

Review

Risk Factors for Breast Cancer, Including Occupational Exposures

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The knowledge on the etiology of breast cancer has advanced substantially in recent years, and several etiological factors are now firmly established. However, very few new discoveries have been made in relation to occupational risk factors. The International Agency for Research on Cancer has evaluated over 900 different exposures or agents to-date to determine whether they are carcinogenic to humans. These evaluations are published as a series of Monographs (www.iarc.fr). For breast cancer the following substances have been classified as "carcinogenic to humans" (Group 1): alcoholic beverages, exposure to diethylstilbestrol, estrogen-progestogen contraceptives, estrogen-progestogen hormone replacement therapy and exposure to X-radiation and gamma-radiation (in special populations such as atomic bomb survivors, medical patients, and in-utero exposure). Ethylene oxide is also classified as a Group 1 carcinogen, although the evidence for carcinogenicity in epidemiologic studies, and specifically for the human breast, is limited. The classification "probably carcinogenic to humans" (Group 2A) includes estrogen hormone replacement therapy, tobacco smoking, and shift work involving circadian disruption, including work as a flight attendant. If the association between shift work and breast cancer, the most common female cancer, is confirmed, shift work could become the leading cause of occupational cancer in women.

Key Words: Breast cancer, Occupational exposure, Risk factors, Shift work, Work schedule tolerance, Ethylene oxide

Descriptive Epidemiology - The Burden of Breast Cancer

Breast cancer is the most common malignancy affecting women worldwide. Indeed, incidence and mortality is elevated in all high- and low-and-middle-income countries, with 13.8 million new cases in 2008, corresponding to 23% of all cancers. The incidence varies greatly, being highest among White women in the United States, Australia and New Zealand, and Western and Northern Europe (incidence over 80/100,000); and lowest

among Asian women living in Asia and African women living in sub-Saharan Africa (incidence around or below 30/100,000). The wide range of female breast cancer mortality rates is less marked than variations in incidence, due to better survival in high-income countries compared to low-and-middle-income countries [1].

Time trends of the incidence of female breast cancer also vary markedly worldwide. In general these trends have been increasing over the last 5 decades, including in Asia and Europe. In the United States, following a period of steady increase, the trend has been declining over the last few years, probably due to the interruption of large-scale prescription of hormone replacement therapy in the last decade [2,3]. Mortality trends generally follow trends of invasive breast cancer incidence.

Male breast cancer is a rare disease with incidence rates varying from 5 to 15 per 1,000,000. Rates are higher in North America and Europe, and extremely low in Asian populations.

Received: January 13, 2011, **Accepted:** February 20, 2011

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Indeed, female breast cancer incidence is 100% higher than male breast cancer incidence, which represents less than 1% of the cancers affecting men worldwide [4]. Studies on the time trends of male breast cancer indicate that its incidence is increasing, mimicking that of female breast cancer, although on a much smaller scale [5,6].

General Epidemiology and Lifestyle-Related Risk Factors for Breast Cancer

Female breast cancer

Reproductive factors

Early age at menarche (≤ 11 vs. ≥ 15 years: 1.1-to-1.9-fold increased risk) [7,8], late age at menopause (≥ 55 vs. ≤ 45 years: 1.1-to-1.9-fold increased risk) [7,8], nulliparity (nulliparous vs. parous women: 1-to-2-fold increase in risk; inconclusive after 1 child) [9], and age at first full-term pregnancy above 30 years (1-to-2-fold increased risk compared to women with first full-term pregnancy before 20 years of age) [8-13], have all been consistently shown to be associated with increased female breast cancer risk, although results vary slightly between studies. There is a suggested protective effect of lactation (i.e., breastfeeding) against both pre and postmenopausal breast cancer (Relative risk (RR) 0.98, 95% CI 0.97-1.00 for ever vs. never, especially for long-term lactation at a young age) [14,15].

Use of exogenous hormones

According to the International Agency for Research on Cancer (IARC), in-utero exposure to diethylstilbestrol, i.e., when a pregnant woman uses the drug, increases a female child's risk of developing breast cancer [16,17].

Use of estrogen-progestogen contraceptives (RR-1.50 in particular among current vs. never users; increased risk for women with benign breast disease, women who used contraceptives in the peri- or postmenopausal period, or women who used contraceptives at < 20 years of age and/or before their first full-term pregnancy) [8,9], and use of estrogen-progestogen hormone replacement therapy (RR < 2 , in particular for women who took them for several years or in high doses, or women > 60 years old) increase breast cancer risk, while hormone replacement therapy with estrogen alone (without progestogen) is probably associated with an increased risk of developing female breast cancer [8,9,18-20].

Diet, body size, and physical activity

The World Cancer Research Fund (WCRF) [15] evaluated the available evidence in relation to diet, physical activity and body size in relation to female breast cancer risk. Similar evaluations

have been carried out earlier on and published in the IARC Handbooks of Cancer Prevention [21,22].

Overall, there is limited evidence suggesting that consumption of total fat is associated with postmenopausal breast cancer risk [15]. No other dietary factors have been compellingly linked to breast cancer risk either in pre or postmenopausal women [15,22].

There is consistent epidemiological evidence of a dose-response relationship, indicating that high body fatness probably protects against breast cancer risk among premenopausal women (RR 0.94, 95% CI 0.92-0.95 per 2 kg/m²), but the mechanistic evidence is speculative [15,21]. In contrast, there is consistent epidemiological evidence and a clear dose-response relationship, with robust evidence for mechanisms operating in humans, indicating that greater body adiposity is associated with postmenopausal breast cancer risk (RR 1.50, 95% CI 1.50-1.60 per 2 kg/m²) [15,21]. Abdominal fatness is associated with postmenopausal breast cancer risk (RR 1.19, 95% CI 1.10-1.28 for waist-to-hip ratio per 0.1 increment), as is adult weight gain (RR 1.05, 95% CI 1.04-1.07 per 5 kg gained), whereas high birth weight is associated with premenopausal breast cancer risk (RR 1.08, 95% CI 1.04-1.13) [15].

In respect to height, there is abundant prospective epidemiological evidence, which is generally consistent, of a clear dose-response relationship, and evidence for plausible mechanisms in humans (RR 1.03, 95% CI 1.01-1.04 per 5 cm increase). There is convincing evidence that factors that lead to greater adult attained height, or their consequences, are associated with risk of both pre and postmenopausal breast cancer [15].

As for physical activity, the evidence from prospective studies is inconsistent, but in general suggests that physical activity protects against premenopausal breast cancer. There is also ample evidence from prospective studies showing a lower risk of postmenopausal breast cancer with higher levels of physical activity, though there is some heterogeneity in the dose-response relationship (RR = 0.97, 95% CI 0.95-0.99 per 7 metabolic equivalents (METs)-hours per week (METs describe intensity relative to a person's resting metabolic rate). There is little evidence on frequency, duration, or intensity of activity, but evidence is robust for mechanisms operating in humans. In summary, physical activity probably protects against postmenopausal breast cancer [15,21].

Alcoholic beverages

In agreement with the IARC evaluations, which considered alcohol as "carcinogenic" (Group 1) to the human breast [23], the WCRF also classified the consumption of alcoholic beverages

ages as “convincingly increasing risk” for both pre and postmenopausal breast cancer, irrespective of the type of alcoholic beverage (i.e., no difference between wine, beer, liquor, etc.). A dose-response relationship is apparent: all studies able to analyze dose-response found an increase in risk with increasing alcohol consumption (RR 1.10, 95% CI 1.06-1.14 per 10 g/day). In addition no threshold was identified, and there is robust evidence for mechanisms operating in humans [15].

Tobacco smoking

There is limited evidence with inconsistent results suggesting that tobacco smoking is associated with female breast cancer risk, in particular when smoking starts early, and before a woman's first full-term pregnancy (before the breast tissue matures) and continues for several decades [23,24].

Ionizing radiation

The IARC classified X-radiation and gamma-radiation as carcinogenic agents with sufficient evidence in humans in relation with female breast cancer risk (2-4-fold increase in risk for high doses compared to minimal exposure; risk may be higher when exposure occurs from puberty to child bearing years, when breast tissue is proliferating) [9,25]. However, the evidence on which the evaluation was based emanates from 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) [26]. A recent study from Korea [27] does not suggest an increase in breast cancer risk among women with occupational exposure to ionizing radiation.

Electromagnetic fields

Recent studies, including meta and pooled analyses, do not support the hypothesis that exposure to electromagnetic fields increases female breast cancer risk [28-34]. Goodman et al. reviewed how spurious confounding could have biased risk estimates in early studies [35].

Family history of breast cancer and genetic susceptibility

Family history of breast cancer increases female breast cancer risk substantially depending on the age at diagnosis of the affected relatives, the age of the woman and the number of affected relatives, and the generational distance of the relatives to the women (1st degree relative with premenopausal bilateral breast cancer > 4-fold increase in risk (Yes vs. No); one 1st degree relative with any form of breast cancer 2-4-fold increase in risk (Yes vs. No); two 1st degree relatives with any form of breast cancer RR > 4-fold increase in risk) [7-13,36,37]. In recent years sev-

eral large-scale genetic studies have been carried out. Besides mutations in high-penetrance genes, such as BRCA1, BRCA2, TP53, PTEN, STK11, and CDH1, variations in moderate- and low-penetrance genes have been identified as increasing female breast cancer risk to various degrees (RRs range from 1.00 to 1.40) [37]. However, only a minority of familial relative risk, defined as the ratio of the risk of disease for a relative of an affected individual to that of the general population, is explained by genetic variants discovered to-date [37].

Male breast cancer

Following Bernardino Ramazzini's report of an increased occurrence of breast cancer among nuns more than 300 years ago, Domenico Antonio Rigoni-Stern made the same observation among male priests in 1842 [38,39]. One and a half centuries later, the etiology of male breast cancer is still rather poorly understood. This may be due to the relative rarity of male breast cancer incidence, 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 increased risk of male breast cancer in several studies. In particular, genetic susceptibilities related to male breast cancer include mutations in BRCA1, BRCA2 and possibly other genes (Cyp17, AR, CHEK2). Klinefelter's syndrome and a few other rare disorders also seem to be associated with risk. Similarly, associations with education, religion, marital status, clinical disorders related to hormonal imbalance (infertility, testicular injury, liver lesions, and gynecomastia), and estrogen intake are controversial. Among the environmental 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 are equivocal. There are insufficient studies to allow any conclusions about the effect of exposure to ionizing radiation or electromagnetic fields on male breast cancer [4,39-48].

Occupational exposures and breast cancer risk

According to the IARC, there are no agents with sufficient evidence in humans that can be classified as “carcinogenic to humans” (Group 1) to the human breast which could be considered directly occupationally related. Although ethylene oxide is classified as a Group 1 carcinogen, the evidence for carcinogenicity in epidemiologic studies, and specifically for the human breast, is limited. Shift work that involves circadian disruption is classified as “probably carcinogenic to humans” (Group 2A) based on epidemiological evidence on breast cancer occurrence in occupationally exposed groups [49].

Ethylene oxide

Human exposure to ethylene oxide occurs mainly during the sterilization of medical equipment, although ethylene oxide is also used for the production of some chemicals. Although the epidemiological evidence was deemed “limited”, the IARC Working Group classified ethylene oxide as a Group 1 carcinogen, taking into consideration the studies on mechanisms of carcinogenicity and studies in animal models [50,51]. The IARC evaluation was based mainly on an internal analysis in a study of 7,500 women [52], which showed a significant dose-response relationship between ethylene oxide exposure and female breast cancer incidence, with the risk doubling among women with higher cumulative exposures. However, an increase in female breast cancer risk has not been consistently reported in other studies [50,51].

Shift work involving circadian disruption

The IARC evaluation [49,53] of female breast cancer was based on relatively few studies in humans (only 9, 6 of which found an association). These studies used very different definitions of shift work, and different methodologies: two were prospective cohort studies [54,55], one was a nationwide census-based cohort study [56], three were nested case-control studies [57-59], and two were retrospective case-control studies [60,61]. These studies basically included only Caucasian postmenopausal women. The main occupational categories included in these studies were nurses, marine telephone operators and female flight attendants. There were several methodological weaknesses in these studies, particularly relating to the definition of shift work [49,62,63].

Clearly more studies in humans are needed to allow a thorough understanding of the possible association between shift work and breast cancer risk, and to assess the details of a possible relationship, which could lead to preventive measures. These studies should have strong methodological planning and execution, and should include different ethnic groups as well as premenopausal women. Moreover, they should include several industry groups that use shift work, and pay particular attention to the classification and measurement of patterns of shift work. When reaching conclusions about potential carcinogenicity to humans, the IARC evaluation [49] carefully considered the biological mechanisms of carcinogenicity as well as the sufficient evidence in experimental animals regarding the carcinogenicity of light during night time (biological night).

A recent study reported that of all female breast cancers in the United Kingdom, 4.6% could be attributed to shift work. The study further estimated that the nearly 2,000 registered breast cancer cases due to shift work corresponded to 54.0% of

all registered occupation-related female cancer cases [64]. Given the large proportion of women working irregular hours and doing shift work worldwide, as well as the very high incidence rates of female breast cancer in general, more research is clearly needed both to confirm the association between shift work and breast cancer, as well as to answer several questions related to the patterns of the association. Future research should investigate if different patterns of shift work are similarly harmful; if exposure to shift work in a particular period of life (for example before first full-term pregnancy) is especially harmful; if there are interactions between shift work with other lifestyle factors, such as alcohol consumption, physical activity, or body size and shape; if women who does shift work should be screened more frequently than the general population; if there is a dose-response relationship in terms of number of years (or numbers of days/nights per month) spent doing shift work and breast cancer risk, and, if so, if policy makers should regulate the maximum amount of years women are allowed to work in shifts [65].

Other inconclusive exposures

Most of the studies on occupation or occupational exposures and breast cancer risk were carried out using self-administered questionnaires or registry linkages to job titles, and derived occupational exposures via job exposure matrixes.

Several epidemiological studies have been published reporting the association between specific occupational categories or job titles in relation to female breast cancer risk. The methodology in these studies varies widely, as do the results [66-68]. Confounding due to lifestyle factors was not always taken into account, making the overall pattern of association rather unclear. For example, exposures to solvents [69], manufacturing of chemicals where known or potential carcinogens are used such as vinyl chloride, 1,3-butadiene, benzene, nitrosamines, and other solvents [70]; service industries including the health care industry [70]; and studies among religious workers [71], military personnel, dentists, journalists, physicians, administrators and artistic workers [68], laboratory technicians, telephone and telegraph operators, leather and fur processors, glass manufacturing workers, inspectors, analysts [72], teachers [73,74], librarians and counselors [74] have all been reported to be associated to female breast cancer risk in at least one study.

Studies among air crews, particularly flight attendants, were also evaluated by the IARC [49]. These studies tended to show an increase in female breast cancer risk. They do, however present some methodological problems, such as lack of controlling for the possible confounding effect of occupation-related lifestyle factors also known to be associated with breast

cancer risk (such as alcohol consumption, lower parity and late age at first full-term pregnancy). The possibility of breast cancer over-diagnosis due to more frequent mammography screening than the general population also cannot be ruled out. Moreover, an air crew is exposed to cosmic radiation, the effect of which has been suggested to increase female breast cancer risk [49].

Regarding male breast cancer, the largest study published so far on specific job titles was carried out in the Nordic countries, and reported a higher than expected standardized incidence rate among journalists, cooks, stewards, printers, artistic workers and building caretakers. Intriguingly, the common characteristic of these professions is that they are usually performed in shifts [68]. A recent case-control study in Europe found increased male breast cancer risk, especially among motor vehicle mechanics (OR 2.10, 95% CI 1.00-4.40), with suspect exposures to organic petroleum solvents, petrol and polycyclic aromatic hydrocarbons [75]. The male breast cancer risk for exposure to alkylphenolic compounds, known endocrine disrupting chemicals, also increased (OR 3.80, 95% CI 1.50-9.50) [75].

Breast Cancer and Occupation - Final Considerations

So far the literature is not clear about the specific clinical and pathological features of breast cancer possibly related to occupation, nor are there any molecular markers that can be used specifically to identify occupational exposures related to breast cancer. Likewise, there are no genetic susceptibility tests that can be used to screen women particularly susceptible to occupational exposure-related breast cancer.

Breast cancer risk is obviously influenced by a number of hormonal factors and may be influenced by endocrine-disrupting agents. These exposures may be mediated by environmental determinants, such as lifestyle (hormonal therapies, diet, alcohol consumption, and smoking), work schedule (e.g., shift work), and various medical conditions. It is interesting to note that while there are multiple toxicants and hormone-mimicking compounds which can alter mammary gland development in rodents, and even cause cancer in some experimental rodent models, there are not many that have been shown to do so in humans. This may be due to the lack of ability to measure the exposures in the right time frame. As the mammary gland has certain critical periods during development, adverse effects may necessitate the presence of 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 can happen through mechanisms such as hormonal disrupting agents, agents with hormonal influences, alkylating carcinogens capable of causing mutations in critical genes during key stages of development, or influences on hormone transport and receptor expression patterns.

While there are many critical periods during the 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, it is ultimately the observations in humans that will dictate if what is possible from a theoretical point of view can be realized in real-life conditions. The issues involved, such as the possible interactions between potential risk factors, including critical exposures early in life and during breast gland development, and the great diversity of breast cancer itself, are very complex and challenging to study in humans.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

The authors would like to thank Dr Kurt Straif, International Agency for Research on Cancer, Lyon, France, Professor Tar-Ching Aw, Department of Community Medicine, United Arab Emirates University, Al Ain, United Arab Emirates, and Dr France Labrèche, Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montreal, Quebec, Canada, for providing materials for the manuscript; and Ms Trudy Perdrix-Thoma for manuscript editing and language review. No financial support was received for this work.

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