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REVIEW

Incidence and Mortality in Breast Cancer – Are We Doing Better?

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ABSTRACT

Breast cancer in women is a major health problem: each year, more than 1 million new cases are diagnosed worldwide. One in 8 women will be confronted with breast cancer during her lifetime. The objective of this review is to present an overview of the epidemiology of breast cancer i.e. the incidence and mortality rate of breast cancer. In other words, how often does breast cancer occur and how often it is lethal? The geographical variation and the evolution over time are discussed - are we now doing better than 10 or 20 years ago? Possible ways of preventing breast cancer are also presented.

KEY WORDS: *Breast cancer, Epidemiology, Incidence, Mortality, Time trends*

INTRODUCTION

Breast cancer in women is a major health problem. Each year, more than 1 million new cases are diagnosed worldwide (www.WHO.int). In the United States, the lifetime probability of being diagnosed with an invasive breast cancer is 12%; this means that 1 in 8 women will be confronted with breast cancer during her lifetime (1). The three most commonly diagnosed types of cancer in women, in 2008, are breast, lung and bronchus, and colorectal cancers accounting for about 50% of estimated cancer cases in women. In the United States, among the three, breast cancer is the most frequent and accounts for 26% of all new cancer cases among women (1). This review presents an overview of the worldwide incidence of breast cancer and of its evolution over time. Breast cancer mortality rates are also discussed and possible ways of preventing breast cancer are presented.

DEFINITIONS AND DATA SOURCES

Breast cancer incidence is the number of new breast cancer cases in a specific time period per 100 000 subjects, usually expressed as the number of new cases per 100 000 women in a specific year. Similarly, the breast cancer mortality rate is the rate of deaths per 100 000 women in a specific year. Both the incidence and mortality rates are standardized, i.e. they are age-adjusted and calculated for a reference population in order to improve comparability of incidence and mortality rates between different countries.

There are two important epidemiological databases: SEER (Surveillance, Epidemiology and End Results, http://seer.cancer.gov) and CI5 (Cancer Incidence in 5 continents, http://www-dep.iarc.fr). The former one presents data for the United States while the aim of the latter one is to give an overview worldwide. Both SEER

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data and CI5 data do not cover the whole population, because not all countries participate to the data collection and the population in a country is often not completely covered by the registration systems. The SEER contains data from 1973-2005, while the CI5 contains data from 1960-2002. In contrast to CI5, SEER also provides mortality rate estimates.

BREAST CANCER INCIDENCE WORDLWIDE IN 2002

A large geographical variation in breast cancer incidence was evident in the year 2002 (see Figure 1). The incidence rates were high in the more developed areas such as the United States, Canada, Australia and in some European countries as the United Kingdom and France; all had estimated incidence rates of more than 81.7 new cases per 100,000 women. Breast cancer incidence was low in Asia and Africa with an incidence rate below 42.8 per 100,000 women. Half of the new breast cancer cases in 2002 were in industrialized countries—about 361,000 in Europe (27.3% of cancers in women) and 230,000 in North America (31.3%) (2). To some extent, the geographical differences are, undoubtedly, spurious: countries with a screening program as the United States, France, the United Kingdom have a higher reported incidence rate and countries with an incomplete recording have a false lower reported breast cancer incidence rate. Genetic background factors as the BRCA1 and BRCA2 gene mutation may account for up to 10% of breast cancer cases in developed countries (3), but their prevalence in the population is too low to explain much of the international variation. The international variation is mainly due to the exposure to known or suspected risk factors related to lifestyle or environment (2;4;5). This is evident from migrants studies, which show quite clearly that incidence rises after migration from low to high incidence countries, particularly if the move takes place at young ages (6;7). For example, the incidence rates for Japanese women living in San Francisco or Los Angeles are twice those of Japanese women in Japan. Apparently, breast cancer risk among migrants approaches the risk among native populations and it is affected by the time since migration: recent Asian migrants have a lower risk than migrants who have lived in the Unites States for more than 20 years.

EVOLUTION OF BREAST CANCER INCIDENCE OVER TIME

Table 1 presents the evolution of breast cancer incidence over time for selected countries.

Until the year 2002, incidence rates of breast cancer were increasing in most countries, and the largest changes were usually seen in countries with a previously low incidence rate (8). Between 1990 and 2002, there has been an overall increase in incidence rates of about 0.5% annually. However, cancer registries in China were recording annual increases in incidence of 3% to 4%, and increases were not much lower in those elsewhere in eastern Asia, (9-11).

Main risk factors for breast cancer are related to the female hormones estrogen and progesterone produced in the body or given as hormone replacement therapy. Changes in reproductive factors (age at menarche, age at menopause, number of children), use of postmenopausal hormone replacement therapy, and lifestyle factors (body size/obesity, alcohol consumption, physical activity) have contributed to the breast cancer increase over the last 20 years in developed countries (12-14). Such changes to the environment or society influence a specific generation or birth cohort and are therefore called cohort effects. Each successive generation (or birth cohort) is influenced by intervening changes in environment and society and the incidence increases when the oldest generation is replaced by the most recent one who was more exposed to these risk factors. Cohort effects result in a slow increase of the incidence. Period effects on the other hand are responsible for sudden increases/decreases in breast cancer incidence. For example, the introduction of a screening program in a country results in an increase of the reported incidence due to the fact that breast cancer tumours are detected earlier than before. Other examples of period effects are new diagnostic techniques, a carcinogen that acts in the late stage of tumorigenesis, or an improvement in the completeness of data registration (15). A period effect influences all generations in the same way.

Figure 2 shows the breast cancer incidence rate by age group. In the less developed countries with a low incidence of breast cancer, the incidence rate is stable or even slightly decreasing after menopause. This is in contrast to more developed countries with a high incidence of breast cancer, where the incidence rate still increases even after the menopause. The increase is slower than before the menopause, which can be explained by the decreasing oestrogen level in postmenopausal patients. The difference in the two age-specific patterns, between high and low incidence countries, has been attributed to increasing incidence among young birth cohorts in low-risk countries due to environmental and lifestyle changes in these countries, but it could also indicate that oestrogen receptor positive tumours are more prevalent in the high incidence countries, e.g. the United States (16).

BREAST CANCER INCIDENCE DECREASING SINCE 2003?

In 2002, a report of the randomized trial of the Women's Health Initiative was published, reporting a significant increase in breast cancer associated with the use of estrogen-progestin combination therapy (17). The year after, in 2003, breast cancer incidence decreased in the United Stated by 6.7% compared to the rate in 2002 (18). In 2004, the incidence rate stabilized at

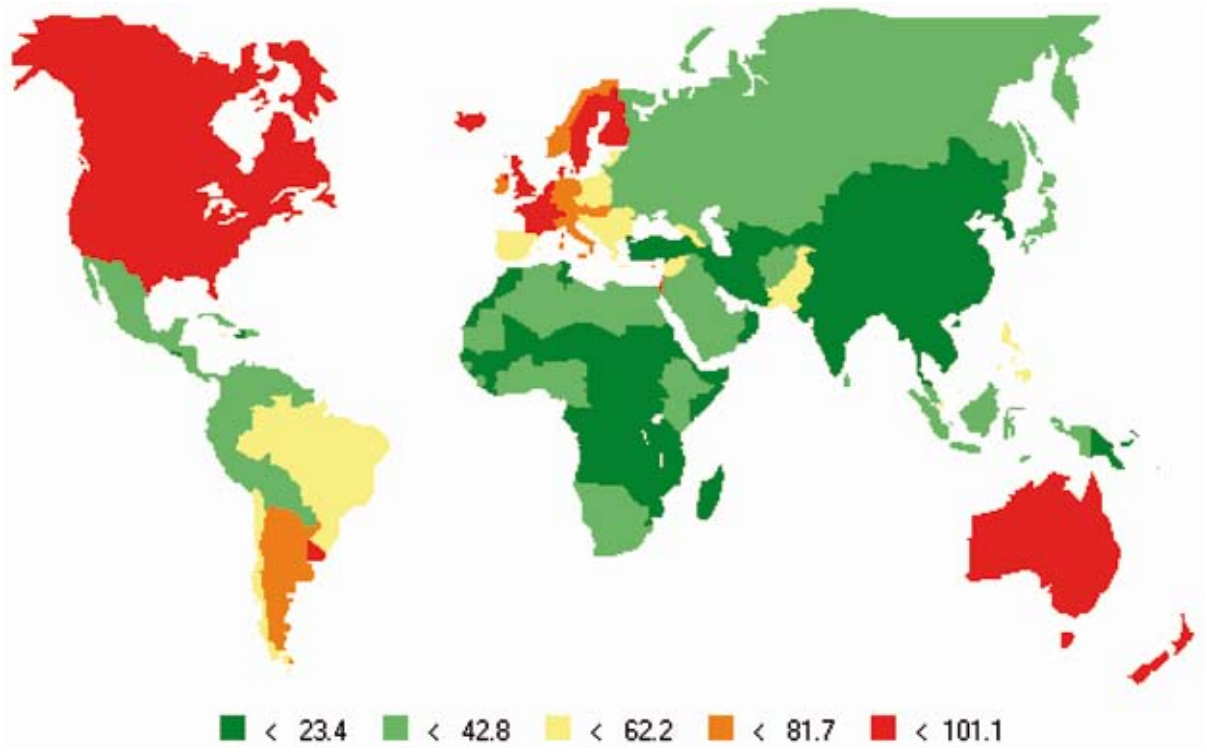

FIGURE 1. Age-standardized (world population) breast cancer incidence rate per 100,000 women (International Agency for Reseach on Cancer (IARC), estimates for the year 2002).

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	1973-1977	1978-1982	1983-1987	1988-1992	1993-1997	1998-2002
North Amercia, SEER, white	74.96	73.40	85.92	91.09	92.55	97.1
China, Hong Kong	29.69	28.41	32.35	34.05	36.41	41.3
Japan, Nagasaki City	18.76	22.82	27.80	32.83	36.95	38.1
Denmark	61.00	64.19	68.83	75.87	80.02	83.7
Norway	49.03	50.88	54.13	55.80	67.07	71.0
Italy, Parma Province		60.30	64.50	74.98	84.08	96.3
Australia, New South Wales	53.25	53.11	57.75	67.24	80.73	83.1
New Zealand			64.47	75.37	75.77	86.5

the level of 2003. Changes in reproductive factors, in the use of hormone replacement therapy (HRT) during menopause, in mammographic screening, in environmental exposures, and in diet could have been an explanation for the sudden decrease. Although screening mammography decreased by 3.2% between 2000 and 2003 (18), the decrease was probably too small to explain the change in the breast cancer incidence rate. The most likely explanation is the substantial change in the use of HRT between 2002 and 2003. By the end of 2002, the use of HRT was decreased in the United States by 38%, approximately 20 million prescriptions less in 2003 compared to 2002 (19;20). The decrease of HRT as the main reason for the sudden decrease in breast cancer incidence was confirmed by the observation of a larger decrease in estrogen receptor positive tumours compared to estrogen receptor negative tumours: the incidence rate in women aged 50 to 69 decreased between the year 2001 and 2004 by 14.7% in estrogen receptor positive tumours, while only a decline of 1.7% was observed in

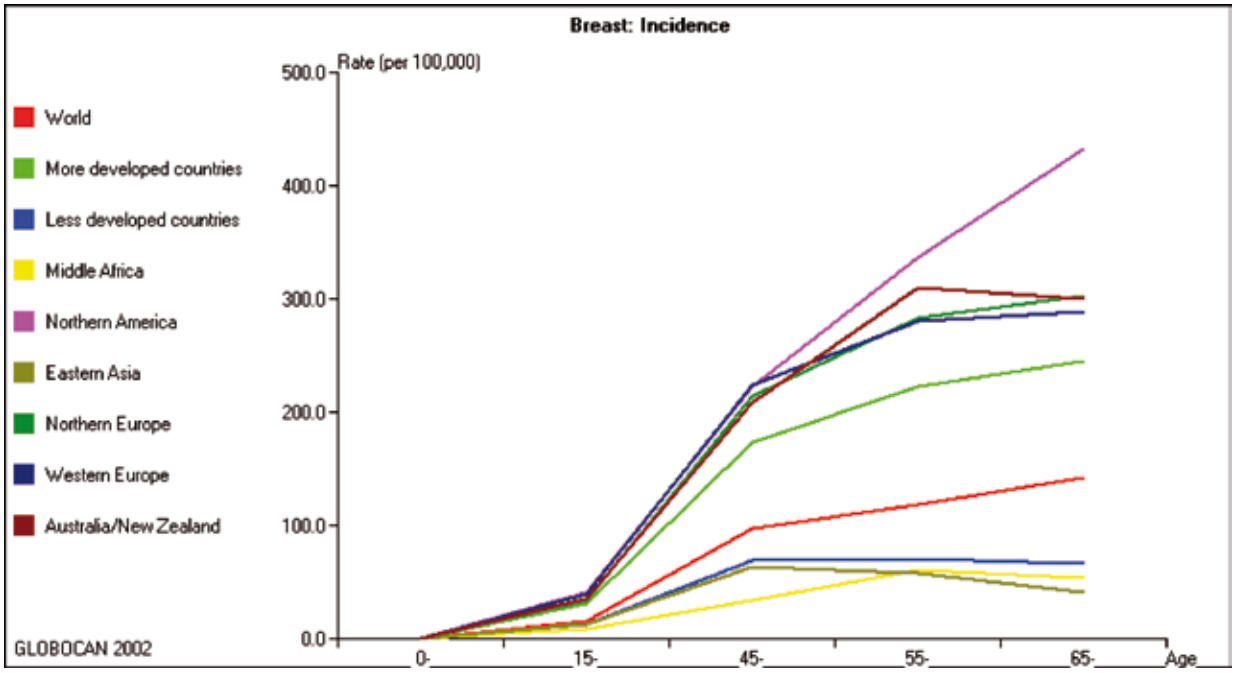

FIGURE 2. Breast cancer incidence rate per 100,000 women by age group (0-14, 15-44, 45-54, 55-64, 65+) (International Agency for Reseach on Cancer (IARC), estimates for the year 2002).

estrogen receptor negative tumours (18). A similar decreasing trend in breast cancer incidence after a decrease in the HRT has been observed in Australia (21), Canada (22), Germany (23) and France (24). A small impact of the decrease in the use of HRT on breast cancer incidence is expected in countries with a low HRT use such as Spain, the Netherlands or Italy (5% to 8%), in contrast to countries with a high HRT use such as Belgium or France (32% to 38%) (25;26).

BREAST CANCER MORTALITY WORLDWIDE IN 2002

Breast cancer is still the leading cause of cancer mortality in women: 1 in 7 female cancer deaths is due to breast cancer (2). Figure 3 shows the geographical variation in breast cancer mortality. Overall, the differences are less pronounced than those of incidence. Countries with high incidence of breast cancer like Canada and the United Kingdom is logical to figure with high breast cancer mortality rates: age-standardized mortality rate above 29.6 per 100,000 women. Unfortunately, some countries in Africa with low incidence rates have also a high breast cancer mortality. More than 55% of breast-cancer–related deaths, occur in low- and middle-income countries (www.iarc.fr). Little attention is currently paid to breast care in these less developed countries due to other health priorities. Asian countries have the lowest breast cancer mortality rates: less than 10.5 per 100,000 women.

BREAST CANCER MORTALITY BY RACE AND ETHNICITY

Mortality rates differ by race and ethnicity. Although breast cancer mortality decreases overall in the United States since 1990, this is particularly true in white women. African-American women are more likely to be diagnosed with poor prognosis breast cancers (late stage, large size, lymph node positive, estrogen receptor negative) compared to white American women; Asian/Pacific Island women tend to have breast cancers of better prognosis (early stage, small size, lymph node negative, estrogen receptor positive) (27-30). A possible explanation might be a difference in attending screening mammography resulting in differences in tumor stage and size at diagnosis (31;32). Socioeconomic factors and consequently inadequate access to appropriate treatment might also play an important role (30;33;34).

BREAST CANCER MORTALITY DECREASE IN THE LAST 20 YEARS DUE TO MAMMOGRAPHY SCREENING AND ADJUVANT THERAPY

In the United States, breast cancer mortality rate was 49.7 per 100,000, but dropped to 38.0 by the year 2000: a decrease of 24% (35). Similar decreases were observed in other countries

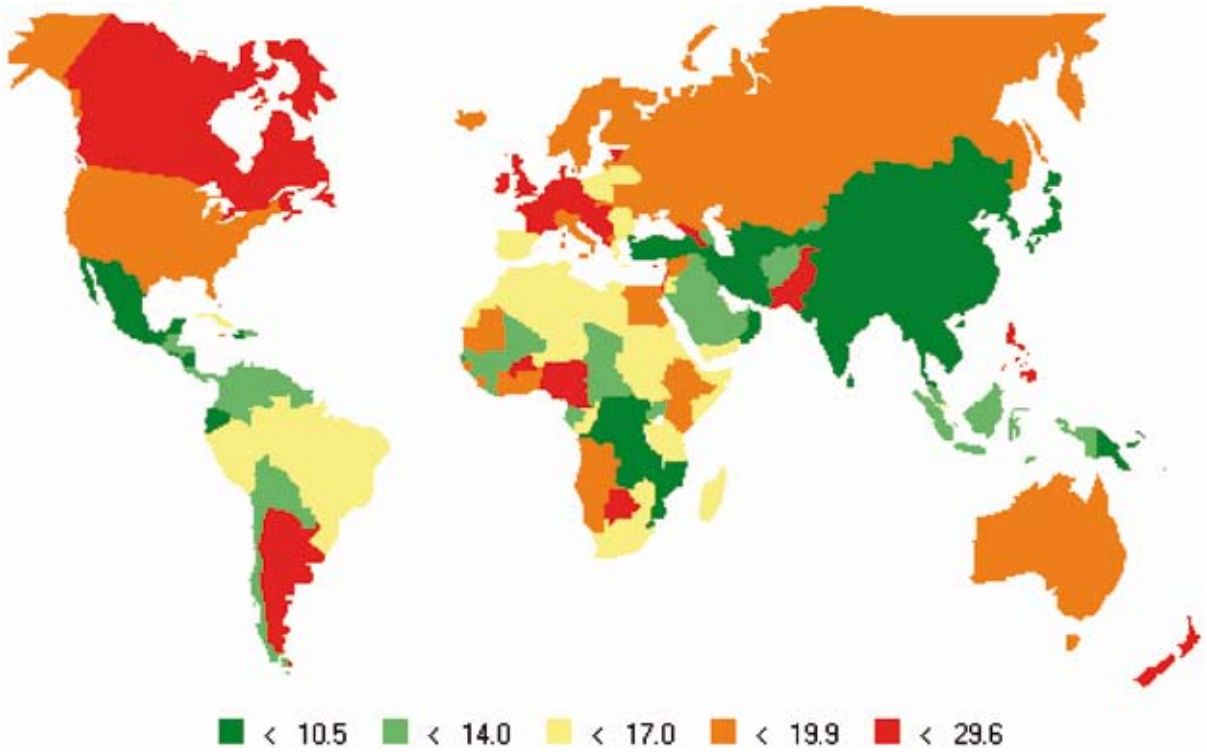

FIGURE 3. Age-standardized (world population) breast cancer mortality rate per 100,000 women (International Agency for Research on Cancer (IARC), estimates for the year 2002).

(8). A plausible explanation for these decreases is the early detection of breast cancer tumours by mammography screening. This has been investigated in randomized controlled trials with two arms: an intervention group undergoing annual mammography screening and a control group receiving the usual medical care. In women aged 50 or older it has been shown that screening reduces breast cancer mortality by approximately 25% (36) but there is less evidence that screening is efficient for women younger than 50 years: a small, but statistically non significant reduction in breast cancer mortality at 10-year follow-up due to mammography screening was shown (37).

Between 1985 and 2000, the use of mammography screening increased highly. While 75% of the women did not undergo screening in the year 1985, this figure decreased to less than 20% in the year 2000 (38). Not only the use of mammography screening has changed over time, but adjuvant treatments have also improved. Nowadays, the combination of chemotherapy and endocrine therapy is much more frequently applied than 20 years ago (39). Berry et al. (40) used modeling techniques to assess the contributions of screening mammography and adjuvant therapy to the reduction in breast cancer mortality, in the United States, from 1975 till 2000. Seven groups of investigators developed, independently of each other, a model of breast cancer incidence and mortality. In the seven models, the proportion of the total reduction in breast cancer mortality rate from 1975 to 2000 attributed to screening varied from 28% to 65% (median 46%); the proportion attributed to adjuvant therapy varied from 35% to 72% (median 54%).

BREAST CANCER PREVENTION?

Most of the known breast cancer risk factors are not preventable since they are related to the reproductive cycle and inheritance (BRCA1 and BRCA2 gene mutation) (2;4;5;41). Unfortunately, only half of the breast cancer cases can be explained by the currently identifiable risk factors (6). It is hypothesized that non-estrogenic environmental carcinogens (e.g., excess ionizing radiation, human-made chemicals, or biological agents such as viruses), which may cause genetic alterations, may also play an important role in the development of breast cancer. But it is difficult to provide the evidence because the majority of environmental exposure has mainly effects on the development of breast cancer through interactions (environment-environment, environment-genetic predisposition and environment-time of exposure): there is a greater vulnerability during in utero period, early woman's life, or during early breasts development (41;42). Moreover, potential environmental carcinogens are widely prevalent with the result that it is difficult to find non-exposed women. And finally, breast cancer is not one entity but at least two (pre and post- menopausal) or according to ER/PR receptors status

up to six subgroups with different etiologic factors causally related to the disease (4).

Until recently, there was no way to prevent breast cancer. The primary message of health care awareness programs was that early detection offered the best protection against breast cancer, so-called secondary prevention (43). Nowadays, also primary prevention is investigated. In women with a high risk of developing breast cancer, chemoprevention could be considered. Large trials have shown that selective estrogen receptor modulators (SERMs) reduce the risk of invasive breast cancer by about 50% (44). These SERMs reduce the risk of estrogen receptor positive cancers, but not of estrogen receptor negative cancers (45-47). Reported adverse events of SERMs are an increase in thromboembolic disease and the development of endometrial cancer. Data on the efficacy of aromatase inhibitors for adjuvant therapy in breast cancer have shown that these agents possess significant chemopreventive effectiveness (48;49). Their value in chemoprevention is limited by potential adverse effects such as bone mineral loss with an increased risk of fractures (50). In selected very high risk patients i.e. those with BRCA1 and BRCA2 gene mutation, prophylactic bilateral mastectomy or prophylactic bilateral oophorectomy might be reasonably considered (43).

Use of shorter duration HRT or better targeted might also prevent development of some estrogen positive breast cancers (18).

CONCLUDING DISCUSSION

A large geographical variation in breast cancer incidence is present. The environment has undoubtly a major impact on the risk of developing breast cancer. This means that where you are living really matters. But within a specific country, the incidence rate varies with race and ethnicity: breast cancer is more common in African American women than it is among Asian Americans. Breast cancer incidence was increasing year by year for a long period of time. But in 2003, a sudden drop in the incidence was noticed in the United States and shortly after, similar results were reported in Australia, Canada, Germany and France. The most plausible explanation for this drop is the decline in the use of HRT in the preceeding years as the drop is only seen in estrogen receptor positive tumours.

Future will reveal if the incidence rates will decrease further, become stable or increase again; in the latter case, this would mean that HRT has only accelerated the induction of breast cancer but these cases would be unavoidable. In countries with a low use of HRT, no decrease in the incidence rates has been reported so far. In some European countries as Spain and Italy, HRT is less frequently used and its use is of shorter duration compared with the United States.

Breast cancer mortality rates are declining in the last 20 years thanks to mammography screening and adjuvant therapy. Further improvements are expected due to the application of neoadjuvant therapy and the use of Trastuzumab in case of Her2 positive tumours, ...

Are we doing better? The answer is Yes!

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