of this insecticide induced proliferation in MCF-7 cells [99]. Combination of an environmental substance such as the pesticide malathion and an endogenous substance such as estrogen can enhance the

deleterious effects in human mammary glands inducing cancer, and atropine is able to diminish these effects [100].

Organic solvents

Most organic solvents are highly lipophilic and are readily absorbed and distributed throughout the body *via* the bloodstream. They are biotransformed mainly in the liver and the kidney through a series of oxidative and reductive reactions, some of which result in bioactivation. The breast physiology, notably the parenchyma, is embedded in a fat depot capable of storing lipophilic xenobiotics [101]. Once stored in fat tissues, the organic solvents and their metabolites could migrate to the breast parenchyma and are then transferred to the mammary lobules through continuous apocrine secretions. These secretions may reside in the ductular system long enough for the solvents, and their bioactivated metabolites may locally exert detrimental effects. Many organic solvents have been detected in breast milk, and the majority of carcinomas occur in the ductular system [102]. Organic solvents are ubiquitous in occupational settings where they may contribute to risks for carcinogenesis. Therefore several research groups investigated the effects of organic solvents on human breast carcinogens [103-111].

Oddone et al [103] carried out a nested case-control study within a cohort of women employed in a large electrical manufacturing plant located in Lombardy in the Province of Milan. All incident cases during 2002 to 2009 of female breast cancer in individuals who worked at least a 1 year in the factory and resided in Lombardy, Italy, were selected, and controls were randomly sampled from all women who worked in the same plant and resided in Lombardy as of December 31, 2005. The odds ratios were adjusted for several potential confounders, namely, other known risk factors. The researchers found that the ORs for female breast cancer were significantly increased for exposure to chlorinated solvents (OR 1.65, 95% CI 1.04-2.62), and there was a twofold increase (OR 2.10, 95% CI 1.21-3.66) among women exposed for at least 10 years.

On the other hand, Ekenga et al [104] found that the overall risk of invasive breast cancer was not associated with lifetime exposure to solvents (hazard ratio (HR), 1.04; 95% CI, 0.88-1.24). However, parous women who worked with solvents before their first fullterm birth had an increased risk of ER-positive invasive breast cancer compared with women who never worked with solvents (HR, 1.39; 95% CI, 1.03-1.86). Nevertheless, a significantly elevated risk for ER-positive invasive breast cancer was associated with solvent exposure among clinical laboratory technologists and technicians (HR, 2.00; 95% CI, 1.07-3.73). These results indicate that occupational exposure to solvents before first birth, in a critical period of breast tissue differentiation, may result in increased vulnerability for breast cancer.

The study of Peplonska et al [105] provided weak evidence for a possible association between occupational exposure to organic solvents as a class and breast cancer risk, whereby the association might be limited to hormone receptor-negative tumours (OR 1.40; 95% CI 1.1-1.8). Increasing the level of exposure and known breast cancer risk factors did not modify the association between organic solvents and breast cancer risk, and no association with breast cancer was found for benzene exposure (OR 1.00; 95% CI 0.8-1.3). Rennix et al [106] investigated the risk of breast cancer among active duty Army women occupationally exposed to volatile organic chemicals (VOCs) and found that women who

worked in occupations with a moderate to high exposure potential to at least one VOC had a 48% increased risk ($p < 0.05$) of breast cancer while on active duty between 1980-1996 when compared to those women with low to no exposure potential. Moreover, the incidence of breast cancer in the cohort was significantly elevated in women younger than 35 years of age, especially among black women, when compared to the age-specific rates in the general population.

The results of a study which examined the possible association between the cancer risk and exposure to the chlorinated organic solvents in an electronic factory in Taiwan suggested a possible association between exposure to chlorinated organic solvents and female breast cancer [107, 108]. Investigation of breast cancer risk among relatively young Danish women (20-55 years) employed in industries with extensive use of organic solvents (*ie* metal product, wood and furniture, printing, chemical and textile and clothing industries) showed that long-term occupational exposure to organic solvents may play a role in breast cancer risk, because the adjusted relative risk for breast cancer for the group with over 10 years of employment was significantly elevated (twofold) [109]. Statistically elevated standardized incidence ratios (SIRs) for breast cancer among women in Shanghai exposed to organic solvents were significantly elevated (SIR = 1.4), and for benzene exposure also excess for overall exposure (SIR = 1.1) was found [110].

The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men showed that male breast cancer incidence was particularly increased in motor vehicle mechanics (OR 2.1, 95% CI 1.0-4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers and furniture manufacturing workers. Consequently, petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspected because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics [111].

Atmospheric pollutants

Traffic emissions are the major source of air pollutions in urban areas and contain many potential carcinogens, e.g., polycyclic aromatic hydrocarbons (PAHs) and benzene. Moreover, many chemicals identified as endocrine-disrupting compounds (mainly phthalates, *o*-phenylphenol, 4-nonylphenol and adhesive 4-*tert*-butylphenol with typical concentrations in the range of 50-1500 ng m^{-3}) were detected in indoor air and dust [112, 113]. Evidence from several studies has revealed that air pollution is associated with the increased morbidity and mortality of breast cancer patients [114-117]. The postulation that a mechanism by which vehicle exhaust emissions might increase the risk of breast cancer occurrence could be related to the fact that airborne particles contain PAHs, which are lipophilic and may therefore reach elevated concentrations in breast tissue and promote carcinogenesis in the cells of the breast [118].

In 1996 one study suggested that there was an increased breast cancer risk among women living close to industrial sites and heavy traffic in Long Island (NY) [114]. Increased total suspended particulates exposure was associated with increased postmenopausal breast cancer risk for birth residence exposure [115]. Higher exposure to traffic emissions at the time of menarche was associated with an increased risk of premenopausal breast cancer (OR 2.05, 95% CI 0.92-4.54) and at the time of a woman's

first birth for postmenopausal breast cancer (OR 2.57, 95% CI 1.16-5.69), which indicates that early life exposures impact the breast cancer risk and provide an indication of potential importance of traffic emissions in the risk of breast cancer [119]. Patients living in highly polluted areas demonstrated a younger age at menarche ($p < 0.001$), a greater family history of breast cancer ($p = 0.034$) and more invasive cancers ($p = 0.028$) with higher tumour grades ($p = 0.028$) and ER-positive status ($p = 0.022$) [116]. Thus, long-term air pollution exposure may contribute to the development of breast cancer by playing the role of a xenoestrogen. The relationship between breast cancer mortality and air pollution was examined using an ecological design in 61 municipalities in Taiwan [117]. Age-standardized mortality rates for breast cancer mortality were calculated for the studied municipalities for the years 1999-2008 and a weighted multiple regression model was used to calculate the adjusted risk ratio in relation to fine particulate matter (PM2.5) levels; the results showed that individuals who resided in municipalities with the highest PM2.5 were at an increased risk of death from breast cancer [117].

Also a case-control study conducted in Montreal, Quebec, in 1996-1997 found that exposure to traffic-related air pollution in Montreal, Canada was associated with postmenopausal breast cancer [120]. Based on determined concentrations of nitrogen dioxide (NO_2) in 2005-2006, two methods were developed to extrapolate the estimates to 1985 and 1996. It was found that for each increase of 5 ppb NO_2 estimated in 1996, the adjusted odds ratio was 1.31 (95% CI 1.00-1.71) indicating that there was the increased risk of approximately 25% for every increase of 5 ppb in exposure.

Bisphenol A

Bisphenol A (4,4'-propane-2,2-diyldiphenol, BPA) a synthetic chemical used in the production of plastics since the 1950s and a known endocrine disruptor, is a ubiquitous component of the material environment and human body. In more than 80 biomonitoring studies it was reported that BPA was overwhelmingly detected in individual adults, adolescents, and children; unconjugated BPA was routinely detected in blood and conjugated BPA in the vast majority of urine samples (both in the nanograms per milliliter range) [121]. However, research on very low dose exposure to BPA suggested an association with adverse health effects, including breast and prostate cancer, obesity, neurobehavioral problems, and reproductive abnormalities [122]. For example, a dose of BPA that is 2,000 times lower (0.025 μg kg^{-1} d^{-1}) than the reference dose for human populations (50 μg kg^{-1} d^{-1}) can stimulate mammary gland development in animal offspring whose mothers were exposed to this low dose [123, 124]. There is a concern that exposure to low doses of BPA, defined as less than or equal to 5 mg kg^{-1} body weight per day, may have developmental effects on various hormone-responsive organs including the mammary gland. Thus, perinatal exposure to environmentally relevant doses of BPA alters long-term hormone response that may increase the propensity to develop breast cancer [125]. In mice, perinatal exposure to environmentally relevant BPA levels induced alterations of the mammary gland architecture which manifested during fetal morphogenesis [126-129] and throughout life, including the development of pre-neoplastic lesions, while in rats gestational exposure to BPA induced pre-neoplastic lesions and carcinoma *in situ* that manifested in adulthood in the absence of any additional treatment [130]. In rats high-dose BPA exposure induced changes in genes related to differentiation suggesting alterations in

the normal development of the gland. The increase of undifferentiated structures and the changes in the gene expression profile at different ages suggested that prenatal exposure to BPA can affect the susceptibility of the mammary gland to transformation [131]. Gestational exposure to the estrogen-mimic BPA also altered the developing mammary glands of rhesus monkey female in a comparable manner to that observed in rodents [132].

Environmental levels of BPA can expand numbers of mammary stem cells and potentially increase breast cancer risk [133]. In examination of epigenetic changes in breast epithelial cells treated with low-dose BPA and the effect of BPA on the ER-α signalling pathway and global gene expression profiles, 170 genes with similar expression changes in response to BPA were identified, and the gene suppression by BPA was mediated in part through an ER-α dependent pathway [134]. Administration of BPA to mice confirmed that DNA adducts are formed in target mammary cells (4.7-fold higher than in controls) [135]. Although DNA adducts do not necessarily evolve into tumours or other chronic degenerative diseases, the formation of these molecular lesions in target mammary cells may bear relevance for the potential involvement of BPA in breast carcinogenesis. Lozada and Keri [136] examined the impact of BPA exposure on fetal programming of mammary tumour susceptibility as well as its growth promoting effects on transformed breast cancer cells *in vivo*. Fetal mice were exposed to 0, 25 or 250 $\mu g \cdot kg^{-1}$ BPA by oral gavage of pregnant dams and offspring were subsequently treated with the known mammary carcinogen, DMBA. Statistically significant increase in susceptibility to DMBA-induced tumours compared to controls was observed in both low and high dose BPA cohorts indicating that exposure to BPA during various biological states increases the risk of developing mammary cancer in mice. Increased mammary tumourigenesis by BPA could be connected with molecular alteration of fetal glands without associated morphological changes and direct promotion of estrogen-dependent tumour cell growth. Moreover, developmental exposure to environmentally relevant levels of BPA during gestation and lactation induced mammary gland neoplasms in rats in the absence of any additional carcinogenic treatment indicating that BPA may act as a complete mammary gland carcinogen [137]. On the other hand, in rats maternal exposure to BPA during lactation was found to increase DMBA-induced mammary carcinogenesis in female offspring [138].

Cell culture and mouse models were used to elucidate whether the loss of BRCA1 function could affect BPA-mediated cell proliferation [139], and it was found that at BPA levels comparable to human exposures loss of the tumour suppressor gene BRCA1 enhanced BPA-induced cell proliferation in both systems; it enhanced BPA-induced ER-α signalling *in vitro*, while *in vivo* BPA administration stimulated mammary gland epithelial tissue/cell proliferation leading to hyperplasia in BRCA 1 mutant mice compared to wild-type control mice. BPA was also found to antagonize the cytotoxicity of multiple chemotherapeutic agents in both ER-α-positive and -negative breast cancer cells and consequently, at environmentally relevant doses, it reduced the efficacy of chemotherapeutic agents [140].

BPA together with other bisphenols constitute a family of compounds that includes many substances having two phenolic rings joined together through a bridging carbon as a common chemical structure. A study of the estrogenic effect of a series of bisphenol analogues on gene and protein expression in MCF-7 breast cancer cells showed that the polarity and the nature of the substituent in the central carbon determines the estrogenic

potency, and the presence of two propyl chains at the central carbon appears to confer the greatest potency [141].

Phthalates

Phthalates, ubiquitous environmental pollutants, are used primarily as plasticizers of polyvinyl chloride and as additives in consumer and personal care products. Specific members of this family are components of many other consumer products, including building materials, household furnishings, clothing, cosmetics, pharmaceuticals, nutritional supplements, medical devices, dentures, children's toys, glow sticks, modelling clay, food packaging, automobiles, lubricants, waxes, cleaning materials and insecticides. There is a concern whether additives in plastics, such as phthalates, to which most people are exposed may cause harm to human health by altering endocrine function or through other biological mechanisms [142, 143]. A human exposure to indoor dust enriched with endocrine-disrupting chemicals released from numerous indoor sources has been a focus of increasing concern, and longer residence times and elevated contaminant concentrations in the indoor environment may increase chances of exposure to these contaminants by 1000-fold compared to outdoor exposure. For example, in indoor dust samples collected from household vacuum cleaner bags provided by 10 apartments and 1 community hall in Davis, California, USA, bis(2-ethylhexyl) benzene-1,2-dicarboxylate (DEPH) was the most abundant (104-7630 $\mu g \cdot g^{-1}$) [144]. DEHP is a manufactured chemical commonly added to plastics and it is known as a rodent carcinogen. Exposures of humans as well as rodents suggest that DEHP induces cancer through multiple molecular signals, including DNA damage [145]. It has been implicated in the development of male breast cancer and may cause reproductive problems among both men and women who work in PVC fabricating operations [146, 147]. Elevated breast cancer risk among women in phthalate-exposed population in northern Mexico was reported by López-Carrillo et al [148].

However, it could be noted that whereas the exposure to DEHP, the parent compound of 2-(ethoxycarbonyl)benzoic acid (monoethyl phthalate, MEP), may be associated with the increased risk of breast cancer, exposure to the parent phthalates of 2-[(benzyloxy)carbonyl]benzoic acid (monobenzyl phthalate, MBP) and 2-[(3-carboxypropoxy)carbonyl]benzoic acid might be negatively associated. The plasticizer benzyl butyl benzene-1,2-dicarboxylate (benzyl butyl phthalate, BBP) was found to inhibit 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat mammary DNA adduct formation and tumourigenesis. The number of mammary adenocarcinomas per rat was significantly inhibited by 60 and 70% for rats exposed to BBP at the 250 and 500 $mg \cdot kg^{-1}$ doses, respectively, compared to controls and this study indicated that BBP acts as a blocking agent toward DMBA-induced rat mammary DNA adduct formation and mammary carcinogenesis [149].

Significantly increased cell proliferation in MCF-7, but not in MDA-MB-231 cells by BBP (100 μM), dibutyl benzene-1,2-dicarboxylate (dibutyl phthalate, DBP) (10 μM) and DEHP (10 μM) was estimated by Kim et al [150]. Moreover, they observed the promoting effect of BBP, DBP and DEHP on chemotherapeutic drug resistance to tamoxifen in breast cancer, which may be of biological relevance, because phthalates are widely used in cosmetics mainly for women. According to Chen and Chien [151], proliferation of MCF-7 breast cancer cells was significantly increased at 10^{-8}-10^{-5} $mol \cdot dm^{-3}$ of BBP and DBP

treatment as well as at 10^{-8}-10^{-6} mol · dm^{-3} treatment of DEHP indicating that these phthalate derivatives display estrogenic activity. Proliferation of MCF-7 by BBP was confirmed also by Picard et al [152]. Treatments with the BBP and DBP at 1 μmol · dm^{-3} induced proliferation (BBP, 3.2-fold; DBP, 3.2-fold), migration (BBP, 2.6-fold; DBP, 2.6-fold), invasion (BBP, 2.7-fold; DBP, 3.1-fold) and tumour formation (EC_{50} BBP, 0.12 μmol · dm^{-3}; DBP, 0.22 μmol · dm^{-3}) in ER-negative breast cancer cells (MDA-MB-231), and these phthalates stimulated the cell surface AhR [153]. *In utero* exposure to BBP induced a delayed pubertal onset and modified morphology of the mammary gland in Sprague Dawley CD rats; the expression profiles of this gland in the exposed rats were modified in a dose-dependent fashion, and these alterations were accompanied by modifications in gene expression previously associated with an increased susceptibility to carcinogenesis [154]. Moreover, BBP induced geneomic changes in rat mammary gland after neonatal/prepubertal exposure (post-natal days 2-20) [155]. The increase of undifferentiated structures and the changes in the gene expression profile at different ages suggested that prenatal exposure to BPA can affect the susceptibility of the mammary gland to transformation [131].

Sprague et al [156] found that serum levels of MEP were positively associated with breast cancer risk, and after adjusting for age and body mass index, MEP was positively associated with percent breast density. A previous meta-analysis has namely estimated that women with mammographically dense tissue in 75% or more of the total breast area have a 4.2-fold increase in breast cancer risk compared with women with less than 5% mammographic breast density [157]. Moreover, women with detectable MEP levels (>0.4 ng · cm^{-3}) had higher percent breast density than women with no detectable MEP in their serum (16.8% vs. 12.8%). On the other hand, the serum levels of 2-(butoxycarbonyl)benzoate (monobutyl phthalate) and MBP were generally below the limits of detection [156]. Also urinary MEP levels were positively associated with increased rates of breast cancer, and women with the highest levels of MEP were 2.2-fold more likely to develop breast cancer than those with the lowest levels; for premenopausal women the odds ratio was even higher at 4.13 [158].

Parabens

Parabens are a family of related compounds that includes esters of *p*-hydroxybenzoic acid. Parabens are widely used preservatives, mainly in cosmetics and pharmaceuticals. Thus they can be considered the most common ingredient of cosmetics, besides water [159-162], because they are present in approx. 80% of personal care products [163]. Many cosmetic products, including antiperspirants, contain parabens that can be dermally absorbed. Parabens have estrogen-like properties in cell cultures, causing proliferation of estrogen-responsive cells, although they are thousands of times less potent than naturally-occurring estrogen in this regard [164-166]. Parabens were found to activate both estrogen receptors, ER-α and ER-β, with similar or stronger effect versus ER-β receptors [165, 167, 168]. The ability of parabens to transactivate the ER *in vitro* increases with alkyl tail bulkiness [166]. Competitive inhibition of 17β-estradiol binding to estrogen-dependent MCF7 cell ERs could be detected at 1,000,000-fold molar excess of butylparaben (BuP, 86%), propylparaben (PrP, 77%), ethylparaben (EtP, 54%) and methylparaben (MeP, 21%). Molecular modelling has indicated the mode by which paraben molecules can bind into the

ligand binding pocket of the crystal structure of the ligand binding domain of ER-α in place of 17β-estradiol, and it has been shown that two paraben molecules can bind simultaneously in a mode, in which their phenolic hydroxyl groups bind similarly to those of the hexestrol molecule [164].

Parabens that were found to be ubiquitous in the tissue samples of human breast tumours are completely stable in MCF7 breast cancer cell homogenates, and this stability of parabens may lead to their accumulation in breast tumour tissue [169]. Estrogenic activity of EtP, PrP, BuP, isopropyl- and isobutyl parabens in human MCF-7 breast cancer cells [167-171] as well as estrogenic activity of isobutyl- and benzyl parabens in human MCF-7 and ZR-75-1 cell lines [172, 173] were reported previously. Different mechanisms of proliferative action of parabens in MCF-7 human breast cancer cells and MCF-10A human breast epithelial cells were observed. The stimulatory effect of a single exposure of all doses of tested parabens (0.2 nmol · dm^{-3} - 2 μmol · dm^{-3}) and the time dependent effect of repeated exposure to MeP, PrP and BuP, the same as that of 17*b*-estradiol, on proliferation of MCF-7 cells was observed. However, only at low doses of MeP and BuP MCF-10A cells proliferation was increased after the single exposure, but no effect of repeated exposure was noted. Moreover, exposure at low doses of all of the parabens significantly increased 17β-estradiol secretion in MCF-7 cells but had the opposite effect on MCF-10A cells indicating different mechanism of proliferative action of parabens in investigated cell lines [170]. Although parabens have been shown to regulate a few single genes (reporter genes, pS2, progesterone receptor (PR)) in a manner similar to that of 17β-estradiol, the results of an experiment focused on proliferation of the expression of 19881 genes in MCF7 human breast cancer cells following a 7-day exposure to $5 \cdot 10^{-4}$ mol · dm^{-3} MeP, 10^{-5} mol · dm^{-3} BuP and 10^{-8} mol · dm^{-3} 17β-estradiol showed that at these concentrations the parabens gave growth responses in MCF7 cells of similar magnitude as 17β-estradiol**.** However, the majority of genes were not regulated in the same way by all three treatments, and some genes responded differently to parabens than 17β-estradiol, and furthermore, differences in expression of some genes could be detected even between two individual parabens [171]. Combined exposure to five parabens at the same concentrations that corresponded to the concentration levels detected in human breast tissue resulted in a significant increase of proliferation of the MCF-7 cells [174]. Even with long lasting MCF-7 cell exposure (about 2-4 months) to a mixture of five parabens present in the tested breast tumour tissue at the concentrations below the lowest-observed-effect concentrations, an increased cell proliferation in 5 from 6 cases was observed.

Several researchers determined concentration of parabens in breast tumour tissues. Mean concentrations (ng · g^{-1} wet wt.) of parabens in human breast tumour tissue estimated by Shanmugam et al [175] were 802 (MeP), 2657 (EtP), 1136 (PrP) and 5199 (BuP). Thus, the mean levels were decreased in the order BuP > EtP > PrP > MeP, and the highest estimated concentration of BuP may be due to the fact that it is more lipophilic (log k_{ow} = 3.5) than other parabens analysed and/or less metabolizable than MeP (log k_{ow} = 1.91) in humans. In non-cancerous tissue only MeP was detected (26.6 ng · g^{-1}) in an order of magnitude lower than the mean concentration of MeP from cancerous tissues. On the other hand, the mean value of the total paraben concentration in breast tumour tissues estimated by Dabre et al [176] was 20.6±4.2 ng · g^{-1}, *ie* by two orders lower than the above reported values, which could be connected with the enhanced detectability of the

compounds and peak area intensity due to derivatization applied by Shanmugam et al [175]. Moreover, the occurrence of parabens in the unaffected breast tissue adjacent to cancer was found in nearly all of the studied samples (99%, n = 160), at the total median paraben concentration of 85.5 ng · g^{-1} (range 0-5134.5 ng · g^{-1}) [177]. Based on observations showing a disproportionately high incidence of breast cancer in the upper outer quadrant of the breast as well as on the fact that the left breast is more prone to the development of cancer than the right one in women as well as in men, parabens in underarm deodorants has been suspected to be an etiological factor of breast cancer [173, 178]. However, the results of performed studies were controversial.

Whereas McGrath [179] in a retrospective study of 437 women diagnosed with breast cancer associated the frequency of use and early onset use of deodorants/antiperspirants with an earlier age of breast cancer diagnosis, further two researcher groups [180, 181] did not found association between underarm antiperspirant/deodorant use and an increased risk of breast cancer, probably due to rapid metabolization and excretion of parabens from the human body [166]. The increased proportion of breast tissue in the upper, outer quadrant of the breast could explain the higher incidence of breast tumours in this quadrant [182]. However, more studies would be necessary to definitively exclude an association between deodorant/antiperspirant use and breast cancer [183].

Alkylphenols

Alkylphenols (APs) and alkylphenol ethoxylates (APEs), high-performance non-ionic surfactants, are used in detergents, paints, herbicides, pesticides, emulsifiers, wetting and dispersing agents, antistatic agents, emulsifiers and solubilizers, and according to toxicological data sheet are classified as endocrine-disrupting compounds [184]. Their estrogenic activities are mainly dependent on their binding affinity for the ERs *in vitro* and *in vivo* [185, 186]. It was found that APs induce cell proliferation in estrogen-dependent breast cancer cells MCF-7 [187, 188], which can be antagonized by tamoxifen [189]. 4-Alkylphenols and related chemicals were found to show similar effect on the function of human and rat ER-α in reporter gene assay, and the estrogenic activity of compounds increased with an increase of substituent size [190]. In *in vitro* experiments using MCF-7 cell proliferation (E-screen assay) and ER competitive binding assay estrogenic effects of 4-*tert*-octylphenol and 4-nonylphenol were detectable at 1 and 70 μM, respectively, and these compounds inhibited the binding of 17β-estradiol to the ER of MCF-7 cells. Among several APs tested those with bulky alkyl groups or higher carbon numbers possessed higher estrogenic capacity [191]. According to Dundar et al [192], the xenoestrogenic activity of APs is mainly mediated by nongenomic pathway that plays a crucial role in breast, endometrial and ovarian cancers' growth and development.

4-Nonylphenol (a metabolite of APs) can increase breast cancer incidence in mice and was found to be more potent than it was predicted based on its affinity for the ER. Moreover it can also activate the pregnane-X receptor (PXR) and induce P-450 enzymes responsible for the production of estriol, whereby the increased production of the estrogenically active 16-hydroxy products such as estriol may be involved in increased susceptibility to breast cancer [193]. 4-Nonylphenol at 10 ppm increased adenocarcinoma and total mammary tumour multiplicity in female transgenic rats carrying copies of the human c-Ha-ras proto-oncogene that is highly susceptible to DMBA-induced mammary carcinogenesis,

but there was no dose dependence and significant quadratic dose-response trend was observed [194].

Metals

Metalloestrogens are metals that activate the ER in the absence of estradiol [195]. They include metals such as cadmium, calcium, cobalt, copper, nickel, chromium, lead, mercury and tin [196]. Divalent metals and metal anions activate ER-α through the formation of a complex within the hormone-binding domain of the receptor [197]. The four most predominant mechanisms for metal carcinogenicity include (1) interference with cellular redox regulation and induction of oxidative stress, (2) inhibition of major DNA repair, (3) deregulation of cell proliferation, and (4) epigenetic inactivation of genes by DNA hypermethylation [101].

Scientific evidence indicates that long-term exposure to some metallic compounds induces different forms of cancer, including breast cancer [198]. Cadmium and Cd compounds have been classified as known human carcinogens by the IARC and the National Toxicology Program. Epidemiologic studies suggest that cadmium is also associated not only with breast cancer but also with kidney, pancreas and urinary bladder cancer. Although the basic metal cationic portion of cadmium is responsible for both toxic and carcinogenic activity, the mechanism of carcinogenicity appears to be multifactorial [199]. Chronic, low-level exposure to certain heavy metals, *ie* Cd and Ni, can directly result in the development and progression of cancer. These two metals have been hypothesized to play a role in breast cancer development by acting as metalloestrogens, *ie* they bind to ERs and mimic the actions of estrogen and consequently likely contribute to the etiology of the disease [200]. *In vivo*, Cd mimics the effect of estrogens in the uterus and mammary gland, stimulates proliferation in estrogen-responsive breast cancer cell lines and can activate the ER independent of estradiol [201]. Various *in vitro* studies demonstrated that Cd can act as a mitogen, can stimulate cell proliferation and inhibit apoptosis and DNA repair and can induce carcinogenesis in several mammalian tissues and organs [202]. Gallagher et al [203] examined the association of breast cancer with urinary Cd in a case-control sample of women living on Long Island (NY), a region with an especially high rate of breast cancer and in a representative sample of US women in a multivariable logistic model. Both samples showed a significant trend for increased odds of breast cancer across increasing urinary cadmium quartiles. Urinary Cd concentrations are thought to reflect exposure to cadmium during a period of 20-30 years. A statistically significant increase in breast cancer risk with the increasing Cd level in urine of women was reported also by McElroy et al [204]. Multivariable linear regression and logistic regression were used to estimate the strength of association between urinary Cd and mammographic breast density (a strong marker of breast cancer risk, which is influenced by genetic, environmental and hormonal factors) in premenopausal women ages 40-45 years, and it was found that exposure to Cd may be associated with increased breast density in these women [205]. However, according to Silva et al [206], despite of persuasive *in vitro* and *in vivo* evidence of the estrogenic properties of Cd, evidence from population-based human studies remains conflicting because of the existing considerable knowledge gaps on the potential estrogenic effect of Cd in humans. Research that focuses on bridging these knowledge gaps would be useful in preventing and managing estrogen-dependent diseases in humans.

Pathological accumulation of transition metals in breast tissue may be closely related to the malignant growth process. Significant accumulation of Fe, Ni, Cr, Zn, Cd, Hg and Pb was found in the breast cancer samples when compared to the control group. From other metals Cu and Ag showed no significant differences to the control group, whereas tin, gold and palladium were not detectable in any biopsies [207].

Concentration of Cd in breast cancer tissue of women living in the Wielkopolska region in Poland varied in the range from 0.01 to 1.08 mg · g^{-1} wet wt., and a statistically significant difference in the Cd content in breast cancer tissues was found in women inhabiting the Poznan and Pila voivodeships. Metal concentrations [in μg metal · g^{-1} dry tissue] found by Polish researchers [208] in normal breast tissue were 0.61±0.24 for Cd, 1.84±0.67 for Ni and 3.63±1.00 for Al, whereas in breast cancer the corresponding concentrations of metals were 0.76±0.38, 2.26±0.79 and 4.40±1.82, respectively. Thus, the concentration of Cd and Al in normal breast tissue was found to be significantly lower than in breast cancer, while in the case of Ni concentration statistically significant differences between normal and cancerous tissue were not observed. However, the concentration of studied metals in breast cancer in the context of age, menopausal status and cancer histological grading did not show significant differences [208]. On the other hand, the mean serum Cu levels were higher in breast cancer than in benign breast diseases (1673 μg · dm^{-3} vs. 1176 μg · dm^{-3}; $p < 0.001$) and controls (1673 μg · dm^{-3} vs. 988 μg · dm^{-3}; $p < 0.001$), and patients with advanced breast cancer had higher serum Cu levels than did patients with early breast cancer (1779 μg · dm^{-3} vs. 1304 μg · dm^{-3}; $p < 0.001$). The Cu/Zn ratio was increased in breast cancer patients (1.91 vs. 0.86; $p < 0.001$) but not in patients with benign breast diseases [209]. Determination of Cd, Pb, Zn, Cu and Mg levels in human breast cancer tissues and adjacent normal tissues in breast cancer patients showed that samples taken from the central regions of cancer generally had different concentration levels of trace elements than normal tissues with significantly higher levels of these metals in cancerous tissues as compared to the unaffected cells [210].

An ER dependent transcriptional expression assay and E-Screen assay systems were used to evaluate the estrogenicity of various heavy metals. Bis(tri-*n*-butyltin), cadmium chloride, antimony chloride, lithium hydroxide, barium chloride and chromium chloride showed estrogenicity in both assay systems [211]. Proliferation of the MCF-7 cells that respond to estrogens was stimulated by LiCl (1-5 mmol · dm^{-3}) within the concentration range that is encountered during human therapy with lithium. Similar stimulation of growth by Rb, K and Na was not observed. Beside of hormone-dependent breast cancer cells MCF-7, lithium also stimulated the growth of further two hormone-dependent breast cancer cells ZR-75-1 and T47D, but not hormone-independent MDA-MB-231 cells or an estrogen-independent clone of MCF-7 cells [212]. Acute and chronic Ni^{2+} exposure increased ER-positive breast cancer cell (MCF-7) growth [213].

Sharan et al [214] evaluated the estrogenic potential of tributyltin (TBT) *in vitro* in ER+ breast adenocarcinoma MCF-7 cell line and found that tributyltin chloride (TBTCl) had agonistic activities for the ER-α. Low dose treatment of TBTCl had a proliferative effect on MCF-7 cells and resulted in up-regulation of aromatase enzyme activity and enhanced estradiol production in MCF-7 cells. Application of 0.5-1 μM methyl mercury (MeHg) significantly stimulated growth of MCF-7 cells, induced Ca^{2+} mobilization, and activated extracellular signal-regulated kinase (1/2). MeHg modulated estradiol-dependent stimulation of growth in a dose-dependent manner and demonstrated weak ER-binding

ability, indicating that it can significantly modulate the intracellular signalling environment in MCF-7 cells [215].

The possible association between strontium (Sr) and breast cancer risk was studied in a case-control study including 240 incident invasive breast cancer patients and 246 age-matched controls by measuring the urinary concentrations of Sr. Sr-creatinine-adjusted levels [median (25th, 75th) mg · g^{-1}] were 155.59 (99.05, 230.70) in the breast cancer patients and 119.62 (81.97, 163.76) in the controls. Women in the highest tertile for Sr (Sr concentration > 144.29 mg · g^{-1}) showed 124% increased risk of breast cancer, when compared with those in the lowest tertile (Sr concentration < 94.91 mg · g^{-1}) after adjustment for the potential risk factors (OR: 2.24, 95% CI 1.42-3.81), and this association was particularly strong for human epidermal growth factor receptor 2 (HER2) positive breast cancer (OR: 10.92, 95% CI 3.53-33.77), and only occurred among premenopausal women. These results indicate a potential role of Sr in the development of breast cancer [216]. On the other hand, urinary levels of rubidium (Rb) were significantly and inversely associated with the risk of breast cancer, and creatinine-adjusted levels [median (25th, 75th) μg · g^{-1}] of Rb in women with incident invasive breast cancer before their treatments (2253.01 (1606.81, 3110.46)) were significantly lower than that in the age-matched female controls (2921.85 (2367.94, 4142.04)). After adjustment for potential risk factors of breast cancer, women in the second and highest tertiles (Rb concentration > 3633.78 μg · g^{-1}) had a decreased risk of breast cancer in a dose-dependent manner as compared with those in the lowest tertile (Rb concentration < 2522.64 μg · g^{-1}), and the corresponding ORs were 0.45 (95% CI 0.27-0.73) and 0.22 (95% CI 0.13-0.38), respectively. However, it could be noted that the levels of Rb in breast tumour tissues were significantly higher than that in the normal tissues indicating that tumour cells have a greater affinity to Rb than normal cells [217-221].

It was shown that neuron specific enolase (ENO2, γ-enolase) expression in breast epithelial cells was induced by acute and chronic exposure to As^{3+} or Cd^{2+}, and that there is a possible link between As^{3+} and Cd^{2+} exposure and neuroendocrine differentiation in tumours [222]. Pb has been shown to promote the development of mammary tumours in murine mammary tumour virus-infected female C3H mice at levels as low as 0.5 ppm Pb in the drinking water. Moreover, Pb on chronic, low-level exposure also accelerated tumour growth rates. Higher levels of Pb were found in blood and head hair samples of Nigerian women with newly diagnosed breast cancer (all with infiltrating ductal carcinoma), and the Pb levels in hair samples of the patients were directly correlated with the volumes of their tumours, in accord with the tumour growth-promoting effects of Pb [223].

Experimental, epidemiological and clinical studies suggested that calcium and/or its regulating hormones affect breast cancer risk [224-226]. Pre-diagnostic serum Ca levels in premenopausal women were found to be positively associated with increased tumour aggressiveness as determined by a higher risk of nodal metastasis; relative risk (RR) for Ca above median as compared with Ca below median was 1.88 (95% CI 1.04-3.38) [224]. Treatment with extracellular calcium increased the growth of MCF-7 cells through an ER-dependent mechanism, and it is supposed that Ca mediates the cross-talk between ERα-activating signalling pathways and the ligand-binding domain of ER-α providing a potential explanation for the ability of certain environmental metalloestrogens to activate the receptor [225]. High Ca levels have been shown to activate the calcium-sensing receptor

and to stimulate protein kinases resulting in an increased proliferation of cancerous human breast cells [227].

It was found that Se, Zn and Cr elements from the malignant tissues of Sudanese patients with confirmed breast cancer were significantly elevated ($p < 0.05$) compared to the normal tissue [221]. On the other hand, multi-elemental quantitative analyses of paired samples of normal and malignant human breast tissue confirmed significantly elevated concentration levels for Al, Br, Ca, Cl, Cs, K, Na, Zn in malignant compared to normal tissue [220]. According to Drake and Sky-Peck **[**217]) the elements found to be most important in distinguishing between malignant and normal tissues in breast are Ca, Rb and Zn. In an another study significantly large increases ($p < 0.001$) in Ca, V, Cu, Zn, Se and Rb were found in breast tumours, with a less significant increase ($p < 0.05$) for nickel, and comparison between histologically normal and neoplastic tissues from the same individual showed consistently higher Zn and Rb in the tumour, whereas Ca, Cu and V levels varied from normal to high [218].

Ionizing radiation

Ionizing radiation is radiation that carries enough energy to liberate electrons from atoms or molecules, thereby ionizing them. Gamma ray, X-ray as well as UV_A and UV_B radiation at the high-energy end of the UV spectrum are considered as ionizing radiations. Due to the exposure to ionizing radiation direct mutagenesis causing changes in the structure of DNA and genomic instability, which is reflected in the increasing rate of changes in chromosomes and consequently in the increased likelihood of future mutations, can occur and increase the risk for breast cancer [228-230]. Moreover, gene mutations in epithelial cells caused by ionizing radiation can contribute to breast carcinogenesis by perturbing the tissue microenvironment, which leads to dysregulated cell-cell and cell-matrix interactions [231, 232]. It was found that effects of radiation on mammary carcinogenesis may be additive with effects of estrogens [233-235]. An increased incidence of breast cancer due to radiation exposure was observed in the atomic bomb survivors [236-239], and radiation-associated breast tumours were quite aggressive and associated with increased levels of genomic instability and higher histological grade in breast cancer [240]. Also up to 2-fold increase in breast cancer (both localised and metastatic diseases) following the Chernobyl accident in 1986 was estimated during the period 1997-2001 in the most contaminated districts (average cumulative dose of 40.0 mSv or more), whereby the increase appeared approximately 10 years after the accident, and it was highest among women who were younger at the time of exposure [241].

Although radiation carcinogenesis has been shown both experimentally and epidemiologically, the use of ionizing radiation is also one of the major modalities in cancer treatment [242]. About 15% of the ionizing radiation exposure to the general public comes from artificial sources, and almost all of this exposure is due to medical radiation, largely from diagnostic procedures. Of the approximately 3 mSv annual global per caput effective dose estimated for the year 2000, 2.4 mSv is from natural background and 0.4 mSv from diagnostic medical exams [243]. The degree of carcinogenic risk arising from low levels of exposure is more contentious, but the available evidence points to an increased risk that is approximately proportional to the dose received. Available epidemiological data support a linear dose-response relationship down to doses as low as about 100 mSv [244], however

according to Harbron [245] current epidemiological evidence only has sufficient statistical power to detect excess malignancies above around 100 millisieverts (mSv). However, the magnitude of risk per unit dose depends strongly on the time when radiation exposure occurs: exposure before the age of 20 years carries the greatest risk. Following high-dose radiotherapy for malignant diseases, elevated risks of a variety of radiation-related second cancers have been observed [243]. Fractionated exposures for therapeutic radiation are similar to a single exposure of the same total dose in their ability to induce breast cancer; this risk remains high for many years after exposure [246].

It was shown that pubertal murine mammary glands exposed to sparsely or densely ionizing radiation transiently increased stem cell self-renewal that increased susceptibility to developing ER-negative breast cancer [247]. An exposure of six to eight week old female mouse to a clinically relevant radiation dose (2 Gy of whole body γ-radiation) caused long-term activation of mammary gland genes involved in proliferative and metabolic pathways, which are known to have roles in carcinogenesis [248], and a study which evaluated mammary carcinogenesis initiated by combined exposure to various doses of γ-radiation and chemical carcinogens (1-methyl-1-nitrosourea or 1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridin-2-amine), using a rat model and molecular biological approaches, provided evidence of a multilevel interaction: a synergistic interaction between radiation and a chemical carcinogen at the initiation level and an additive interaction in the incidence of resulting carcinomas [249].

Children exposed to ionizing radiation have a substantially greater breast cancer risk than adults, and children have a longer life expectancy in which to express risk. Although radiation dose for a single procedure may be low, paediatric patients often receive repeated examinations over time to evaluate their conditions, which could result in relatively high cumulative doses. Most cancers can be induced by radiation, and a linear dose-response has been noted for most solid cancers. It could be stressed that risks of radiation-related cancer are the greatest for those exposed early in life, and these risks appear to persist throughout life [250]. For patients who had received chest wall radiation therapy for paediatric cancer, the risk of developing breast cancer by radiation therapy dose, patient age and menarche before or after primary treatment was calculated, and it was found that the median age at breast cancer diagnosis was 33 years, and these patients carried a 10-fold breast cancer risk at an age more than 20 years younger than in the general population [251].

Radiation risks after exposure in younger individuals are dominated by initiation processes, whereas radiation risks after exposure at later ages are more influenced by promotion of pre-existing premalignant cells. Radiation-induced breast cancer risks decrease with age at exposure at all ages. For radiation exposure in middle age, most radiation-induced cancer risks do not, as often assumed, decrease with increasing age at exposure, and promotional processes in radiation carcinogenesis become increasingly important as the age at exposure increases. Hence, radiation-induced cancer risks after exposure in middle age may be up to twice as high as previously estimated, which could have implications for occupational exposure and radiological imaging [252].

Investigation of the carcinogenic effect of treatment of skin haemangioma with ionizing radiation in early childhood (the mean age at first exposure was 0.7 years, the mean absorbed dose to the breast 70 mGy) showed that compared to individuals with no radiotherapy, the risk of breast cancer increased with increasing radiation dose with relative risks of 3.2, 6.3, and 8.0 for dose categories of > 0-10, 10-100, and > 100 mGy,

respectively; however, dose-response relationship was not significant. Thus, radiation treatment performed in the past for haemangioma during childhood increased the risk of breast cancer [253].

Hoffman et al [254] evaluated the risk of breast cancer of women with scoliosis exposed to multiple diagnostic X-ray examinations during childhood and adolescence, times when the breast may be highly sensitive to the carcinogenic effects of radiation and found that the risk of breast cancer increased with the number of diagnostic X-ray examinations and with the estimated radiation dose to the breast (mean, 0.13 Gy). This indicates that frequent exposure to low-level diagnostic radiation during childhood or adolescence may increase the risk of breast cancer. The excess risk increased with time since exposure and was highest among those followed for more than 30 years (SIR = 2.4).

Risk factors for early breast cancer include a lean body habitus and recent use of an oral contraceptive, and breast cancers in very young women are typically aggressive, in part owing to the over-representation of high-grade, triple-negative tumours, but young age is an independent negative predictor of cancer-specific survival, whereby very early age of onset also correlates strongly with the risk of local recurrence and with the odds of contralateral breast cancer [255].

Low-dose radiation increased breast cancer risk among high-risk women with familial or genetic aggregation of breast cancer (OR = 1.3, 95% CI 0.9-1.8), and an exposure before age 20 (OR = 2.0, 95% CI 1.3-3.1) or a mean of $\geq$ 5 exposures (OR = 1.8, 95% 95% CI 1.1-3.0) was significantly associated with a higher radiation-induced breast cancer [256]. A study investigating whether women with a genetic predisposition to breast cancer may be at increased risk of cancer after exposure to ionizing radiation because of exposure to mammography found that in women with BRCA1 and BRCA2 mutations it is not associated with an increased risk of breast cancer [257]. Also an another study did not support a positive association between mammogram exposure and breast cancer risk [258] as well as between diagnostic chest X-ray and breast cancer risk before the ages of 50 years for BRCA1 or BRCA2 mutation carriers [259]. On the other hand, breast cells from patients carrying a mutated allele of the genes BRCA1 or BRCA2 cultivated and irradiated with different doses of X-ray generated by commercial mammography equipment showed measurable alterations in breast cell grown [260].

It was reported that exposure to radiation in the same range as used for computed tomography will increase the risk of cancer, and therefore it is the responsibility of individual health care providers who order medical imaging to understand and weigh the risk of any medical procedures against the expected benefit [261].

An excess absolute risk model was used to predict the number of radiation-induced breast cancers attributable to the radiation dose received for a single typical digital mammography examination. For a cohort of 100,000 women each receiving a dose of 3.7 mGy to both breasts who were screened annually from age 40 to 55 years and biennially thereafter to age 74 years, it was predicted that there will be 86 cancers induced and 11 deaths due to radiation-induced breast cancer. Thus, for the mammographic screening regimens considered that begin at age 40 years, this risk is small compared with the expected mortality reduction achievable through screening, and the risk of radiation-induced breast cancer should not be a deterrent from mammographic screening of women over the age of 40 years [262].

In Western Australia at current levels of occupational exposure to ionizing radiation the risk of breast cancer was found to be low (OR = 1.16; 95% CI 0.86-1.57), although the risk of human epidermal growth factor receptor 2-positive cancer may be a concern (OR = 2.57; 95% CI 1.09-6.03) [263]. The female orthopaedic surgeons had a statistically significant 2.9-fold higher prevalence of breast cancer compared to the general U.S. female population (standardized prevalence ratio: 2.9; 95% CI 1.66-4.71) [264]. No clear association was found between exposure to ionizing radiation and breast cancer among Norwegian nurses due to occupational exposure to ionizing radiation [265]. Evaluation of incident breast cancer risks from 1983 to 1998 according to employment characteristics among female radiological technologists who were certified from 1925 to 1980 showed that breast cancer risk was elevated significantly in women who experienced daily low-dose radiation exposures over several years that potentially resulted in appreciable cumulative exposure. It should be noted that the increased risk for total years worked before 1940, but not later, was consistent with decreasing occupational radiation exposures, improvements in radiation technology and more stringent radiation protection standards over time [266]. No clear evidence of an increased breast cancer risk in medical radiation workers (radiologists and radiological technologists) exposed to current levels of radiation doses was estimated [267].

Non-ionizing radiation (electromagnetic fields)

Non-ionizing radiation refers to any type of electromagnetic radiation that does not carry enough energy per quantum to ionize atoms or molecules, i.e. to completely remove an electron from an atom or molecule. Microwaves, radio waves, radar waves and radiation produced by electrical transmission are examples of radiation sources that generate electromagnetic fields (EMF). Fluorescent lighting, computers and many other types of wired and wireless electronic equipment (*eg* mobile phones) all create electromagnetic fields of varying strengths. Evidence for an association between electromagnetic radiation and breast cancer is limited, and electromagnetic radiation may only pose a risk in certain occupations with exposure to very high levels for extended periods of time [268].

Magnetic field (MF) exposure resulted in an enhanced proliferative activity of the mammary epithelium of female Sprague-Dawley rats [269]. Differences in the extent of cell proliferation after MF exposure determined in different substrains of SD rats indicated that the genetic background plays a key role in effects of MF exposure, and different strains or substrains of rats may serve to evaluate the genetic factors underlying sensitivity to cocarcinogenic or tumour-promoting effects of MF exposure [270]. EMF exposure of human breast tumour (MCF-7) cells in an *in vitro* experiment resulted in activation of genes that have been associated with the induction of metastasis in breast cancer cells [271].

It was observed that MF exposure may potentiate the effects of known carcinogens only when the rats are exposed to both MF and carcinogen during an extended period of tumour development, i.e. when the carcinogen is given repeatedly during MF exposure. For example, flux densities of 50 or 100 μT significantly increased the growth of mammary tumours, independently of whether DMBA was given in a single administration or repeatedly over a prolonged period [272, 273].

Since pineal melatonin production can also be disturbed by electromagnetic field exposure, a possible association between melatonin depression by MF exposure and DMBA-induced breast cancer growth in female rats was studied [274], and it was found that

MF exposed rats had significantly lower nocturnal melatonin levels in serum than sham-exposed animals. However, exposure of female rats to 50 Hz, 10 μT MF that significantly decreased circulating melatonin, was not associated with a significant effect on development or growth of DMBA-induced mammary tumours. Evaluation of breast cancer risk of women who were occupationally exposed to EMF showed that, when compared with the referent of background exposure, the odds ratio adjusted for age and state of residence was 1.06 (95% CI 0.99-1.14) for low exposure, 1.09 (95% CI 0.96-1.23) for medium exposure, and 1.16 (0.90-1.50) for high exposure. The estimated odds ratios suggested that exposure to EMF in the workplace may be associated with a slight elevation in breast cancer risk [275]. Similarly, a meta-analysis performed by Sun et al [276] suggested that EMF exposure may be associated with the increased risk of male breast cancer, and the connection between EMF exposure and male breast cancer was shown also in further papers [277-280]. Milham [280] reported about three cases of male breast cancer which were diagnosed among a small group of men who worked in a basement office of a multi-story office building. This office was adjacent to an electrical switchgear room that generated high magnetic fields in their work space. The risk of male breast cancer in this group was increased about 100-fold (observe three cases, expect 0.03 cases; $p < 0.00001$).

Feychting et al [281] tested the hypothesis whether the residential magnetic field exposures increase the incidence of breast cancer. The study was based on people who had lived within 300 m of 220 or 400 kV power lines in Sweden at any time between 1960 and 1985. Magnetic field exposure was assessed through calculations of the magnetic fields generated by the power lines before diagnosis, and for calculated magnetic field levels $\geq$ 0.2 μT closest in times before diagnosis and the relative risk 1.0 (95% CI 0.7-1.5) for women and 2.1 (95% CI 0.3-14.1) for men was estimated. However, women younger than 50 years of age at diagnosis had a relative risk of 1.8 (95% CI 0.7-4.3). For women with ER-positive breast cancer, the relative risk was estimated at 1.6 (95% CI 0.6-4.1), using the exposure cut-off point $\geq$0.1 μT, however if these women were younger than 50 years at diagnosis, the relative risk increased to 7.4 (95% CI 1.0-178.1).

In a similar case-control study which investigated whether residential and occupational exposures to magnetic fields increased the risk for breast cancer among women living near a high-voltage power line in Norway in 1980 or between 1986 and 1996 was shown that women with residential exposure to magnetic fields had an odds ratio of 1.58 (95% CI 1.30-1.92) when compared with unexposed women. The odds ratios for exposed women versus unexposed women with ER-positive and ER-negative breast cancer were 1.33 (95% CI 0.93-1.90) and 1.40 (95% CI 0.78-2.50), respectively (ER status was available for 44% of the cases). Women with the highest occupational exposure had an odds ratio of 1.13 (95% CI 0.91-1.40) when compared with those unexposed at work [282].

Large population-based case-control study showed that the occupational exposure of women to 60 Hz magnetic fields enhanced the risk of breast cancer, and the risk among premenopausal women in the highest-exposure category was higher (OR = 1.98; 95% CI 1.04-3.78) than for postmenopausal women (OR = 1.33; 95% CI 0.82-2.17) [283]. Increased mortality from breast cancer was observed in women employed in the telephone industry [284].

By contrast to the hypothesis that exposure to EMF can increase the risk of breast cancer by inhibiting the normal nocturnal rise in melatonin levels, in a large, 2-stage, population-based case-control investigation of breast cancer no association was found with

breast cancer for ever-use of electric blankets, current or former use, use directly on the body, or use throughout the night in either pre- or postmenopausal women (range of adjusted odds ratios for ever vs. never use: 0.9-1.2) [285]. Exposure to residential magnetic fields was not found to be associated with an increased risk of developing breast cancer also by Davis et al [286]. Similarly, a meta-analysis of epidemiologic studies focused on possible associations between exposure to electric and magnetic fields at work or at home and risks of breast cancer in women and men carried out by Erren [287] as well as meta-analysis investigating breast cancer risk in women exposed to extremely low-frequency electromagnetic fields (ELF-EMF) [288] suggested that EMF or ELF-EMF exposure has no association with the susceptibility of female breast cancer. On the other hand, other epidemiological studies revealed that EMF and mostly EMF of extremely low frequency could be also associated with breast carcinoma [289, 290].

West et al [291] published in 2013 a case report concerning multifocal breast cancer in 4 young women with prolonged contact between their breasts and their mobile phones. These young women (ages 21-39) who had no family history of breast cancer, tested negative for BRCA1 and BRCA2 and had no other known breast cancer risks, regularly carried their smartphones directly against their breasts in their brassieres for up to 10 hours a day, for several years, and developed tumours in areas of their breasts immediately underlying the phones. It could be noted that all detected tumours were hormone-positive, low-intermediate grade, having an extensive intraductal component. However, to verify the possible effect of prolonged direct contact with cellular phones on breast cancer widespread studies would be necessary.

Light pollution

Melatonin is the major secretion product of the pineal gland; this mammalian hormone is involved in circadian rhythms and sleep and potentially in restraining tumour growth [292]. Pineal secretion follows a circadian rhythm with low levels during the day and high levels at night and in people who work in night shifts, melatonin suppression following nocturnal exposure to artificial light results in high estrogen levels, directly linked with the incidence of breast cancer [293]. Melatonin suppresses ER gene, modulates several estrogen dependent regulatory proteins and pro-oncogenes, inhibits cell proliferation and impairs the metastatic capacity of MCF-7 human breast cancer cells. It acts as antiestrogen and decreases the formation of estrogens from androgens *via* aromatase inhibition. Circulating melatonin levels were found to be abnormally low in ER-positive breast cancer patients [294]. Melatonin may modulate breast cancer through modulation of enhanced oxidative stress and Ca^{2+} influx in cell lines [295]. Suppression of melatonin by light or melatonin deficiency plays a major role in cancer development. Women who worked at night and who experienced sleep deprivation, circadian disruption and exposure to light at night were at an increased risk of breast cancer [296]. Night shift work may disrupt the normal nocturnal rise in melatonin, resulting in increased breast cancer risk, possibly through increased reproductive hormone levels [297]. A significant increase in the breast cancer risk among postmenopausal women exposed to shift work was reported by several researchers [298-301], and an increased risk of breast cancer due to longer occupational exposure to light at night at flight attendants was estimated as well [302, 303]. Frequent night shift work was found to increase the risk for breast cancer, and higher risk was

connected with longer duration of intense night shifts. Moreover, women with morning preference who worked on night shifts tended to have a higher risk than those with evening preference [297]. Long-term (≥ 30 years) night shift work in a diverse mix of occupations was associated with increased breast cancer risk (OR = 2.21, 95% CI 1.14-4.31) and this association was showing similar results for both health and non-health care workers [304]. Positive association of extended periods of rotating night work and breast cancer risk (more than 30 years of rotating night work) was reported also by Schernhammer et al [301].

Conclusions

The widespread research studies suggested that exposure to environmental contaminants in combination with genetic pre-disposition, age at exposure and hormonal milieu has a cumulative effect on breast cancer risk. For breast cancer timing of exposure (mainly exposition during development of the mammary gland) and life style are very important, whereby higher risk may occur among persons whose enzymes either are more active in the production of procarcinogens or fail to detoxify carcinogenic intermediates formed from chemicals in the environment. Sometimes different conclusions regarding the risk of breast cancer when exposed to the environmental contaminant presented in papers of various research groups may be related to methodological problems including inadequate exposure assessment, lack of access to highly exposed and unexposed population and lack of preclinical markers suitable for diagnosis at an early stage of disease. Reducing human exposure to organic chemical carcinogens in the workplace, the home and the ambient environment as well as application of precautionary principle must be a key component of a comprehensive breast cancer prevention strategy. It would be desirable to secure rigorous testing of all novel chemicals introduced in the practice, which could enter in the environment, on potential estrogenic activity, to extend environmental and biological sampling programs for endocrine-disrupting compounds in drinking water and household air and dust and to intensify the application of geographic information systems for surveillance and historical exposure assessment.

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WPŁYW ZANIECZYSZCZENIA ŚRODOWISKA NA RAKA PIERSI

Abstrakt: Rak piersi jest najczęściej występującym rakiem u kobiet. Uważa się, że jedną z przyczyn tego raka są czynniki dziedziczne, którym przypisuje się jedynie 5-10% zachorowań, a ekspozycja na zanieczyszczenia środowiska stanowi dodatkowe 30-50%. Artykuł ten podsumowuje wyniki badań nad ryzykiem zachorowania na raka piersi w związku z narażeniem na następujące zanieczyszczenia środowiska: wielopierścieniowe węglowodory aromatyczne, polichlorowane bifenyle i dioksyny, pestycydy chloroorganiczne, pestycydy fosforoorganiczne, bisfenol A, ftalany, parabeny, rozpuszczalniki organiczne, zanieczyszczenia powietrza, alkilofenole, metale, promieniowanie jonizujące, pole elektromagnetyczne i zanieczyszczenie światłem. Przedstawiono wyniki badań uzyskane *in vitro* na liniach komórek raka piersi, *in vivo* na modelowych gryzoniach, a także wyniki badań przypadków w populacji, opartych na sposobie działania poszczególnych substancji zanieczyszczających środowisko na gruczoły sutkowe. Badano również wpływ czasu ekspozycji na zanieczyszczenia środowiska (głównie ekspozycja podczas rozwoju gruczołu sutkowego) na ryzyko zachorowania na raka piersi. Przeanalizowano także wpływ zawodowego narażenia na niektóre zanieczyszczenia na ryzyko zachorowania na raka piersi.

Słowa kluczowe: rak sutka, chemiczne substancje rakotwórcze, promieniowanie jonizujące, pole magnetyczne