Breast Cancer

24

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Female Breast Cancer

Descriptive Epidemiology

Breast cancer is the most common malignancy affecting women. Indeed, among all cancers affecting women, breast cancer has the highest incidence and mortality, in more developed and less developed countries. In 2018, 2.09 million new cases were reported in the world, corresponding to 24.2% of all cancers occurring in women that year. The incidence rates of female breast cancer vary greatly, being highest among women in North America, Southern, Western, and Northern Europe, and Australia and New Zealand (greater than 80 new cases annually per 100,000 women). Incidence is lowest in South-Central Asia, and in Eastern and Middle Africa (incidence below 30 new cases annually per 100,000 women). The range of mortality rates for female breast cancer is narrower than that of incidence rates, due to better survival in more developed countries as compared to less developed countries (Fig. 24.1) [1].

Incidence rates have been decreasing in North America, a few European countries and Australia and New Zealand, but are currently increasing in less developed countries. In the United States, the decrease in incidence rates over the last few years has been attributed to the reduction of large-scale hormone replacement therapy prescription [2, 3]. Secular time trends in mortality rates have generally been more stable than those of incidence and have, in fact, decreased particularly in more developed countries [4].

General Epidemiology and Lifestyle-Related Risk Factors

As is the case for most cancers, breast cancer is a multifactorial disease. Several nonoccupational factors have been found to be consistently associated with increased risks of developing breast cancer; a selection of these is presented in Table 24.1.

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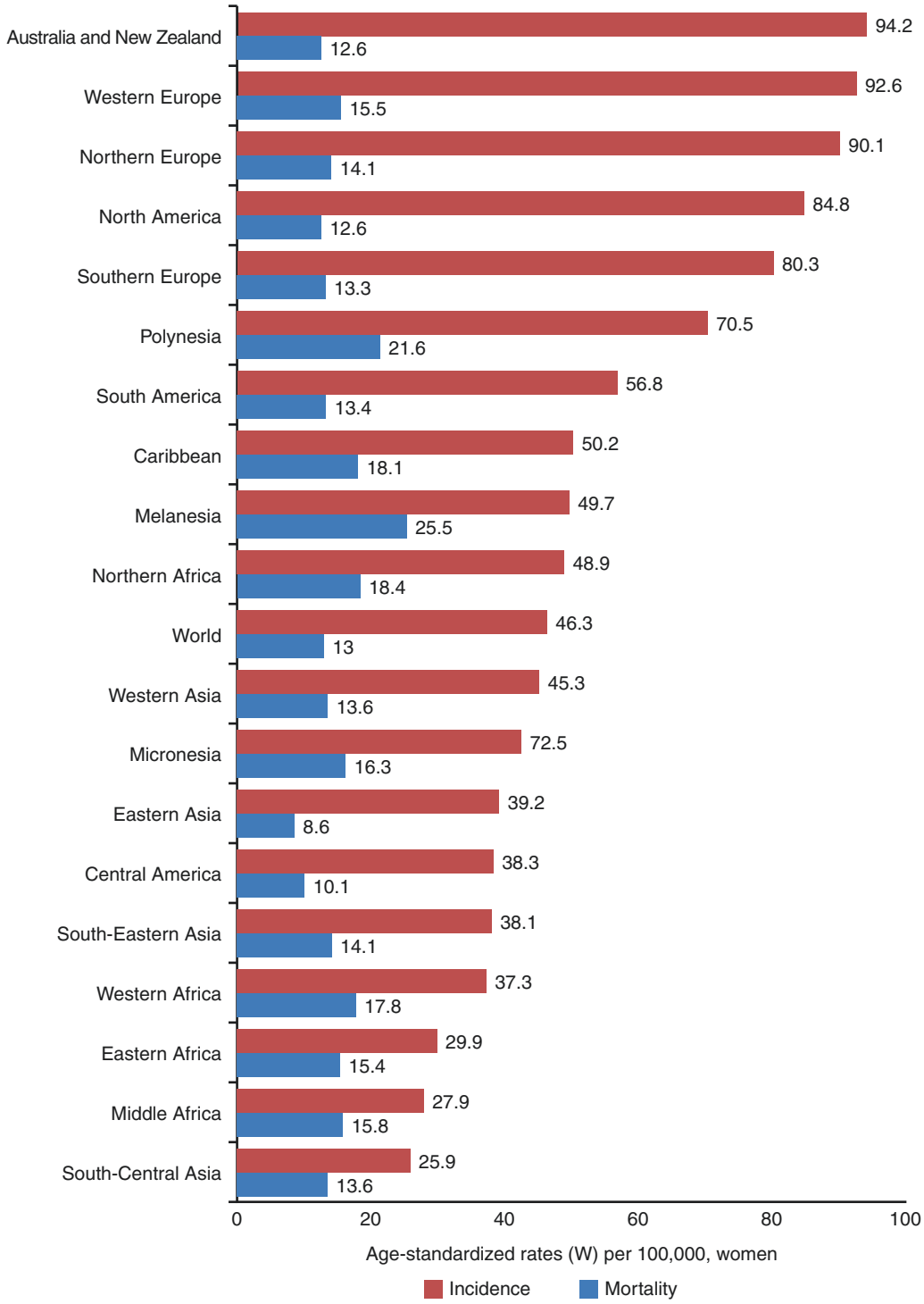

Fig. 24.1 Age-standardized incidence and mortality rates of female breast cancer in different world regions. GLOBOCAN 2018 (W: Standardization done according to the average-age structure of the world) (Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [16 March 2019])

Reproductive Factors

Early age at menarche (≤11 vs. ≥15 years, 1.1–1.9-fold increased risk) [5, 6], late age at menopause (≥55 vs. ≤45 years, 1.1–1.9-fold increased risk) [5, 6], nulliparity (nulliparous vs. parous women: one to twofold increase in risk, inconclusive after one full-term pregnancy) [7], and age at first full-term pregnancy above 30 years (one to twofold increased risk compared to women with first full-term pregnancy <20 years of age) [6–11] have been consistently associated with an increased risk of breast cancer. Breastfeeding reduces risk in both pre- and postmenopausal women [14, 19]; a pooled analysis showed a decreased risk of 4% for every 12 months a woman breastfeeds, regardless of whether a woman breastfeeds in consecutive children or not [12].

Table 24.1 Selected nonoccupational risk factors associated with the development of breast cancer

Risk factor	Definition	Range of risk	Menopausal status	References
Reproductive risk factors				
Age at menarche	≤11 vs. ≥15 years old	1.1–1.9	Any	[5, 6]
Age at first full-term pregnancy	≥30 vs. <20 years old	1.1–1.9	Any	[6–11]
Parity	Nulliparous vs. ≥1 child	1–2	Any	[7]
Breastfeeding	Per 12 months (continuous or not)	Decrease of 4% in risk	Any	[5, 7]
Age at menopause	≥55 years vs. ≤45 years old	1.1–1.9	Postmenopausal	[5, 6]
Medication				
Diethylstilbestrol	Use during pregnancy	1.3–1.5	Not specified	[12, 13]
Oral contraceptives with combined estrogen-progestogen	Ever vs. never	1.6–2.1	Premenopausal	[6, 7, 12, 13]
Hormone replacement therapy (estrogen alone or in combination with progestogen)	Several years or in high doses	<2	Postmenopausal	[6, 7, 13]
Lifestyle and personal risk factors				
Height (as a marker of factors affecting growth)	Per 5 cm increase	Increase of 2–11% in risk	Any	[14]
High body fat	Exposure–response relationship	Decrease in risk	Premenopausal	[11, 15]
High body fat	Exposure–response relationship	Increase in risk	Postmenopausal	[14, 16]
Physical activity	Per 7 MET h/week	Decrease of 3% in risk	Any	[14–16]
Alcohol consumption	Per 10 g ethanol consumed daily	Increase of 10% in risk	Any	[14, 17]
Total fat consumption		Increased risk	Postmenopausal	[7, 14]
Other exposures				
Chest irradiation (X- and γ-radiation)	High doses vs. minimal (irradiation from puberty to childbearing years)	2–4	Any	[7, 18]

METs describe the energy cost of physical activity relative to a person's resting metabolic rate

Use of Exogenous Hormones

According to the International Agency for Research on Cancer (IARC), diethylstilbestrol may cause breast cancer in women exposed during pregnancy [13]. The use of oral contraceptives comprising estrogen and progestogen among current and recent users only is also associated with an increased risk of developing breast cancer in young women [13]; the risk is particularly increased among women with benign breast disease who use oral contraceptives, and among women who used oral contraceptives either before 20 years of age (relative risk ~2.1) or before their first full-term pregnancy (relative risk ~1.6) [6, 7, 13]. The use of hormone replacement therapy containing estrogen and progestogen also increases the risk of developing breast cancer (relative risk <2 for women who took them for several years or in high doses), as does hormone replacement therapy containing estrogen only [6, 7, 13, 15].

Diet, Body Size, and Physical Activity

The World Cancer Research Fund [14] evaluated the available evidence on the risk of cancer and several aspects of diet, physical activity, and body size. The *IARC Handbooks of Cancer Prevention* series also included similar evaluations [16, 17]. The results from the World Cancer Research Fund and IARC are of major importance and are summarized below.

There is evidence suggesting that total fat consumption may be associated with the risk of developing postmenopausal breast cancer, but the relationship has not been clearly established [14]. Regarding body fatness, an international panel of experts judged the evidence that supports an exposure–response relationship convincing for postmenopausal women, whereas the same group judged probable a protective effect among premenopausal women [11, 16]. There is robust evidence for a mechanistic explanation indicating that greater body adiposity after menopause is associated with tissue inflammation, which may play a part in initiation or promotion of cancer [14, 17]. According to the evaluation of the World Cancer Research Fund, increased abdominal fat is associated with increased risk of developing postmenopausal breast cancer (relative risk 1.19, 95% confidence interval [CI] 1.10–1.28 per 0.1 increment in waist-to-hip ratio), as is weight gain in adults (relative risk 1.05, 95% CI 1.04–1.07 per 5 kg gained), whereas higher birth weight is associated with an increased risk of premenopausal breast cancer (relative risk 1.08, 95% CI 1.04–1.13) [14].

With respect to height, prospective epidemiological studies show a clear exposure–response relationship, and there is some evidence for plausible mechanisms in humans. The World Cancer Research Fund considers that there is convincing evidence that factors that lead to greater adult attained height (relative risk 1.03, 95% CI 1.01–1.04 per 5 cm increase) are associated with increased incidence among both pre- and postmenopausal women [14].

Evidence from prospective studies on physical activity suggests a protective effect against both pre- and postmenopausal breast cancer for high levels of physical activity, including occupational active employment [20] but no evidence that breast cancer risk is increased with inactivity, except in relation to occupational sedentariness for which increased risks of about 20% has been reported [21]. The evidence is stronger for postmenopausal breast cancer than for premenopausal breast cancer. There are little data regarding frequency, duration, or intensity of activity, but the evidence is robust for mechanisms operating in humans [14, 16].

Alcoholic Beverages

In agreement with the IARC evaluation, which considered alcohol as carcinogenic (Group 1 agent) to the human breast [22], the World Cancer Research Fund also classified the evidence as "convincing" that consumption of alcoholic beverages increases incidence in both pre- and postmenopausal breast cancer, irrespective of the type of alcoholic beverage (i.e., no difference between wine, beer, liquor). An exposure–response relationship is apparent: all studies in which an exposure gradient was investigated found that risks increased with increasing alcohol consumption (relative risk 1.10, 95% CI 1.06–1.14 per 10 g/day increase) [14].

Tobacco Smoking

The IARC considers that there is limited evidence suggesting that tobacco smoking may be associated with increasing incidence of breast cancer, in particular risk appears to increase when smoking starts early and before a woman's first full-term pregnancy (before the breast tissue matures) and if it continues for several decades [22].

Ionizing Radiation

The IARC classified X-radiation and γ-radiation as carcinogenic agents with sufficient evidence in humans in relation to developing breast cancer (two- to fourfold increase in risk for high doses compared to minimal exposure; risk may be higher when exposure occurs between puberty and childbearing years, when breast tissue is still proliferating) [7, 18, 23]. The evidence on which the evaluation was based emanates from many studies in special populations, such as atomic bomb survivors, medical patients, and women who were exposed in utero (offspring of atomic bomb survivors and pregnant medical patients) (see Table 24.1) [18, 23, 24]. In addition, α-radiation and neutrons have been classified as carcinogenic agents for several cancer sites, but the evidence is deemed insufficient for female breast [18].

Family History of Breast Cancer and Genetic Factors

Family history of breast cancer increases a woman's risk substantially depending on the age at which affected relatives were diagnosed, as well as the age of the woman herself, the number of affected relatives, and the generational distance between the relatives and the woman. The familial relative risk (FRR) for first-degree relatives of breast cancer patients is about twice that of women without a family history of breast cancer [25, 26] and increases more than fourfold for women who have a first-degree relative with premenopausal bilateral breast cancer or who have two first-degree relatives with any form of breast cancer [5–11, 27, 28]; most of this FRR appears to be due to inherited susceptibility [26, 29, 30].

Several important genetic variants have been found, ranging from high-penetrance but rare mutations that confer very high risks (ranging from 5 to more than 20), moderate-penetrance mutations that are associated with risks between 1.5 and 5, and low-penetrance but frequent polymorphisms associated with lower risks (see Table 24.2) [28, 31]. Based on recent evidence, it appears that genetic susceptibility is involved in a large proportion of breast cancer cases. According to a polygenic model, about half of all breast cancer cases arise in a small, highly susceptible subgroup comprising about 12% of women (those with a risk above 10% by age 70 years). In fact, half of the female population has a breast cancer risk of only 3% or less, accounting for about 12% of all breast cancer cases [32].

About 25% of the FRR is explained by high-risk alleles such as BRCA1, BRCA2, PTEN, and TP53. When the rare intermediate-risk alleles (CHEK2, ATM, BRIP1, PALB2) are also considered, another 2–3% of the FRR is accounted for (see Table 24.2) [33]. In addition to these high- and intermediate-risk alleles, genetic studies have identified 19 common low-risk susceptibility alleles that explain yet another 10% of the FRR [34–43]. Many of these genes are involved in DNA repair mechanisms (see Table 24.2) [28].

In summary, the known susceptibility alleles account for only about one-third of the overall FRR. Recent genome-wide linkage studies did not identify any additional rare variants

Table 24.2 Accepted breast cancer susceptibility alleles

Susceptibility alleles	Frequency in European populations	% of familial relative risk explained
High risk		
BRCA1, BRCA2, TP53, PTEN, STK11/LKB1, CDH1	Rare–0.001	20–25%
Intermediate risk		
CHEK2, ATM, BRIP1, PALB2	0.005–0.01	5%
Low risk		
FGFR2, TOX3, MAP3K1, FAM84B/c-MYC, LSP1, NEK10/SLC4A7, COX11, CASP8 (D302H), TNP1/IGFBP5/IGFBP2/TNS1, NOTCH2/FCGR1B, RAD51L1, MRPS30/FGFR10, ESR1d	0.13–0.52	8–10%

Adapted from Mavaddat et al. [28], Copyright 2010, with permission from Elsevier

that confer large breast cancer risks (relative risk >2) [28]. Thus, the remainder of the FRR could likely be explained by some combination of common variants although certain authors consider that including newly discovered common variants would only modestly improve the performance of risk models for breast cancer [44].

Occupational Exposures

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans series is recognized worldwide as a dependable source to identify carcinogenic agents and circumstances. Agents are classified into one of the five groups: Group 1 agents are deemed to be carcinogenic to humans; Group 2A agents probably carcinogenic to humans; Group 2B agents possibly carcinogenic to humans; Group 3 agents not classifiable as to their carcinogenicity to humans; and Group 4 agents probably not carcinogenic to humans [45]. The evidence considered by the working groups to classify the agents comes mainly from human and animal studies. Thus, some agents may be classified as carcinogenic to humans if there is sufficient evidence in humans, or limited evidence in humans but sufficient evidence in animals. Finally, an agent can be considered carcinogenic to a certain organ, but not necessarily to another one. Table 24.3 shows the known or suspected causes of breast cancer abstracted from the *IARC Monographs* [46].

According to the different IARC Working Groups, the existing Group 1 agents with *sufficient* evidence of carcinogenicity to the human breast are not related to occupational exposures. For example, the available evidence for alcoholic beverages, diethylstilbestrol, and combined estrogen-progestogen oral contraceptives or hormone replacement therapy is derived from personal use, and not from exposures in occupational settings. The rationale presented for X-radiation and γ-radiation is derived from studies carried out on atomic bomb survivors and women who underwent radiation therapy before menopause (for conditions such as acute postpartum mastitis, benign breast disease, and follow-up of tuberculosis by chest fluoroscopies) although a few occupational studies have also shown increased risks among exposed workers [18]. The evidence for polychlorinated biphenyls (PCBs) comes from both nonoccupational and occupational exposures [47]. Only one Group 1 agent, ethylene oxide, is an occupational exposure. However, evidence for carcinogenicity to the human breast is *limited* for this exposure. It is important to appreciate that few studies of occupational risk factors for breast cancer have been carried out, so the paucity of well-established occupational carcinogens may be due to lack of research.

Estrogen-only hormone replacement therapy and active tobacco smoking have been classified by the IARC as probably carcinogenic to the human female breast, with *limited* evidence in humans, but again, these exposures are not considered to be related to occupation.

Occupational Agents with Limited Evidence for Carcinogenicity to the Human Breast

Ethylene oxide (Group 1 agent) [48] and night shift work (Group 2A agent) [49] are considered to be related to occupation (see Table 24.4).

Ethylene Oxide

Ethylene oxide is used mainly as a raw material for the production of several industrial chemicals, including glycols, which are used in the production of a number of consumer goods [65]. Less than 1% is used as a sterilizing agent, a fumigant, or a pesticide by different healthcare facilities, spice manufacturers, or sterilization contractors [65]. In the early 2000s, the approximate estimates of the number of exposed workers in the United States were in the order of 48,000 [66]. In the European Union in the early 1990s, the corresponding estimate was around 47,000 workers [67].

The data used by the IARC to classify ethylene oxide [48] is derived mainly from four occupational cohort studies [50–54]. Because mortality from breast cancer is highly misclassified, one must rely on incidence rates, as reported in three of the four aforementioned cohort studies [50–52, 54]. A US National Institute for Occupational Safety and Health cohort study of 7500 women [52], which had accounted for several important potential confounding variables, showed a clear exposure–response relationship between exposure to ethylene oxide and the incidence of breast cancer, with a relative risk of 1.87 among women in the highest quintile of cumulative exposure as compared to the lowest quintile. A smaller study from the United

Table 24.3 Weight of the evidence of carcinogenicity to the human breast for selected lifestyle and occupational agents or exposure circumstances, as identified in the International Agency for Research on Cancer (IARC) Monographs, Volumes 1–123

Agent	IARC classification[a]	Weight of evidence[b] for causation in breast cancer		
		In humans	In animals	From occupational exposure studies
Lifestyle factors				
Alcoholic beverages	1	S	S	N/A
Tobacco smoking	1	L	L	N/A
Pharmaceuticals				
Diethylstilbestrol	1	S	S	N/A
Digoxin	2B	L	I	N/A
Estrogen menopausal therapy	1	L	S	N/A
Estrogen-progestogen contraceptives	1	S	S	N/A
Estrogen-progestogen menopausal therapy	1	S	S	N/A
Mixed exposures (*environmental and occupational*)				
Dieldrin	2A	L	L	I
PCBs	1	L	L	I
Tobacco smoke (second hand)	1	I	I	I
X-radiation, γ-radiation	1	S	S	L
Occupational exposures				
Benzene	1	I	L	I
ELF-EMF	2B	I	L, I	L, I
Ethylene oxide	1	L	L	L
Organic solvents				
Mixtures	1, 2A, 2B, 3	I	L	I
Tetrachloroethylene	2A	I	L	I
Trichloroethylene	1	I	L	I
Other pesticides	1, 2A, 2B, 3	I	S, L, I	L, I
PAHs	1, 2A, 2B, 3	I	L	I
Pharmaceuticals				
Estrogens	1	S, L	S	I
Antineoplastics	1, 2A, 2B, 3	I	S	I
Night shift work	2A	L	S	L

This table does not include risk factors not covered in *IARC Monographs* Volumes 1–123, notably reproductive and other hormonal factors, diet and nutritional factors, and genetic susceptibility traits

Abbreviations: *PAHs* polycyclic aromatic hydrocarbons, *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PCBs* polychlorinated biphenyls

[a]Group 1 = carcinogenic to humans, Group 2A = probably carcinogenic to humans, Group 2B = possibly carcinogenic to humans, Group 3 = not classifiable as to its carcinogenicity to humans

[b]*S* sufficient evidence, *L* limited evidence, *I* inadequate evidence, *N/A* not applicable to occupational exposures

States also showed increased risks (standardized morbidity ratios 1.57–1.72) among women from a sterilization company [51]. In a Swedish study, no increase in risk was initially found [50], but an internal analysis after a longer follow-up revealed significantly increased risks for women in the two upper quartiles of exposure compared to the lower half of exposure (rate ratios of 2.76 and 3.55) [54]. A few animal studies showed increased risks of mammary tumors in rodents. Additional mechanistic studies showed alkylation, gene mutations, and chromosomal alterations following binding to cellular macromolecules resulting in DNA, RNA, and protein (including hemoglobin) adducts; these led the IARC Working Group to classify ethylene oxide as carcinogenic to humans (Group 1 agent) but with *limited* human evidence for breast cancer and lymphoid tumors [48].

Night Shift Work

Although shift work corresponds to several definitions of work schedules, including hours other than the traditional daytime work period [68], it is generally considered as "…the organization of working time by different teams in succession to cover more than the usual 8-h day, up to and including the whole 24-h period" [69]. Shift work disrupts biological rhythms and the most important factor appears to be the proportion of time worked at night [70, 71]. The industrial sectors with the largest percentages of workers on a non-daytime shift are accommodation and food services, agriculture, health services, and transportation and communication [72]. It was estimated in 2005 that 9–30% of workers in the European Union, depending on the country, worked shifts that included night work [73]; in 2004 that proportion was estimated to be about 15% in the United States [74].

Table 24.4 Occupational[a] exposures with limited evidence for carcinogenicity to the female breast, and their major industries or occupations (*IARC Monographs* Volumes 1–120)

Agents with limited evidence for *occupational exposures* in humans			
Agents	Major industries/occupations	Range of risk ratios considered	References
Ethylene oxide	Ethylene oxide production	Cohort studies	[50–54]
	Chemical manufacture of ethylene glycols	Any duration of exposure: 0.5–1.7	
	Medical facilities with sterilization unit (hospitals, medical and dental clinics)	>14,620 ppm days: 1.9	
	Manufacturers of sterile medical supplies		
	Industrial sterilization contractors (spices, tobacco, furs, museum artifacts, etc.)		
Night shift work	Healthcare sector	Cohort studies	[55–58]
	Transportation	Any duration: ~1.0	
	Accommodation and food services	≥20–30 years (nurses): 1.4–1.8	
	Agriculture	Nested case-control studies	[59–61]
	Manufacturing industry	Any duration: 1.0–1.5	
		≥7–30 years: 1.7–2.2	
		Case-control studies	[62–64]
		Any duration: 0.5–1.6	
		≥5–20 years: 2.3–2.5	

[a]Among carcinogenic agents with sufficient evidence in humans, the following were not considered work-related: diethylstilbestrol and (active) tobacco smoking

The IARC Working Group cited data from eight studies designed specifically to evaluate the relationship between shift work involving night work and the risk of breast cancer [49]. Six of these studies reported a modest increase in risk (generally less than twofold) among women who worked night shifts for a long period of time, or who did rotating work including night shifts as compared to women who worked daytime hours. Several definitions of shift work were used as well as different designs: two prospective cohort studies among nurses [55, 56]; three nested case-control studies [59–61]; and one retrospective case-control study [62]. Two studies showed negative results, a census-based cohort study [57] with important design limitations, and a case-control study initially designed to study the relationship between electromagnetic fields and breast cancer [63]. These studies included mainly white women and women with postmenopausal breast cancer. In some of the studies, not all potential confounding variables were accounted for. Misclassification of exposure may have biased the results toward the null. Studies of aircraft personnel were considered by the IARC Working group to support the association between shift work and breast cancer although these workers had concomitant exposures that could have confounded the association (such as cosmic radiation and electromagnetic fields) [49].

Since the IARC evaluation, several additional studies, including five cohort studies [58, 75–78] and eleven case-control studies [64, 79–89] have been published on shift work in relation to breast cancer risk. Most of these studies have been reviewed in 2016 by an expert working group of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). The working group concluded that these recent epidemiological studies provide more evidence on the increased risk of breast cancer among night shift workers; however, this evidence is still limited and it is not yet possible to rule out, with certainty, the existence of residual confounding factors that could explain some of the observed associations [90, 91].

Seven recent meta-analyses [92–98] reported at least one meta-risk estimate of breast cancer in association with night shift work based on slightly different sets of studies. Overall, meta-risk estimates ranged from 0.99 (ten prospective studies [98]) to 1.40 (nine high-quality studies [93]) for ever/never night shift work exposure. These meta-analyses were not conclusive on other metrics of night shift work exposure or other study characteristics.

The main theory underlying the detrimental effects of shift work is that light at night can disrupt circadian rhythms through its effect on melatonin synthesis and on the circadian gene function of the suprachiasmatic nucleus. This disruption might increase cancer risk through several pathways [99], including a decrease of melatonin's possible oncostatic and free radical scavenging properties, as well as perturbations of the involvement of circadian genes in cell proliferation, apoptosis, cell cycle control, and DNA–damage response [49]. A case-control study nested in a cohort of nurses reported an inverse relationship between the urinary concentration of 6-sulphatoxymelatonin, a biomarker of melatonin concentration, and the incidence of breast cancer [100]; levels of 6-sulphatoxymelatonin decreased with increasing number of nights worked in the 2 weeks prior to

urine collection [101]. However, another cohort study in the general population did not find such a relationship [102]. In classifying shift work that involves circadian disruption as probably carcinogenic to humans, IARC concluded that there was *sufficient* evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night) [49].

Clearly, more studies in humans are needed to allow a thorough understanding of the relationship between shift work and the incidence of breast cancer. A working group convened by the IARC identified several major domains of non-day shift schedules that needed to be captured in a consistent manner to increase the validity of future studies on shift work and cancer [72], and although a few studies already addressed these issues, more evidence needs to be gathered [90].

Occupational Circumstances with Insufficient Evidence for Carcinogenicity to the Human Breast

A few additional agents have been found to be associated with an increased breast cancer risk in women, but the weight of evidence in these studies was not deemed sufficient to support their classification as carcinogenic to the human breast (see Table 24.5).

Ionizing Radiation

Although all forms of ionizing radiation are accepted carcinogens, as they cause direct DNA mutagenesis (in particular double-stranded DNA breaks) and genomic instability [18], studies of occupational exposures to X-radiation or γ-radiation, neutron radiation, or radionuclides emitting α- or β-particles have been largely negative. Limitations of these studies were that the studied cohorts were small and their exposures were much lower than those of atomic bomb survivors or women who underwent radiation therapy.

Occupational exposures occur when either handling radioactive materials or being exposed to natural sources of radiation at work. Aircraft personnel are exposed to cosmic rays that are natural sources of γ-radiation and neutrons, and underground miners to natural radionuclides emitting essentially α-particles. Workers handling radioactive materials or machinery can be exposed to several types of radiation: for example, healthcare workers are exposed in larger numbers to X-radiation, but some may be exposed to radionuclides emitting α- or β-particles; industrial radiographers are exposed to X-radiation; and nuclear energy or nuclear weapon workers are essentially exposed to γ-radiation and α- or β-particles [18]. In 2008, the United Nations Scientific Committee on Exposure to Atomic Radiation estimated that about 22.8 million workers were exposed to ionizing radiation, with 13 million exposed to natural sources and 9.8 million to artificial sources; medical workers are considered to constitute about two-thirds of exposed workers [152]. The doses were relatively low: the annual occupational effective doses have been diminishing and were estimated to vary between 0.1 and 1.0 mSv per year in 2000–2002 for exposures to artificial sources, compared to 2.9 mSv per year for exposure to radon gas [152].

The IARC Working Group that assessed the available evidence of a relationship between breast cancer and occupational exposure to ionizing radiation (X-radiation and γ-radiation) among radiologists and radiology technicians remarked that increased risks appeared to be restricted to women exposed before the 1940s and to women who had been working for more than 30 years as certified radiology technicians [18]. A study of Chinese medical X-ray workers reported increased risks that were more elevated among women who began working before 1970 and before 30 years of age and those with more than 25 years of employment [103]. A small case-control study nested in the same Chinese cohort showed a non-significant exposure–response relation with increasing cumulative dose [153]. This pattern of higher risks among women born before 1940 and 1930 was also confirmed in a study of radiology technicians in the United States [104] and in a follow-up of that same cohort until 2008 [154]. Indeed, most recent cohort studies have not shown evidence of increased risks at current exposure levels [24, 105, 155]. A recent review of epidemiological studies of medical radiation workers concluded that information on average annual exposure to occupational radiation, time trends in radiation exposure, and organ-specific doses was insufficient in most of the available studies to assess the lifetime cancer risk of these workers. The authors stressed the importance of conducting large-scale studies where individual cumulative occupational radiation dose estimates are used to assess dose–response relationships [156].

The available cohort studies of uranium production and of nuclear energy workers have very small numbers of female workers, and consequently very low power to detect increased risks of breast cancer. Cohort studies of workers at a few uranium mines or production facilities in the United States (primarily α-radiation from dusts) did not show any increased incidence or mortality rates of breast cancer among exposed workers, and a small increase was observed among nonexposed workers [106, 157]. A cohort study of French nuclear energy production workers reported a small increased risk of death due to breast cancer (standardized mortality ratio 1.14, 90% CI 0.94–1.37) [107], whereas a study of French uranium fuel cycle workers showed a higher but still non-significant increased risk (standardized mortality ratio 1.53, 95% CI 0.94–2.37) [158]. One case-control study showed a large increased risk (OR 5.3, 95% CI 2.4–14.1) associated with exposure to ionizing radiation, but used rather crude

Table 24.5 Agents or exposure circumstances that have been associated with female breast cancer, but with insufficient evidence

Agents and circumstances with some, but insufficient, evidence in humans			
Agents	Examples of industries/occupations	Range of risk ratios	References
X- and γ-radiation	Diagnostic radiology	0.9–5.3 (depending on cumulative exposure)	[103–112]
	Nuclear medicine		
	Industrial radiology		
	Nuclear workers		
	Uranium workers		
PCBs	Capacitor manufacture	0.8–1.3	[113, 114]
Dieldrin	Spouses of men who had used dieldrin	0.8–1.6 (not statistically significant)	[115]
	Farm spouses who used dieldrin	3.5 for ER-PR-tumors	[116]
Organic solvents (including halogenated solvents), other chemicals	Painting	0.5–2.4 (depending on type of solvent and cumulative exposure)	[108, 117–130]
	Metal products fabrication		
	Wood and furniture industry		
	Printing and publishing		
	Chemical industry		
	Textile and clothing industry		
	Electronics workers		
	Laundry and dry cleaning		
	Aircraft and automotive industries		
	Gasoline service station workers		
	Electronics workers		
	Semiconductor plant workers		
	Manufacturers of electronic capacitors and of electronic coils and transformers		
	Printing machine operators and tenders		
ELF-EMFs	Telephone and telegraph operators	1.0–4.6 (depending on cumulative exposure, age at first exposure, and tumor hormonal status)	[122, 131–135]
	Electronic data processing operators		
	Sewing machine operators, textile workers		
	Denturists		
	Machinists		
PAHs	Paving and roofing (with coal tar) Wood preservation with creosote Aluminum production and anode manufacturing Carbon electrode manufacturing Calcium carbide production Thermoelectric power plants Deep frying Traffic booth attendants	1.1–3.0 (depending on cumulative exposure, age at first exposure, and tumor hormonal status)	[120, 128]
Pharmaceutical drugs	Pharmaceutical workers	0.3–4.1	[122, 130, 136–138]
Several chemicals	Laboratory technicians, chemical workers	1.1–2.3	[129, 130, 139–141]
Pesticides and agrochemicals, solvents, etc.	Farmers and farm workers	0.7–2.8	[129, 130, 133, 142]
EMFs, solvents, pigments, textile fibers	Working in textile and clothing	0.5–4.1	[108, 122, 129, 130, 143]
EMFs, cosmic radiations, shift work	Flight personnel	0.8–3.3	[144–148]
Organic solvents, EMFs, metals, welding fumes	Semiconductor and computer manufacturing industries	0.7–1.3	[125, 130, 149]
PAHs, EMFs, cleaning chemicals	Chefs and cooks	0.7–1.6	[122, 129, 130, 150]
Organic solvents, glues, etc.	Cosmetologists and manicurists	0.7–1.2	[108, 130, 151]

Abbreviations: *ELF-EMF* Extremely-Low-Frequency Electric and Magnetic Fields, *PAH* polycyclic aromatic hydrocarbons, *ER-PR-tumors* Estrogen-Receptor and Progestogen-Receptor-negative tumors

exposure assessment methods (expert assessment based on occupational history) [108]. Another case-control study estimated occupational exposure to ionizing radiation using automatic assignments to occupational histories; it showed an increased risk of human epidermal growth factor receptor 2-positive (HER2+) breast cancer with occupational exposure in premenopausal women (OR = 2.57; 95% confidence interval, 1.09–6.03) [159]. An analysis of the Canadian National Dose Registry did not show an excess risk of breast cancer in women with occupational exposure to ionizing radiation [160]. As exposure decreases over the years, risks are presumably being reduced and very large studies will be needed to detect excess risks.

Polychlorinated Biphenyls (PCBs)

PCBs are a group of 209 aromatic hydrocarbons that were widely used because of several interesting properties (non-flammability, chemical stability, high boiling point, and high dielectric constant). Although their production and use was banned worldwide (dates vary from the 1970s in the United States to 2006 in Korea), they can still be found in numerous products manufactured before the ban. Workers are therefore mainly exposed during abatement in construction, in waste incineration, and recycling of electronic equipment and fluorescent lights [47]. PCBs were classified as carcinogenic to humans, with sufficient evidence for malignant melanoma, and limited evidence for breast cancer [47].

The available evidence for breast cancer comes from case-control studies based on levels of PCBs measured in serum and adipose tissues of women, without certainty on the source of exposure [47]. The occupational data comes mainly from mortality studies of capacitor manufacturing cohorts with small numbers of female workers; these mortality studies were negative [114, 161], and only one suggested a relatively small increased risk of breast cancer incidence following occupational exposure to PCBs [113]. Thus, the extent to which occupational exposures to PCBs can be linked to increased incidence of breast cancer is still debated.

Dieldrin

Dieldrin (and aldrin, which is metabolized into dieldrin) is an organochlorine pesticide that has been banned since the 1970s in several countries because of environmental concerns on its environmental persistence [162]. Dieldrin is still measurable in the air, soil, ground water, and food in several developing [163, 164] and developed countries [165, 166]. Dieldrin was classified as probably carcinogenic to humans, with limited evidence for breast cancer [162].

As for PCBs, most of the evidence for breast cancer comes from studies based on serum levels of dieldrin. A prospective Danish study found a significant dose–response relationship between the risk of breast cancer and increasing serum dieldrin levels [167, 168], whereas a similar study in Norway was negative [169]. Positive associations with breast cancer were also reported in spouses of men who had used dieldrin in the US Agricultural Health Study, regardless of their own direct exposure to the pesticide [115, 116]. Hence, there appears to be an association between dieldrin burden and the incidence of breast cancer, but the importance of the contribution of occupational exposure to the increased risk will probably not be elucidated given the ban of organochlorine pesticides.

Occupational Exposure to Hormones, Antineoplastic Drugs, or Other Pharmaceuticals

So far, a few pharmaceutical drugs have been classified as carcinogenic or probably carcinogenic to the female breast of treated patients. Among these, diethylstilbestrol used during pregnancy, oral contraceptives or hormone replacement therapy containing estrogens only or estrogen-progestogen combinations [13] and digoxin [170] have been classified as carcinogenic (Group 1 agents) by the IARC. However, occupational exposures to these pharmaceuticals were not addressed in the corresponding issues of the IARC Monographs, other than to report on chromosomal aberrations in healthcare personnel handling antineoplastic drugs [13].

Several studies among pharmaceutical and healthcare workers reported evidence of elevated levels of urinary metabolites of antineoplastic drugs [171], or of effects linked to exposure to steroids (e.g., gynecomastia and loss of libido in men and menstrual problems in women) [172]. However, only a few epidemiological studies reported, more than 20 years ago, on the risk of cancer among pharmaceutical workers. Elevated risks of breast cancer in the order of 1.5–2.9 were reported in a Danish record-linkage study [136] and in two of four cohort studies of pharmaceutical workers [173, 174]. Another cohort study reported a small increase in incidence among women in the highest exposure groups [137], whereas in the fourth cohort study, only mortality was assessed and there were very few breast cancer deaths to draw conclusions [138]. Not enough data are available to draw conclusions about whether the fabrication or handling of pharmaceutical drugs is associated with an increased risk of breast cancer.

Other Occupational Exposures

The available evidence for other occupations or occupational exposures comes from studies that have varying levels of precision. Linkage studies combining records or registries have usually relied on occupation and/or industry titles,

whereas other designs such as case-control or cohort studies have complemented job titles and industry with information on specific exposures gathered by questionnaires or derived from job-exposure matrices. During the last 15 years, few studies have been conducted on the role of other occupational exposures in female breast cancer.

Organic Solvents and Aromatic Hydrocarbons

There is some evidence of increased breast cancer risk associated with exposures to several categories of organic solvents, including halogenated solvents [117–119] and solvents that metabolize into reactive oxygen species [120]. Industries and occupations that entail exposure to organic solvents have also been associated with increased breast cancer risk [121, 175]: laundry and dry cleaning occupations; working in the aircraft and automotive industries, including service attendants at gasoline stations [122]; electronic workers and those in semiconductor plants [118, 123, 124]; and printing machine operators and tenders [123]. However, in some studies the risks were very low [124, 125] or even nonexistent, such as for styrene [126]. Etiological factors for breast cancer appear to differ according to the hormonal receptor status of the tumor. For example, exposure to solvents appears to increase the risk of breast tumors with certain hormonal receptor status, such as estrogen receptor-positive tumors [120, 175] and some progesterone-negative tumors [119, 120]; younger age at first exposure appears to increase the risk [117, 118, 120, 175].

Aromatic hydrocarbons are a large family of molecules containing at least one benzene ring (i.e., a six-carbon structure with alternating double and single bonds between carbon atoms). Some of these are also considered organic solvents, and the simplest of these chemicals is benzene; aromatic hydrocarbons with one benzene ring are called monocyclic aromatic hydrocarbons (MAHs), whereas those with two or more fused benzene rings are referred to as polycyclic aromatic hydrocarbons (PAHs) [176]. PAHs are derived from incomplete combustion of organic material, and their concentrations are influenced particularly by industrial and traffic-related sources [48, 176]. Some PAHs are carcinogenic in humans, while a few others are classified as probably or possibly carcinogenic to humans.

Exposure to benzene [128], to MAHs as a group [120], and to PAHs [129] has been associated with an increased incidence of about 30%, but not consistently [177]. The increased risk has been observed in both premenopausal [128] and postmenopausal women [120]. The effects of exposure to PAHs appear to be influenced by genetic susceptibility [178]. Aromatic amines, a subgroup of aromatic hydrocarbons often used as pigments, have also been found to be associated with an increased risk of breast cancer, with a clear exposure–response relationship [179], and with risk patterns that may differ according to the hormonal receptor status of the tumor [180]. Finally, a small risk has also been reported for exposure to soluble metalworking fluids [181].

Extremely-Low-Frequency Electric and Magnetic Fields

In 2000, a review of the literature concluded that occupational exposure to extremely-low-frequency electric and magnetic fields (ELF-EMFs) could possibly be associated with female breast cancer [182]. However, in its 2002 monograph on nonionizing radiation, the IARC mentioned such a possible increased risk of breast cancer among men, without referring to female breast cancer. It was also pointed out that the available studies on women from the 1980s and early 1990s had presented methodological limitations, including lack of appropriate exposure measurements, and a possible publication bias toward those studies showing positive associations [183]. Moreover, Goodman and colleagues studied the effect of uncontrolled potential confounding factors in early studies of EMF exposure and concluded that they could account for an OR of about 1.2–1.3 [184].

More recent studies, including meta-analyses, have not found that exposure to EMFs increases the risk of female breast cancer [131, 185–187]. Specifically, a large population-based case-control study showed a slight increase in risk [132], whereas another case-control study showed a fourfold increased risk among telephone and telegraph operators [133]. A few additional studies suggested a moderately increased risk for postmenopausal breast cancer in certain subgroups of women, such as those exposed before age 36 years and whose tumor was progesterone-positive [134], and premenopausal women with estrogen receptor-positive breast cancer were associated with a long duration of high occupational exposures [135].

Other Pesticides and Other Organochlorines

Results from most of the recent studies show either none or only a very small increased risk of breast cancer after exposure to pesticides [188] or other organochlorines [189]. However, one cohort study of chemical workers exposed to dioxins showed an increase of breast cancer mortality (standardized mortality ratio (SMR) = 1.86) based on 19 deaths, but no clear exposure–response pattern [190]. In a few recent papers, increased risks were linked to certain polymorphisms, notably of cytochrome P-450 1A1 [191] and GSTM1 [192]: it is possible that small increased risks of breast cancer do exist, but only in the presence of certain polymorphisms.

Specific Job Titles

The first published mention of an "occupational" increased risk of breast cancer occurred more than 300 years ago by

Bernardino Ramazzini, who reported on increased occurrence of breast cancer among nuns, which he attributed to celibacy, sensing a relationship with nulliparity [193]. Several clerical and professional occupations, such as those of administrators, teachers, librarians, journalists, inspectors, and others, have repeatedly been associated with an increased risk of incidence or mortality in different settings, often in studies based on routinely collected data [129, 130, 133, 150, 194–198]. The increased risk presented by these professional occupations has been ascribed by most authors [129, 130, 150, 196, 197, 199] (but not all [198]) to peculiar reproductive and other lifestyle factors and residual confounding associated with indicators of higher socioeconomic status that would be more frequent among women occupying these professions: high education level; having less children, at a later age; higher use of hormone replacement therapy; and higher alcohol consumption.

Increased risks have also been reported for farming occupations [133, 142], textile and clothing workers [108, 130, 200], leather and fur processors and glass-manufacturing workers [133], nurses [61], dentists [201], electricity power plant workers [202], semiconductor and computer manufacturing industries [125, 149], metalworking and automotive plastics manufacturing [203], rubber industry workers [179, 200], and scientists and laboratory workers [141, 150]. However, similar occupations have also been associated with absence of risk in other studies, for example, the occupation of farm worker [130, 204–206], garment worker [143], glass manufacturer [129], dentist [201], and cosmetologist and manicurist [151].

Air transport crews, particularly flight attendants, showed increased risks of female breast cancer in several studies in the Nordic countries and in the United States [207]. After adjusting for possible confounding by reproductive factors, a few studies still showed an increased risk [144, 145] although there were a few negative studies [146–148, 208, 209].

In summary, several high-quality studies have been conducted, but our understanding of how occupational and environmental agents affect female breast cancer risk is still limited partly because of inconsistencies and partly because only a handful of potentially hazardous agents have been investigated. In many studies on specific industries or occupations, other lifestyle factors known to be associated with breast cancer (such as alcohol consumption, lower parity, and late age at first full-term pregnancy) were often not taken into account, so confounding could not be ruled out. Subtleties of the mechanistic relationships are also difficult to capture in epidemiological analyses, due to difficulties in past exposure assessment, not knowing the ages at which women may be highly susceptible, and because effects may be restricted to a subset of women with specific genotypes.

Other Inconclusive Environmental Exposures

Cadmium and other heavy metals that have estrogenic activity in animal studies have been postulated to be associated with increased risks [210], but little human data are available and the association with human breast cancer remains unclear [211].

Since the improvement and accessibility of traffic-related air pollution exposure assessments, a handful of studies on traffic-related air pollution exposure and breast cancer have been conducted. In a case-control study based in New York State, an association was found with increased volumes of vehicular traffic [212] and higher concentrations of total suspended particulates were associated positively with exposures to benzo[a]pyrene [213, 214]. In the Nurses' Health Study II, no associations were found for incident breast cancer and fine particulates, but increased rates were found among premenopausal and postmenopausal women living within 50 m of major roads [215]. In the Sister Cohort [216], increased risks for nitrogen dioxide (NO_2) exposure measured by fixed-site monitors were also found among cases with positive estrogen receptor and positive progesterone receptor status (hazard rate: 1.10; 95% CI: 1.02–1.19). A hospital-based case-control study by Crouse and colleagues [217] reported increased risks of postmenopausal breast cancer with exposure to traffic-related air pollution in Montreal, using ground-level concentrations of nitrogen dioxide, a reliable marker of traffic-related air pollution. A subsequent population-based case-control study of postmenopausal breast cancer from 2008 to 2011 was conducted by Goldberg and colleagues [218] in the same city. They found an increased breast cancer risk per increase in the interquartile range (IQR = 5.8 ppb) of NO_2: OR: 1.10; 95% CI: 1.02–1.19. The study was also the first to examine associations of breast cancer with ultrafine particles (<0.1 μm in aerodynamic diameter); however, there was little evidence of association in any of the models or sub-analyses and little variability in the ORs. In another population-based case-control study conducted in eight provinces of Canada from 1975 to 1994, positive associations between incident premenopausal breast cancer and ground-level concentrations of NO_2 were found: for a 10 part per billion (ppb) the ORs varied between 1.26 and 1.32 and the 95% confidence intervals excluded the null. Lower ORs were found for postmenopausal breast cancer, in the order of 1.10 [219].

Air pollution is a complex chemical and physical mixture, and many of the pollutants are also found in the workplace. Indeed, a few studies have shown associations between the incidence of breast cancer and occupational exposure to chemicals that are present in vehicular exhaust and thus in urban air pollution, such as benzene, carbon monoxide, and PAHs [119, 120, 127]. Should traffic-related air pollution

prove to be a risk factor, a very large number of cases may be attributed to it, as exposure is ubiquitous in both working and nonworking populations.

Interaction Between Genetic Susceptibility and Various Exposures

The study of joint effects of genetic and environmental factors is crucial in understanding the etiology of breast cancer because it allows the identification of subgroups of women with specific genotypes who may be at higher risk after exposure to xenobiotics or whose risk may be reduced by other exposures [220]. These studies provide insights into mechanisms and can help to determine possible enzymes or proteins that can act on potential carcinogens [220]. For example, if null alleles are present in detoxification reactions (e.g., no enzyme synthesized), carcinogens or carcinogenic metabolites, especially lipophilic ones, may concentrate in adipose breast tissue. A major issue in such studies is having sufficient statistical power, and only studies with thousands of subjects can produce reliable results, and many of the studies reported below may not have been large enough.

A few gene–environment studies have reported that certain single-nucleotide polymorphisms (SNPs) involved in the biotransformation of xenobiotics are associated with increased breast cancer risk. Numerous polymorphisms of P-450 cytochromes have been identified, and further study of gene–environment interactions has been recommended [221]. In a German study [222], urinary concentrations of metabolites of PAHs were associated with certain polymorphisms of CYP1A1 and GSTP1. Elevated relative risks of breast cancer were found for high levels of plasma PCBs and CYP1A1 variants in case-control studies [223, 224] and in the Nurses' Health Study [225], but in another case-control study no associations between occupation and CYP1A1∗2 polymorphisms [226] were found. Results between the risk of breast cancer and exposure to smoking or second hand tobacco smoke are inconsistent in relation to slow and rapid NAT2 acetylators [227–229], and with exposures to aromatic and heterocyclic amines [180]. Elevated risks of breast cancer were suggested for current alcohol consumption with certain glutathione *S*-transferase genotypes (null GSTM1, GSTT1, and GSTM3) [230–232], and there was an inverse association between breast cancer risk and frequency of alcohol consumption with alcohol dehydrogenase II polymorphism [233]. The Breast Cancer Association Consortium recently published an analysis of the interaction between 70 single-nucleotide polymorphisms (identified by genetic fine-scale mapping of susceptibility loci) and 11 breast cancer risk factors: they notably found interactions between CFLAR-rs7558475 and current smoking, and between 5q14-rs7707921 and alcohol consumption for estrogen-receptor-negative tumors [234].

It has also been determined that carriers of two high-risk alleles, BRCA1 and BRCA2, show increased sensitivity to the effect of clastogens as measured by micronucleus formation [235]. Polymorphisms of p53, a protein involved in the regulation of the cell cycle and apoptosis, were associated with increased risks in association with exposures to ionizing radiation in the Carolina Breast Cancer Study [236].

In summary, several studies have shown that interactions between certain genetic variants and exposure to xenobiotics can affect the risk of breast cancer, but the findings still need to be replicated before any firm etiologic conclusion can be drawn.

Proportion of Female Breast Cancer Attributable to Occupation

As of 2017, four groups of researchers had published estimates of the burden of breast cancer attributable to occupational exposures now or in the future. The first study included ionizing radiation and exposure to hair dyes among hairdressers and concluded that 1.7% of breast cancer in Finland could be attributed to occupational exposures [237]. The second study, considering shift work and flight personnel, estimated that 4.6% of female breast cancers in Great Britain could be attributed to occupational exposures [238]. The third study calculated that 5.7% of breast cancers in the United States could be attributed to shiftwork [239]. Finally, the last study predicted that 0.7% of breast cancers diagnosed among women at work in 2012, until they are 100 years of age, would be caused by exposure, as of 2012, to ionizing radiation, ethylene oxide, and shift work [240] (see Table 24.6).

Male Breast Cancer

Descriptive Epidemiology

Male breast cancer is a very rare disease, with incidence rates varying from 0.1 to 2 per 100,000 men worldwide [241]. Rates are higher in North America and Europe (estimated at 0.47 per 100,000 [242]) and extremely low in Asian populations. Indeed, female breast cancer incidence is 100 times higher than male breast cancer incidence, which represents less than 1% of all breast cancers worldwide [241]. Studies on the time trends of male breast cancer indicate that its incidence is increasing in North America, the United Kingdom, Singapore, and possibly some African countries, mimicking time trends of female breast cancer although on a

Table 24.6 Estimated proportions of female breast cancer attributable to occupation now or in the future

Population	Occupational exposures considered	Attributable proportions (95% confidence interval)	Comments	References
Finland	Ionizing radiation, hair dyes (hairdressers)	1.7	Proportion of attributable deaths by breast cancer	[237]
Great Britain	Shift work, flight personnel	4.6 (3.3–6.0)	Proportion of attributable deaths by breast cancer	[238]
United States	Shift work	5.7 (0.0–11.9)	Proportion of attributable deaths by breast cancer	[239]
Australia	Ionizing radiation, ethylene oxide, shift work	0.7	Future excess fraction (FEF)	[240]

much smaller scale. Conversely, in the Nordic countries and Switzerland, incidence has been stable over the last 40 years [243–245].

General Epidemiology and Lifestyle-Related Risk Factors

The etiology of male breast cancer is poorly understood. This may be due to the rarity of the disease and, consequently, the scarcity of published studies. Genetic, hormonal, and environmental risk factors have been reported to be associated with male breast cancer risk. Family history of breast cancer has been associated with an increased risk of male breast cancer [27]. In particular, genetic susceptibilities related to male breast cancer include mutations in BRCA1, BRCA2, and possibly other genes (CYP17, AR gene, CHEK2) [246]. Klinefelter's syndrome and a few other rare disorders have also been associated with increased risk. Similarly, associations with education, religion, marital status, clinical disorders related to hormonal imbalance (e.g., infertility, testicular injury, gynecomastia), and estrogen intake are controversial. Hormonal imbalance appears to lend to an increased risk [247].

Among the lifestyle exposures studied, alcohol consumption and related liver cirrhosis, heavy tobacco smoking, and obesity were associated with increased male breast cancer risk in a few studies, but results were equivocal. There are an insufficient number of studies to allow any conclusions about the effect of exposure to ionizing radiation or electromagnetic fields on male breast cancer [247–251]. So far, the IARC has not identified any carcinogens specifically for male breast cancer.

Occupational Exposures

Some evidence of carcinogenicity to the male human breast has been gathered for Group 1 agents outside the occupational setting, e.g., alcoholic beverages [249] and X-radiation and γ-radiation [109, 252]. Some evidence of a relationship with occupational ionizing radiation exposure has also been reported [110], and a recent analysis of the Japanese Atomic Bomb Survivors data reported higher radiation-associated relative risk for male breast cancer compared to the risk in women [253].

Inconclusive Occupational Exposures

A few occupational exposures have been associated, albeit inconclusively, with male breast cancer [246, 247, 254].

Extremely-Low-Frequency Electric and Magnetic Fields

In its 2002 monograph, the IARC Working Group on non-ionizing radiation mentioned a possible increased risk of male breast cancer in association with ELF-EMFs. The committee also pointed out that the available studies from the 1980s and early 1990s presented methodological limitations, lack of appropriate exposure measurements, and a possible positive publication bias [183]. Since then very few studies and one meta-analysis have been published regarding male breast cancer risk. A modest increased risk of male breast cancer (OR of 1.31, 95% CI 0.94–1.81) has been reported in men exposed to ELF-EMFs above 0.12 microteslas (exposure attributed using a job-exposure matrix); those exposed intermittently showed indications of an exposure–response trend, which led the authors to conclude that variations in exposure levels within work days could be associated with an increased risk [255]. In a meta-analysis of 18 cohort and case-control studies, a pooled risk estimate of male breast cancer of 1.32 (95% CI 1.10–1.59) was estimated with any occupational exposure to EMF from seven studies that used job title or a job-exposure matrix to assess exposure [256]. In conclusion, the available evidence does not allow to draw firm conclusions on the effect of exposure to ELF-EMFs on male breast cancer risk.

Polycyclic Aromatic Hydrocarbons and PCBs

The few epidemiological studies investigating the relationship between exposure to PAHs and male breast cancer did not show consistent findings. In a record-linkage study, Hansen [257] reported a significantly increased risk among

workers potentially exposed to combustion products (as a proxy for PAHs) when compared with other workers; the risk was particularly elevated for exposures starting before age 40 years [257]. However, in an Italian case-control study, no association was found between male breast cancer and occupational exposure to PAHs [258]. Two recent studies of capacitor workers showed non-statistically significant increases in mortality and in incidence of male breast cancer based on very little numbers ([259], based on two deaths; [161], based on six cases).

Heat

A few reviews mentioned that occupational exposure to high temperatures has been associated with increased risk of breast cancer in men, possibly because of testicular dysfunction resulting from high temperatures [246, 247]. However, these reviews refer to a small number of studies with a number of methodological limitations. Three small case-control studies (52, 91, and 71 cases) reported an increased risk for men "with occupations that involved heat exposure" [260–262], whereas a larger one reported that working in blast furnaces, steel works, and rolling and finishing mills (occupations with elevated heat exposures) conveyed a threefold increased risk of male breast cancer [258]. Nevertheless, several other carcinogens are also found in these workplaces and their potential confounding effects cannot be excluded.

Various Occupations

In 1842, Domenico Antonio Rigoni-Stern reported an increased occurrence of breast cancer among male priests, but his findings have not been confirmed in more recent studies [248, 263–265]. A cohort study of men exposed to ethylene oxide (a carcinogen linked to breast cancer in women) did not report the occurrence of breast cancer in the studied workers [266]. A large study carried out in the Nordic countries reported higher than expected standardized incidence rates among journalists, cooks, stewards, printers, artistic workers, and building caretakers [129]; the authors underscore a common characteristic of these occupations—they usually include shift work, which has been associated with increased breast cancer risk in women [49]. A significantly increased risk of dying from breast cancer has been reported in policemen [267] and in professional firefighters [268, 269], but the incidence of breast cancer was not increased in the same cohort [270]. More recent studies of firefighters showed non-significant increases of incidence [269, 271] or of both mortality and incidence [271]. A European case-control study found a twofold increased risk, possibly due to petroleum and other organic solvents, especially among motor vehicle mechanics and painters. The risk was also increased for elevated exposure to alkylphenolic compounds, which are known endocrine-disrupting chemicals (OR 3.8, 95% CI 1.5–9.5) [272]. One study reported a relationship between carrier status for BRCA1/2 mutations and the occupation of truck driver in male breast cancer risk [273].

Conclusion

In conclusion, a handful of occupational exposures have been linked, with reasonable evidence, to an increased risk of breast cancer in women, but none have yet been linked to male breast cancer, although similarities between male and female breast cancers [274] suggest potential common causal factors. As the most common cancer among women, breast cancer represents an important global burden. There are no certainties regarding the importance of occupational or environmental exposures in the etiology and development of breast cancer, but the fact that only about 30% of the risk is explained by known risk factors [272] means that continuous research on the relationship between occupational exposures and breast cancer is warranted.

Breast cancer risk is influenced by a number of hormonal factors and may thus be influenced by endocrine-disrupting agents. These exposures may be mediated by environmental determinants, such as lifestyle (hormone therapy, diet, alcohol consumption, smoking), work schedule (e.g., shift work), and various medical conditions. As the mammary gland passes through certain critical periods during development, particularly in women, adverse effects may necessitate exposure to carcinogens during the short window of time when the structures of the gland are sensitive. These toxicants could lead to an increase in the incidence of mammary tumors if they alter circulating or tissue-localized hormone levels. This could happen through mechanisms such as hormonal disruption, mutations in critical genes caused by alkylating carcinogens during key stages of development, or influences on hormone transport and receptor expression patterns.

While there are many critical periods during mammary gland development and a large array of potential toxicants which may be able to act as cancer-causing agents under some conditions in experimental models, there are not many that have been shown to do so in humans. However, it is ultimately the observations in humans that will dictate if what is possible from a theoretical point of view can happen in real-life situations. The issues involved, such as the possible interactions between potential risk factors, including critical exposures before complete maturation of the breast gland, and the great diversity of breast cancer itself, are very complex and challenging to study in humans.

The absence of specific molecular markers and genetic susceptibility tests hampers early identification of

women and men who would be particularly susceptible to occupation-related breast cancer, but does not preclude preventive activities that are well known to the occupational hygiene field: anticipation of potential carcinogens, followed by their recognition, evaluation, communication, and control (elimination, substitution, and reduction of exposure) in the workplace.

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