1. BREAST CANCER

1.1 The global burden of breast cancer: incidence, mortality, survival, and prevalence

1.1.1 Global burden

Breast cancer is the most commonly diagnosed cancer in women and the most common cause of cancer death in women worldwide. Globally, it is estimated that in 2012 there were 1.68 million new diagnoses (25% of all new cancer diagnoses in women) and 0.52 million deaths (15% of all cancer deaths in women) from invasive breast cancer, corresponding to age-standardized incidence and mortality rates of 43.3 and 12.9 per 100 000, respectively (Ferlay et al., 2013, 2014a). Unless otherwise stated, all further references in Section 1 to breast cancer refer to invasive breast cancer in women.

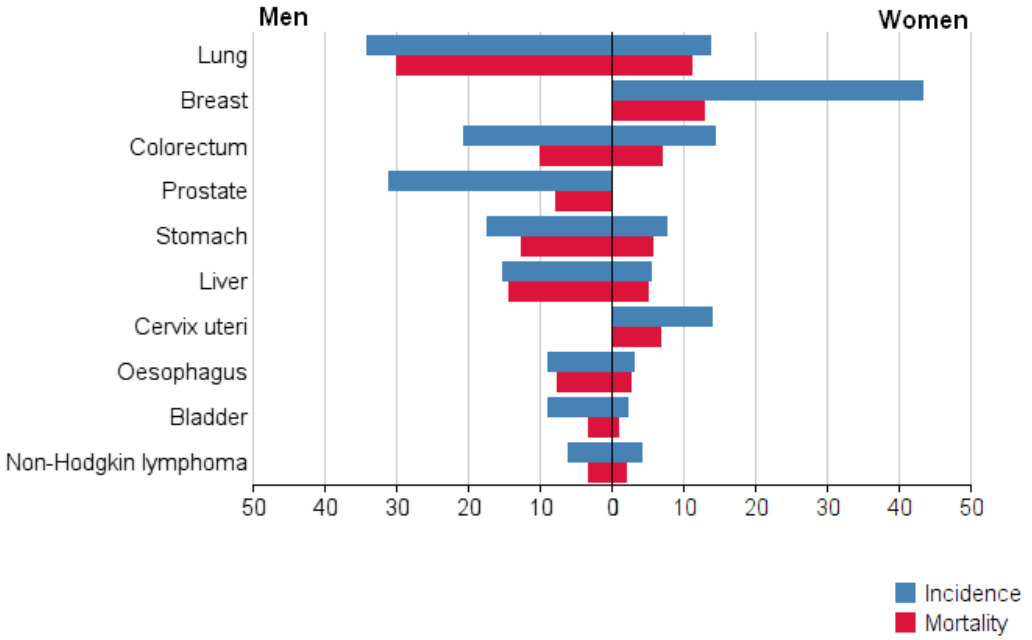
Before age 75 years, 1 in 22 women will be diagnosed with breast cancer and 1 in 73 women will die from breast cancer, worldwide. Breast cancer in men is a very rare disease, with incidence rates of about 1% of those for women and with little evidence for changes over time (Ly et al., 2013). Male breast cancer is not considered further in this Handbook.

The estimated global incidence of breast cancer in 2012 was 3 times that of the next most common types of cancer in women: cancers of the colorectum (0.61 million new cases, 14.3 per 100 000), lung (0.58 million, 13.6 per 100 000), and cervix (0.53 million, 14.0 per 100 000) (Fig. 1.1; Ferlay et al., 2013, 2014a). Mortality from breast cancer was broadly similar to that from lung cancer in women (0.49 million deaths, 11.1 per 100 000) and substantially greater than that from the next most common causes of cancer death in women: cancers of the colorectum (0.32 million, 6.9 per 100 000) and cervix (0.27 million, 6.8 per 100 000) (Fig. 1.1; Ferlay et al., 2013, 2014a).

About one quarter of the breast cancer cases and deaths in the world in 2012 occurred in Europe, and approximately 15% of the cases and 9% of the deaths occurred in North America (Fig. 1.2; Ferlay et al., 2013, 2014a). However, the largest contributor to the global burden was East and Central Asia, where 36.3% of the cases and 41.5% of the deaths occurred. Within East and Central Asia, China and India contributed substantially to the global burden, with 11.2% and 8.6% of the cases, respectively, and 9.2% and 13.5% of the deaths, respectively. Latin America and the Caribbean contributed 9.1% of the cases and 8.3% of the deaths, whereas sub-Saharan Africa was estimated to contribute 5.6% of the cases and 9.1% of the deaths (Fig. 1.2).

For women diagnosed in 2005–2009, 5-year net survival rates from breast cancer generally exceeded 80% in Europe (excluding eastern Europe), in Australia and New Zealand, and in some countries in South America and Asia, and reached almost 90% in the USA (Allemani et al., 2014). High 10-year relative survival rates have also been reported in the more-developed regions of the world, such as 71.0% in Europe (Fig. 1.3; Allemani et al., 2013) and 82.7% in the

Fig. 1.1 Estimated age-standardized (World) cancer incidence and mortality rates (ASR) per 100 000, for 10 major sites, in men and women, 2012



From GLOBOCAN 2012 (Ferlay et al., 2013).
Male breast cancer rates not available.

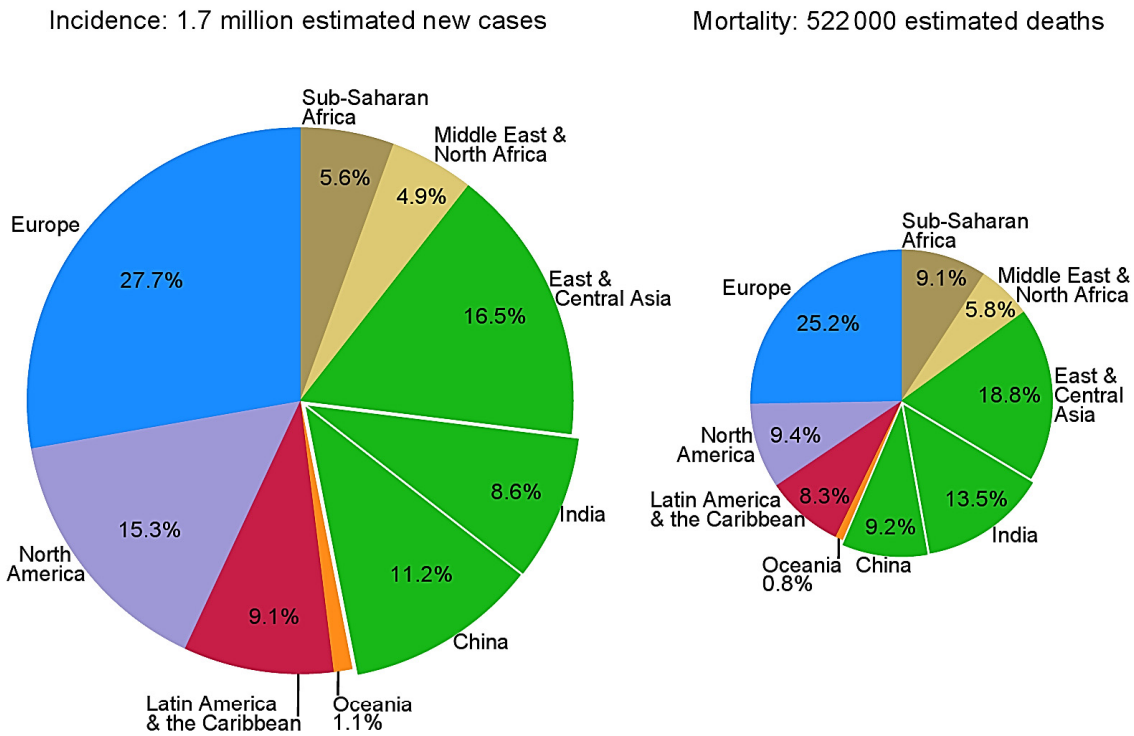
USA (SEER, 2014a). A combination of this level of survival with high incidence rates results in a high global prevalence of breast cancer. Thus, in 2012 there were an estimated 6.3 million women alive who had had a diagnosis of breast cancer in the previous 5 years (Ferlay et al., 2013). This represents more than one third (36.4%) of all 5-year prevalent cancer cases in women and almost one fifth (19.2%) of those in both sexes combined. There are many more women living with a history of breast cancer than there are people living with a history of any other type of cancer (excluding non-melanoma skin cancer); the next highest estimated 5-year prevalence rates are for prostate cancer (3.9 million) and colorectal cancer (3.5 million in both sexes combined) (Fig. 1.4; Ferlay et al., 2013).

Similarly to most cancer types, both incidence and mortality rates of breast cancer increase with increasing age (Fig. 1.5), although (in the absence of screening) not as rapidly as for most other cancers; the majority of breast cancer cases and deaths occur in women older than 50 years. Of the worldwide burden of 1.68 million incident cases in 2012, 0.55 million (33%) were estimated to occur in women younger than 50 years, 0.91 million (54%) in women aged 50–74 years, and 0.22 million (13%) in women aged 75 years and older. Of the 0.52 million deaths in 2012, 0.13 million (25%) were estimated to occur in women younger than 50 years, 0.27 million (52%) in women aged 50–74 years, and 0.12 million (23%) in women aged 75 years and older (Ferlay et al., 2013).

1.1.2 International variation

Breast cancer was the most frequently diagnosed cancer among women in 140 (76%) of the 184 major countries included in the GLOBOCAN database (Ferlay et al., 2013). In most of the remaining countries, breast cancer was the

Fig. 1.2 Estimated global number of new cases and deaths with proportions by major world regions for breast cancer in women, 2012



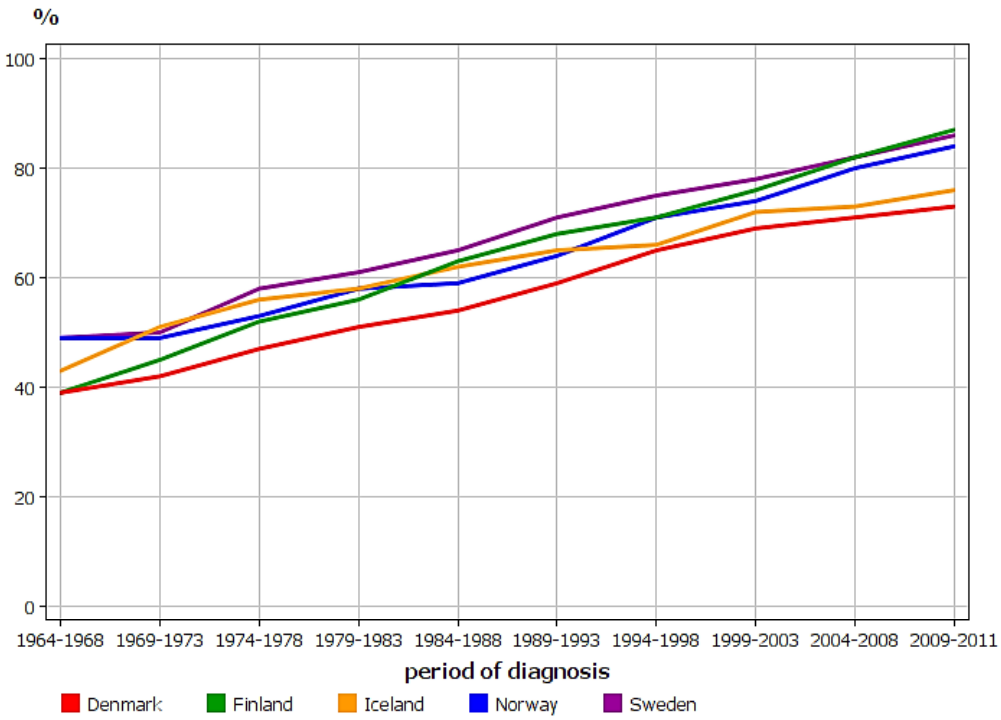
From GLOBOCAN 2012 (Ferlay et al., 2013).

second most frequently diagnosed cancer, after cervical cancer. However, there are substantial regional variations in breast cancer incidence rates worldwide (Fig. 1.6). In 2012, more than a 3-fold variation in the age-standardized breast cancer incidence rates was recorded between North America and western Europe (rates > 90 per 100 000) and Central Africa and East and South-Central Asia (rates < 30 per 100 000) (Fig. 1.7).

At the country level, data from Volume X of *Cancer Incidence in Five Continents* for 2003–2007 showed an approximately 5-fold variation in risk, which can reach 10-fold at the extremes (Fig. 1.8; Forman et al., 2013). In populations with incidence rates higher than 90 per 100 000, such as USA SEER, US Non-Hispanic White (92.5), the Netherlands (93.5), and Belgium (110.8), the risk of a woman being diagnosed with breast cancer before age 75 years is about 1 in 10, whereas in populations with rates lower than 20 per 100 000, such as Thailand, Khon Kaen (18.6), Malawi, Blantyre (14.3), and India, Dindigul (12.0), this risk is less than 1 in 50. Between these extremes, a gradient in risk is observed, including within the same continent. For example, within Europe, rates per 100 000 in Latvia (48.4), Bulgaria (52.7), and Spain, Granada (54.8) were less than half those in Belgium (110.8); similarly, within South America, rates in Ecuador, Quito (38.0) were about half those in Argentina, Córdoba (78.1).

The general shape of the age–incidence curve (Fig. 1.5) – a rapid rate of increase before age 50 years and a general flattening in later years – is observed in many populations. However, there is some variation between countries in the shape after age 50 years. Some populations show a plateau (e.g. Tunisia, North), whereas others show a decline

Fig. 1.3 10-Year age-standardized relative survival (age at diagnosis, 0–89 years) for breast cancer in Nordic countries, 1964–2011

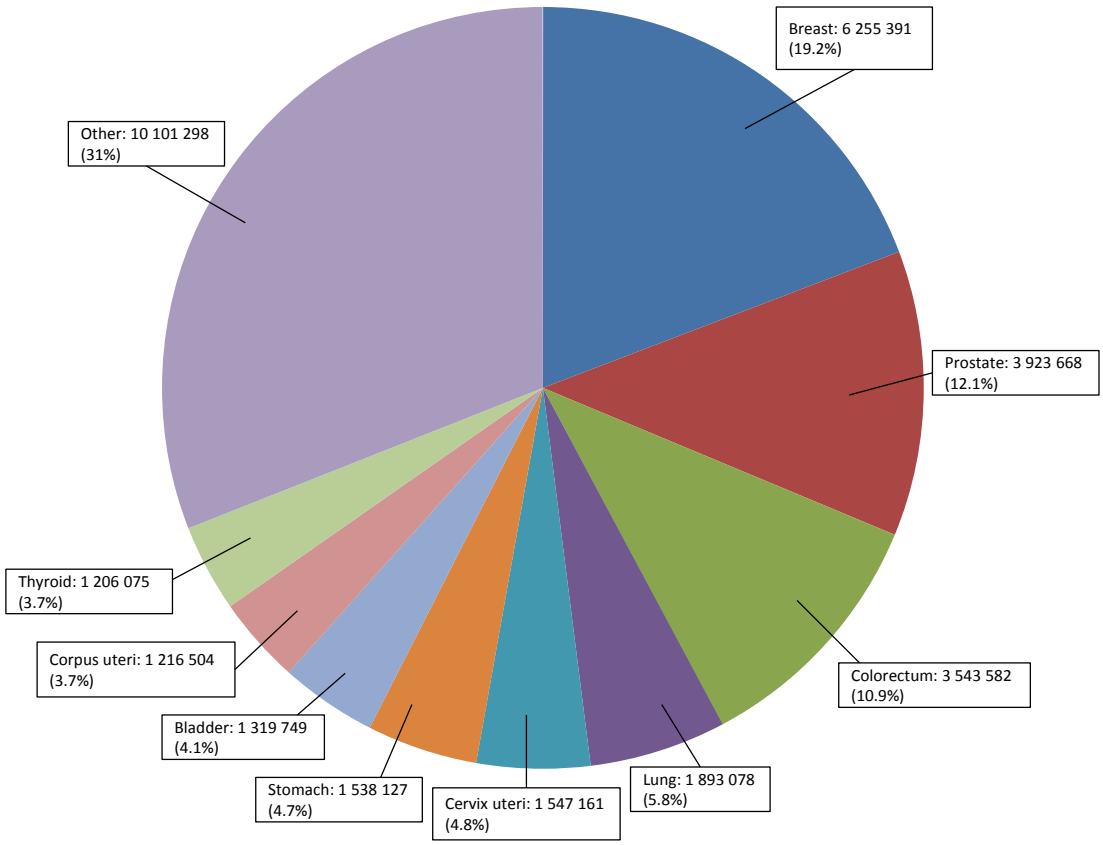


From Engholm et al. (2014). NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.0 (17.12.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from: http://www.ancr.nu, accessed 5 December 2014.

(e.g. Thailand, Khon Kaen), which may be due to an increasing risk of occurrence in successive generations rather than to a real decline in risk with age (Moolgavkar et al., 1979). In less-developed countries, which are characterized by both a generally young age structure and a flat age–incidence curve, the increasing occurrence translates to a considerably lower mean age at diagnosis compared with more-developed countries. Although it has been suggested that this indicates different biological characteristics of breast cancer in women in less-developed countries, the evidence does not generally support such an interpretation (McCormack et al., 2013). Nevertheless, the existing variations in mean age at diagnosis can have important implications for early detection strategies (Harford, 2011; Corbex et al., 2012).

International variation in breast cancer mortality is also evident, although considerably less so than for incidence (Fig. 1.9). Regions with the highest age-standardized mortality rates (> 17 per 100 000) were Melanesia, North Africa, and West Africa; the lowest rates (< 10 per 100 000) were seen in East Asia and Central America (Fig. 1.10). At the country level, selected results from the World Health Organization (WHO) Mortality Database for the period 2003–2007 showed the highest age-standardized mortality rates (~20 per 100 000) in Denmark (21.6), the Netherlands (20.8), Argentina (19.3), and the United Kingdom (19.3); the lowest rates (≤ 6 per 100 000) were seen in Ecuador (6.0), Egypt (5.6), and the Republic of Korea (4.9) (Fig. 1.11; WHO, 2014).

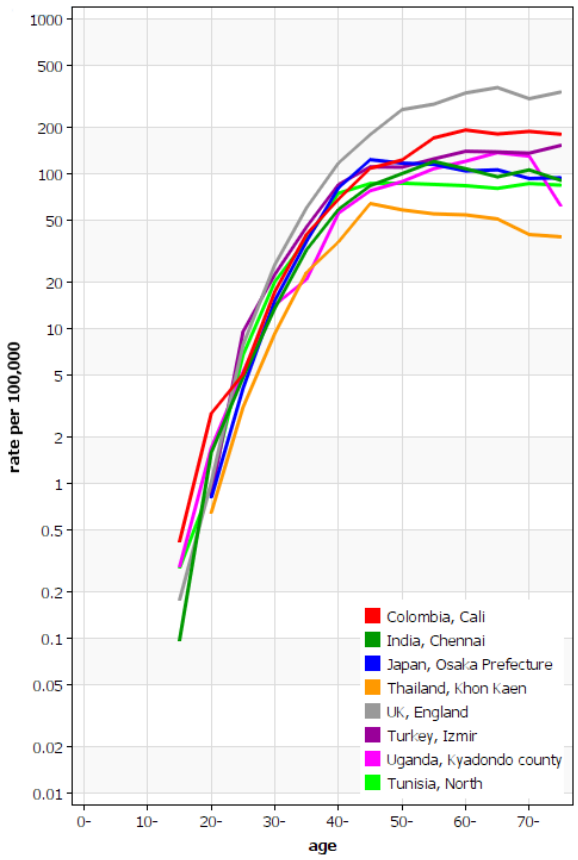
Fig. 1.4 Estimated global number of 5-year prevalent cancer cases in the adult population (total: 32 544 633 for all sites combined) with proportions by major sites for both sexes, 2012



From GLOBOCAN 2012 (Ferlay et al., 2013).
Excluding non-melanoma skin cancer.

This observed smaller variation in mortality rates than in incidence rates is mainly a consequence of the relatively improved survival and lower case fatality rates that are seen in high-incidence, high-income countries and are not generally seen in lower-incidence, lower-income countries. Thus, as stated above, whereas the 5-year survival rate is usually more than 80% in high-income countries, it is about 60% in countries such as Algeria and India (Allemani et al., 2014). Within Europe, 5-year survival ranges from 71% in Latvia to 87% in Finland (Allemani et al., 2014), and 10-year survival ranges from 54% in eastern Europe to 75% in northern Europe (Allemani et al., 2013). In another international comparative study, of women mainly diagnosed in the mid-1990s, the 5-year relative survival rate varied from 82% in China to 47% in the Philippines, 46% in Uganda, and 12% in The Gambia (Sankaranarayanan et al., 2010). Lower relative survival rates are explained largely by lower proportions of women presenting with localized disease, within both high-resource settings (Walters et al., 2013a) and low-resource settings (Sankaranarayanan et al., 2010). Comparable differences can also be observed within countries, among different socioeconomic, racial, or ethnic groups. For example, within the USA in 2011, White women had a slightly higher age-standardized breast cancer incidence rate compared with Black women (127.2 vs 122.7 per 100 000, respectively) and a lower

Fig. 1.5 Age-specific incidence rates per 100 000 for breast cancer in women in selected cancer registry populations, 2003–2007



From *Cancer Incidence in Five Continents*, Volume X (Forman et al., 2013).

age-standardized mortality rate (20.9 vs 30.2 per 100 000, respectively) (SEER, 2014a). This finding reflects substantially different survival rates (90.0% vs 77.3% at 5 years and 84.3% vs 68.4% at 10 years, respectively) (SEER, 2014a).

1.1.3 Incidence and mortality in relation to level of development

Table 1.1 compares incidence and mortality estimates for breast cancer among countries aggregated according to four different levels of the Human Development Index (HDI) in 2012 (UNDP, 2012). The HDI is a composite index based on life expectancy at birth, adult literacy rate, education enrolment rate, and gross domestic product (GDP) per capita. In 2012, almost half of the global breast cancer burden (45%; 0.75 million cases) and one third of the breast cancer deaths (33%; 0.17 million) occurred in countries with very high HDI. A substantial number of cases (29%; 0.49 million) and deaths (35%; 0.18 million) occurred in countries with medium HDI, although this includes the highly populous countries of China and India. Whereas age-standardized incidence rates broadly increased with increasing HDI (from 32.6 per 100 000 in countries with low HDI to 79.0 per 100 000 in countries with very high HDI), mortality rates had no equivalent relationship with HDI and were highest in countries with low HDI (17.0 per 100 000), largely in sub-Saharan Africa. The net effect of this is that the ratio of the number of deaths to the number of cases (a crude indicator of survival), by HDI category, increases from 23% for very high HDI to 36% for high HDI, 37% for medium HDI, and 47% for low HDI. Breast cancer was the most commonly diagnosed cancer within all four HDI levels, the most common cause of cancer death within the very high and low HDI levels, and the second most common cause of cancer death (after lung cancer) within the high and medium HDI levels.

1.1.4 Time trends

Figs. 1.11–1.14 show the annual age-standardized breast cancer incidence and mortality trends by year, for all ages and for the age group 50–74 years (which is the age group most likely to have received breast cancer screening), for several representative populations.

The incidence graphs make use of data provided by population-based cancer registries and published in successive volumes of *Cancer Incidence in Five Continents* (Ferlay et al., 2014b). Registries have been selected that represent different world regions and for which

Table 1.1 Breast cancer in women: estimated annual number of cases, age-standardized incidence rate, number of deaths, age-standardized mortality rate, and number of deaths as a percentage of number of cases, by HDI ranking and for the world, in 2012

Level of HDI[a]	Number of cases (millions)	ASIR per 100 000	Number of deaths (millions)	ASMR per 100 000	Number of deaths/ number of cases (%)
Very high	0.75	79.0	0.17	14.1	23
High	0.28	45.2	0.10	14.6	36
Medium	0.49	26.5	0.18	9.8	37
Low	0.15	32.6	0.07	17.0	47
World	**1.68**	**43.3**	**0.52**	**12.9**	**31**

[a] The HDI is a composite index based on life expectancy at birth, adult literacy rate, education enrolment rate, and gross domestic product (GDP) per capita. Predefined categories of the distribution of HDI by country have been used: low (HDI < 0.55), medium (0.55 ≤ HDI < 0.7), high (0.7 ≤ HDI < 0.8), and very high (HDI ≥ 0.8) (UNDP, 2012).
ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; HDI, Human Development Index.
Derived from GLOBOCAN 2012 (Ferlay et al., 2013).

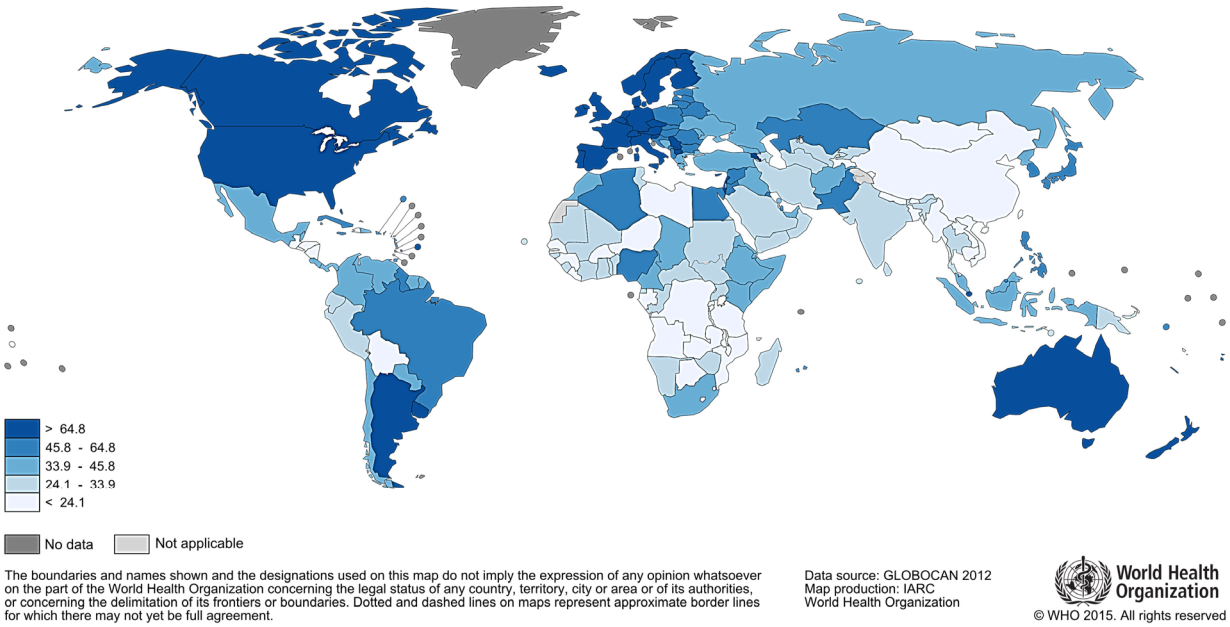
comparatively long time series were available. In general, all-age incidence rates, although variable between populations, have consistently increased over the five decades considered, although without ever exceeding 100 per 100 000. There are signs of the rate of increase slowing down and the incidence rates reaching a plateau since the late 1990s, noticeably in the higher-incidence countries (Australia, Denmark, Finland, Israel, the United Kingdom, and the USA), whereas the lower-incidence countries tend to show ongoing increases and less of an evident plateau effect in the most recent 10 years (Fig. 1.11). A detailed study from India shows that the recent increase in female breast cancer incidence rates is one of the most important secular trends in the overall pattern of cancer applying to both urban and rural populations (Badwe et al., 2014). Incidence trends for the age group 50–74 years are broadly similar to those for all ages, with some evidence of a downtrend beginning in the late 1990s to early 2000s in the higher-incidence countries (Fig. 1.12).

The mortality data are from the WHO Mortality Database (WHO, 2014), and countries were selected according to the same criteria as for the incidence graphs (different world regions and comparatively long time series). All-age mortality rates increased modestly in most populations until the mid-1980s and have since declined in the higher-mortality countries (Fig. 1.13). Data from Japan singularly show a consistent increase since the mid-1960s. The highest mortality rates were observed in Denmark and the United Kingdom, where they approached 30 per 100 000 in the early 1980s (Fig. 1.13). Mortality trends for the age group 50–74 years are, overall, similar to those for all ages, with a decline in mortality rates over the most recent two decades especially notable in the higher-mortality countries (Fig. 1.14). The start of the period of decline in mortality rates varies between countries (the mid-1980s in the United Kingdom and the USA, the early to mid-1990s in Australia, Denmark, and Israel, and the early 2000s in Estonia).

1.1.5 Time trends by age

Using the same sources as for Figs. 1.11–1.14, a more detailed consideration of time trends for selected individual countries is provided in Fig. 1.15 and Fig. 1.16. Each graph shows time trends for age-standardized breast cancer incidence and mortality, within the age groups 25–49 years, 50–74 years, and 75 years and older. Where possible, these figures are based entirely on national data, but for some (Japan

Fig. 1.6 Global distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000 for breast cancer in women, 2012



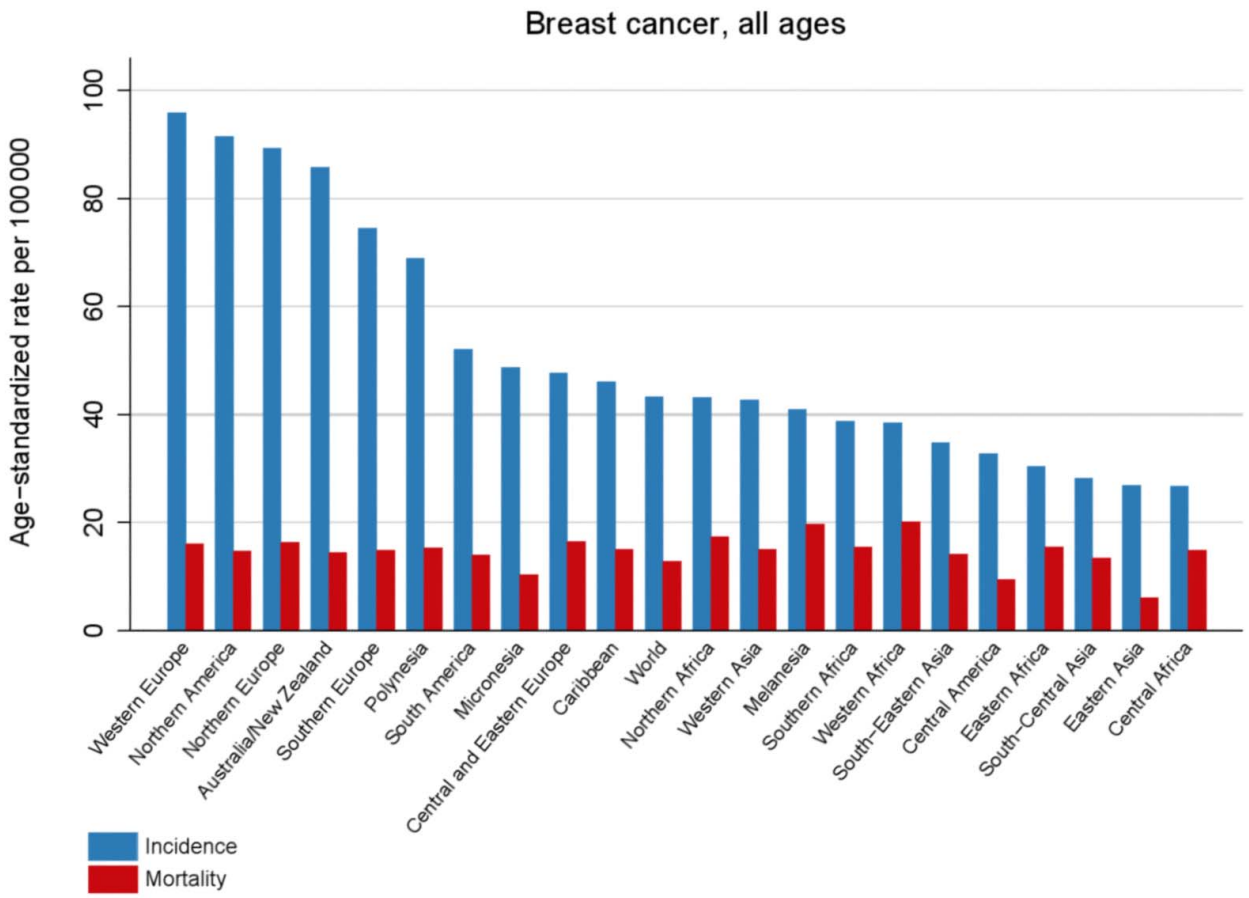
From GLOBOCAN 2012 (Ferlay et al., 2013).

and the USA), regional cancer registry data for incidence and national data for mortality were used. For each country, an indication is provided (by shading) of the period within which population-based breast screening programmes were operational within the age group offered screening (usually the age group 50–69 years) (see Section 3.2). It should be noted that before the implementation of a programme, opportunistic screening would usually have been taking place for subsets of the population, and that after a screening service became operational, full roll-out to eligible women may have taken at least 10 years. In addition, due to the relatively high breast cancer survival rates, several years are required before the impact of a service screening programme becomes discernible in routine cancer statistics. Thus, the time trends shown here are presented to provide context for the incidence and mortality trends, but they do not allow conclusions to be drawn about the impact of breast cancer screening programmes (see Section 5.2.1c for further discussion).

Fig. 1.15 shows trends in countries where national or regional mammography screening services were introduced during the 1980s or the 1990s. An increase in incidence rates in the two younger age groups (25–49 years and 50–74 years) was evident before the introduction of screening; in general, this increase continued after the introduction of screening, but the rate of increase was greater in the age group 50–74 years. Such an increase was generally less evident in the age group 75 years and older, and in Sweden and New Zealand it was hardly evident at all. The introduction of screening tended to coincide with (or to just follow) the beginning of a period of decline in mortality rates in all three age groups. In Denmark, no such decline was apparent in the age group 75 years and older.

Fig. 1.16 shows trends in countries where screening services were introduced after 2000

Fig. 1.7 Estimated age-standardized incidence and mortality rates (ASR) per 100 000 for breast cancer in women, for major world regions, 2012

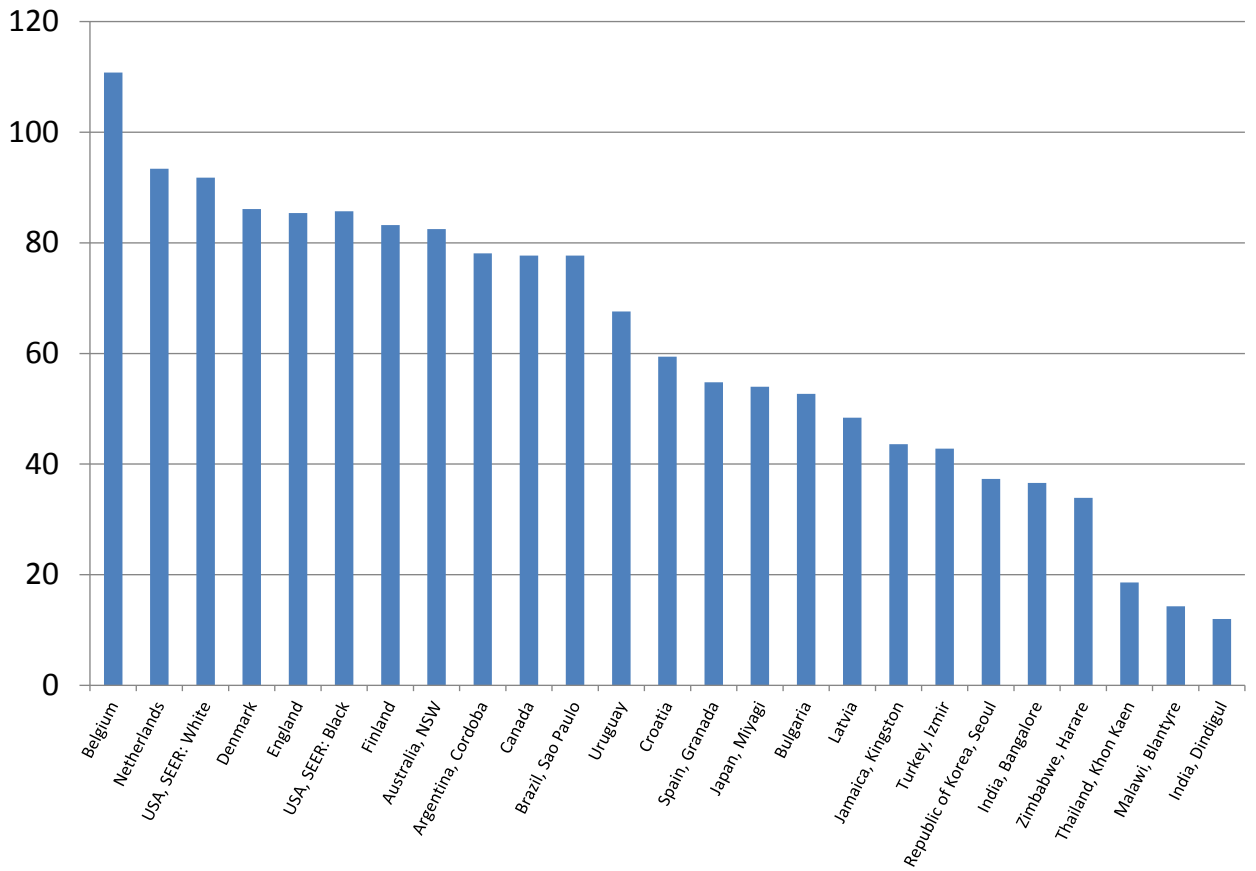


From GLOBOCAN 2012 (Ferlay et al., 2013).

or have never been introduced. In all of these countries, incidence rates increased consistently over time in each of the three age groups. In the Czech Republic, Ireland, Slovakia, and Slovenia, mortality rates declined in the two younger age groups; this decline started before the onset of screening and was less apparent in the age group 75 years and older. In Bulgaria, Costa Rica, Japan, and Singapore, there is evidence of a decline in mortality rates, although this is confined to the age group 25–49 years. In Bulgaria, Japan, and Singapore, mortality rates continued to increase in the two older age groups, whereas in Costa Rica mortality rates increased in the age group 75 years and older but remained stable for the age group 50–74 years.

Overall, Fig. 1.15 and Fig. 1.16 show a general increase in incidence and a general decrease in mortality in all three age groups starting before the introduction of screening programmes. In those countries where screening services were introduced in the 1980s or the 1990s (Fig. 1.15), the increase in incidence was most rapid in the age group 50–74 years. In Bulgaria, Costa Rica, Japan, and Singapore, no decrease in mortality rates was seen in women older than 50 years. It is noteworthy that breast cancer incidence and mortality rates have been changing in different

Fig. 1.8 Age-standardized incidence rates (ASR) per 100 000 for breast cancer in women, in selected cancer registry populations, 2003–2007



Created by the Working Group using data from Forman et al. (2013).

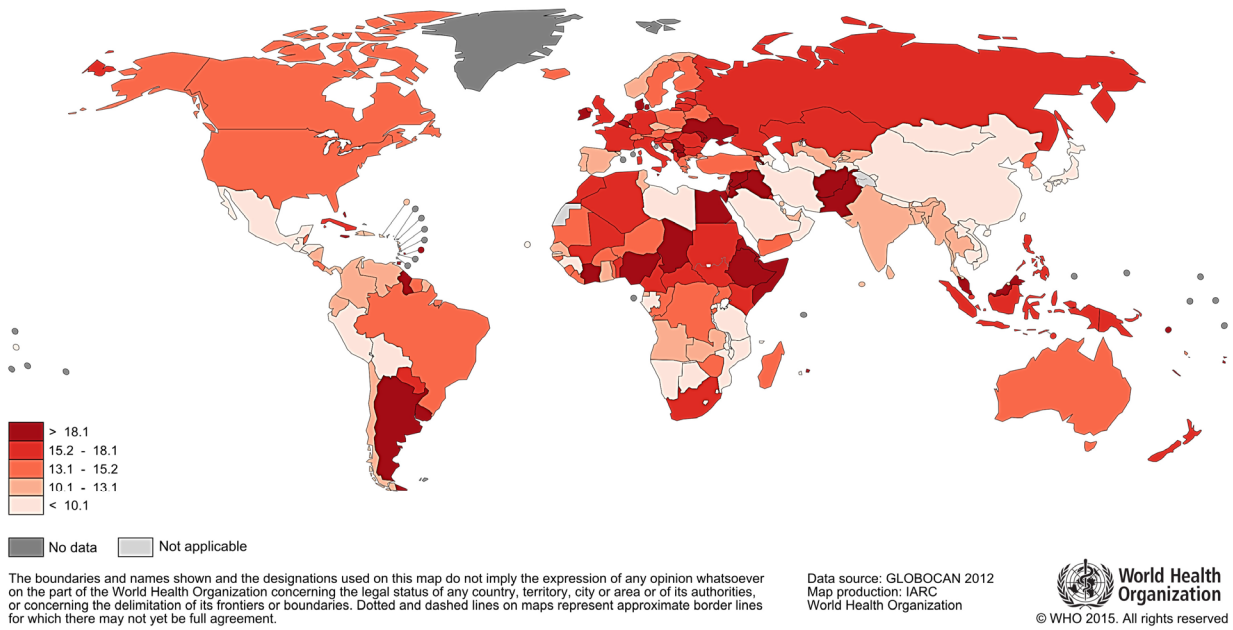
ways during the recent decades, during which national mammography screening programmes have been established.

1.1.6 Projection to 2025

Table 1.2 shows the estimated global burden of incidence and mortality from breast cancer in 2012 projected to 2025, overall and by HDI category. Overall, a 30% increase in the estimated number of new cases (from 1.68 million to 2.19 million) and a 33% increase in the number of deaths (from 0.52 million to 0.69 million) is projected by 2025. Because of differential population growth levels among different HDI categories, the numbers of cases and deaths are projected to increase most rapidly in countries with low HDI. The number of deaths is also projected to increase more rapidly in countries with medium HDI.

It is important to note that these projections only take account of global demographic changes in population structure and growth based on United Nations estimates (United Nations, 2012). The risk of developing or of dying from breast cancer is assumed to remain constant at 2012 levels, and no allowance is made for changes in screening intensity. At least in more-developed countries, the projections in Table 1.2 may well underestimate incidence and overestimate mortality.

Fig. 1.9 Global distribution of estimated age-standardized mortality rates (ASR) per 100 000 for breast cancer in women, 2012



From GLOBOCAN 2012 (Ferlay et al., 2013).

1.2 Classification and natural history

Several guidelines on breast disease classification and on diagnostic criteria with respect to mammography screening are available (NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012; Table 1.3). This section highlights areas of relevance to the different forms of breast screening, i.e. all forms of imaging and of palpation. The section on benign breast disease (Section 1.2.1) describes common breast conditions that may be indistinguishable from invasive ones by palpation and/or imaging, and lesions that may exhibit microcalcifications similar to those seen in some forms of carcinoma in situ. The section on breast carcinoma in situ (Section 1.2.2) provides an overview of those lesions that are found at a higher frequency in mammography screen-detected breast cancers than in symptomatic breast cancers, and may thus contribute to overdiagnosis and overtreatment. The section on invasive breast carcinoma (Section 1.2.3) provides a concise summary of the detailed classification and current understanding of the underlying molecular genetic basis (provided in detail elsewhere; Dixon & Sainsbury, 1998; Lakhani et al., 2012). Section 1.2.4 provides an overview of hereditary and somatic mutations in breast cancers.

1.2.1 Benign breast disease

Benign breast conditions constitute a heterogeneous group of lesions, presenting a wide range of symptoms and leading to mammographic abnormalities or incidentally detected microscopic findings. The frequency of presentation of symptomatic palpable benign lesions and invasive lesions differs according to a woman's age. Fibroadenomas are most frequently observed in women younger than 20 years, representing more than 50% of presentations of women in this age group. Women aged 20–50 years generally present with localized benign lesions, and

Table 1.2 Breast cancer in women: estimated annual number of cases and deaths, by HDI ranking and for the world, 2012 and 2025 projection

Level of HDI[a]	Number of cases (millions)			Number of deaths (millions)		
	2012	2025	Increase (%)	2012	2025	Increase (%)
Very high	0.75	0.87	16	0.17	0.21	24
High	0.28	0.37	32	0.10	0.13	30
Medium	0.49	0.64	31	0.18	0.25	39
Low	0.15	0.22	47	0.07	0.11	57
World	**1.68**	**2.19**	**30**	**0.52**	**0.69**	**33**

[a] The HDI is a composite index based on life expectancy at birth, adult literacy rate, education enrolment rate, and gross domestic product (GDP) per capita. Predefined categories of the distribution of HDI by country have been used: low (HDI < 0.55), medium (0.55 ≤ HDI < 0.7), high (0.7 ≤ HDI < 0.8), and very high (HDI ≥ 0.8) (UNDP, 2012).
HDI, Human Development Index.
Derived from GLOBOCAN 2012 (Ferlay et al., 2013).
The 2025 projection is based on demographic change and constant risk.

only about 20% have invasive breast cancer. In contrast, more than 40% of women aged 51–60 years and more than 80% of women aged 60 years and older present with invasive lesions (Lakhani et al., 2012). A similar age-related pattern of palpable symptomatic lesions is usually detected by breast self-examination (BSE). Most benign breast lesions have no known relationship to the development of breast cancer and merit treatment by excision only if causing symptoms, otherwise requiring no intervention.

(a) Histopathological classification of benign breast disease and molecular genetic characteristics

The current WHO classification of tumours of the breast (Lakhani et al., 2012) categorizes benign breast lesions under the categories shown in Table 1.3. Alternative systems of classification essentially use identical terminology and definitions but classify according to specific entity, associations, or clinical relevance. The European Union and the United Kingdom guidelines for classification of common benign breast lesions in the context of breast screening (NHSBSP, 2005; Perry et al., 2006) use the definitions detailed below.

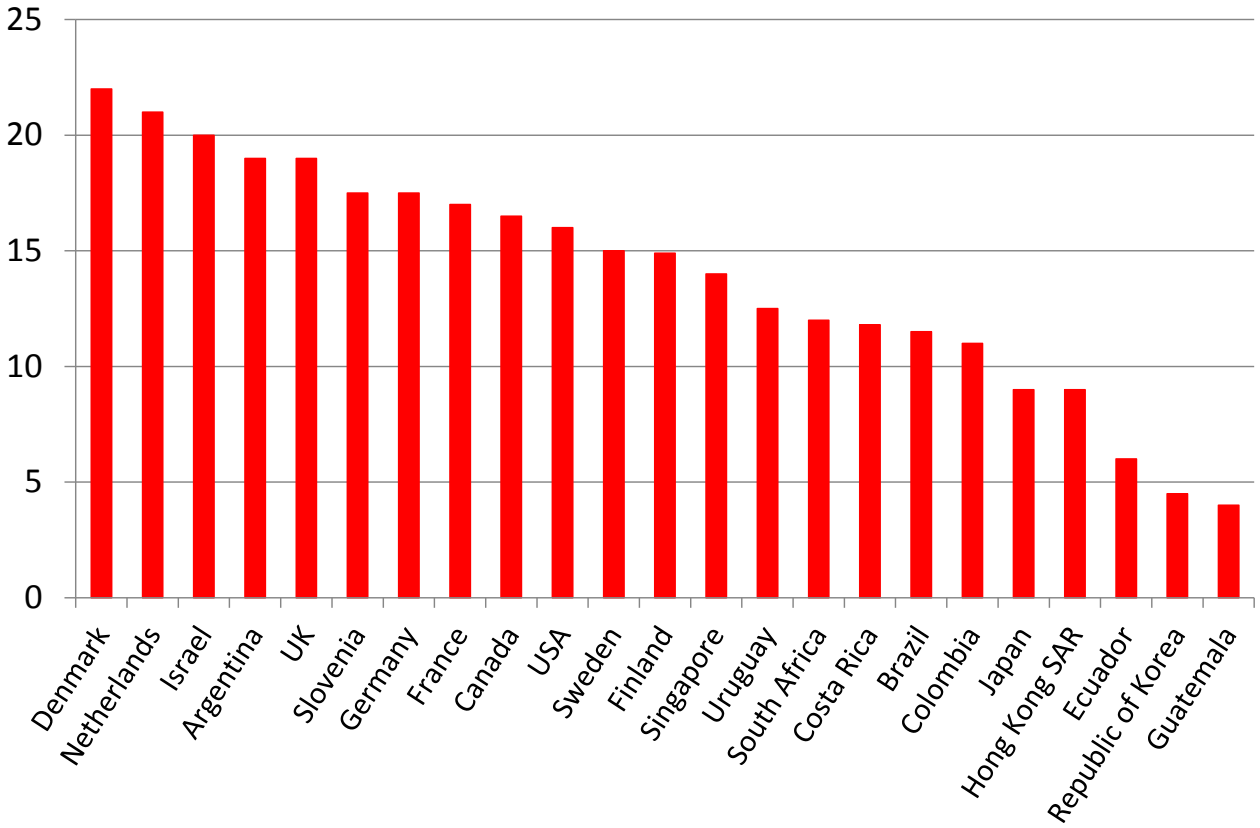
The majority of benign conditions are masses that may be indistinguishable from an invasive breast lesion by palpation or imaging. Some other conditions, particularly forms of benign and neoplastic epithelial proliferations, are also discussed below. These may occur in conjunction with some benign mass-forming entities, for example fibrocystic change, papilloma, and sclerosing lesions, and may present symptomatically or through palpation. In more recent years, they have increasingly been identified (alone or in combination with more subtle forms of related benign breast disease) using mammography, due to their ability to form microcalcifications, particularly of the low-risk clustered type, which can also be associated with low- and intermediate-grade forms of ductal carcinoma in situ (DCIS).

(b) Pathology and molecular genetics of common benign breast conditions

(i) Solitary cyst

This term describes a dilated space with a benign epithelial lining, usually larger than 10 mm and usually attenuated or apocrine in type. No specific molecular genetic changes are associated with this pathology.

Fig. 1.10 Age-standardized mortality rates (ASR) per 100 000 for breast cancer in women, in selected populations, 2003–2007



Created by the Working Group using data from WHO (2014).

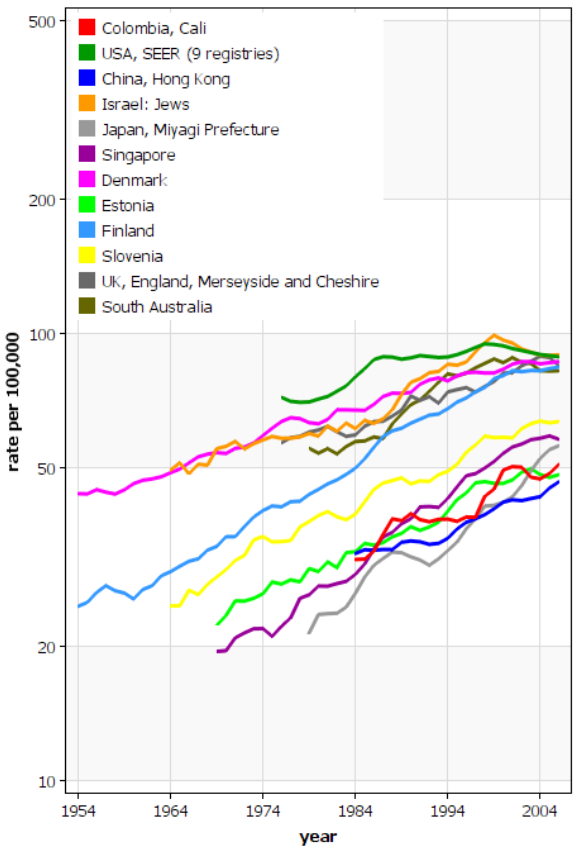
(ii) Fibrocystic change

This term describes a variety of benign features, including cysts (some of which may be lined by apocrine epithelium), fibrosis, usual epithelial hyperplasia, and columnar cell change. No specific molecular genetic changes are associated with this pathology (see also epithelial hyperplasia below).

(iii) Fibroadenoma

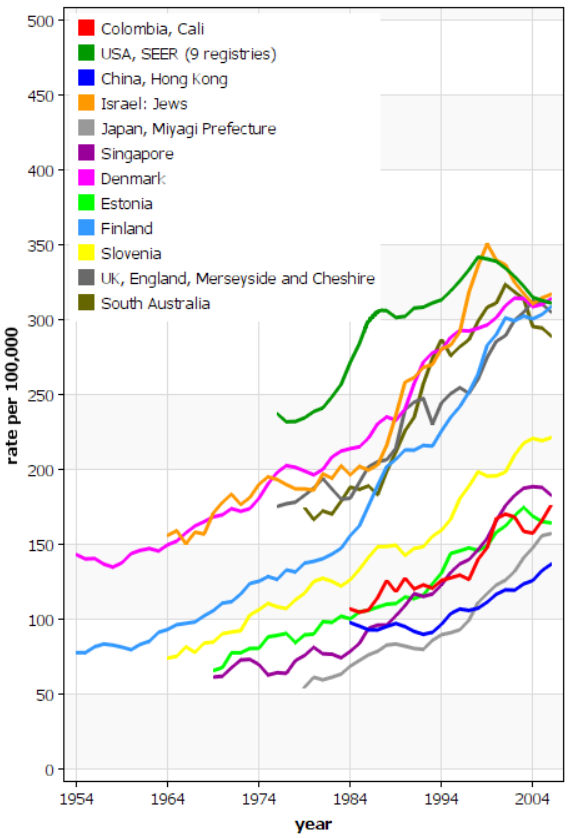
This term describes connective tissue and epithelium exhibiting a pericanalicular and/or intracanalicular growth pattern. The connective tissue is generally composed of spindle-like cells and may rarely also contain other mesenchymal elements such as fat, smooth muscle, osteoid, or bone. The epithelium is characteristically bilayered, but some of the changes commonly seen in lobular breast epithelium (e.g. apocrine metaplasia, sclerosing adenosis, blunt duct adenosis, and hyperplasia of usual type) may also occur in fibroadenomas. Sometimes individual lobules may exhibit increased stroma, producing a fibroadenomatous appearance, and occasionally such lobules may be loosely coalescent. These changes are often called fibroadenomatoid hyperplasia. Consequently, fibroadenomas do not need to be perfectly circumscribed. Old lesions may show hyalinization and calcification (and, less frequently, ossification) of the stroma and atrophy of the epithelium. Calcified fibroadenomas may present as areas of indeterminate calcification, which are detectable by mammography. Fibroadenomas are occasionally multiple.

Fig. 1.11 Age-standardized incidence rates per 100 000 by year in selected populations for breast cancer in women of all ages



From Ferlay et al. (2014b).

Fig. 1.12 Age-standardized incidence rates per 100 000 by year in selected populations for breast cancer in women aged 50–74 years



From Ferlay et al. (2014b).

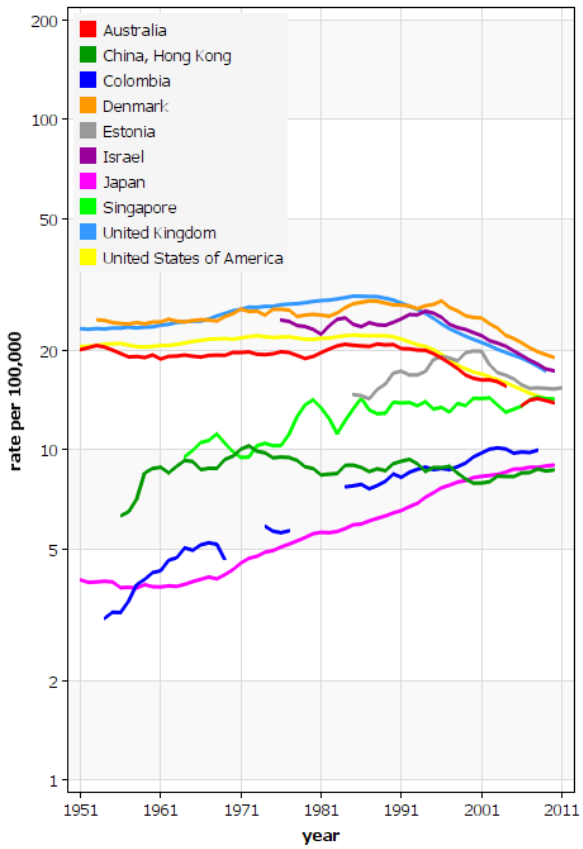
Malignant changes are very rare in the epithelial component, and usually take the form of carcinoma in situ, more frequently lobular carcinoma in situ (LCIS) than DCIS. Fibroadenomas should be distinguished from phyllodes tumours, which are characterized by the presence of increased stromal cellularity and epithelium-lined cleft spaces.

Fibroadenomas have been associated predominantly with polyclonality, although numerical aberrations of chromosomes 16, 17, 18, and 21 have also been described. Phyllodes tumours have been associated with monoclonality, DNA methylation, and alternations of the Wnt signalling pathway.

(iv) Papilloma

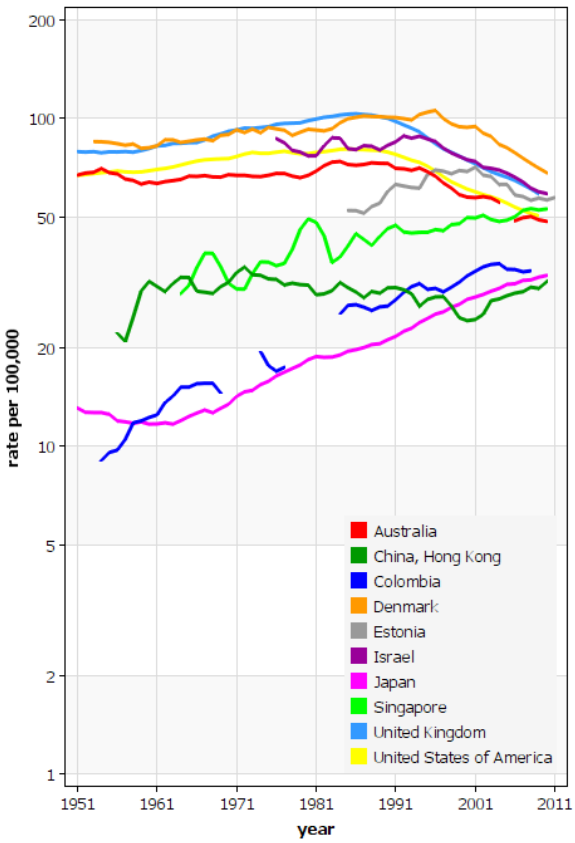
This term describes an arborescent, fibrovascular stroma covered by an inner myoepithelial layer and an outer epithelial layer. Epithelial hyperplasia without cytological atypia is often present, whereas atypical hyperplasia is rarely seen. Solitary papillomas usually occur centrally in subareolar ducts and are associated with low-grade tumours. Multiple papillomas are more likely to be peripheral and to involve terminal duct lobular units, and are frequently associated with atypical hyperplasia and DCIS.

Fig. 1.13 Age-standardized mortality rates per 100 000 by year in selected populations for breast cancer in women of all ages



From WHO (2014).

Fig. 1.14 Age-standardized mortality rates per 100 000 by year in selected populations for breast cancer in women aged 50–74 years



From WHO (2014).

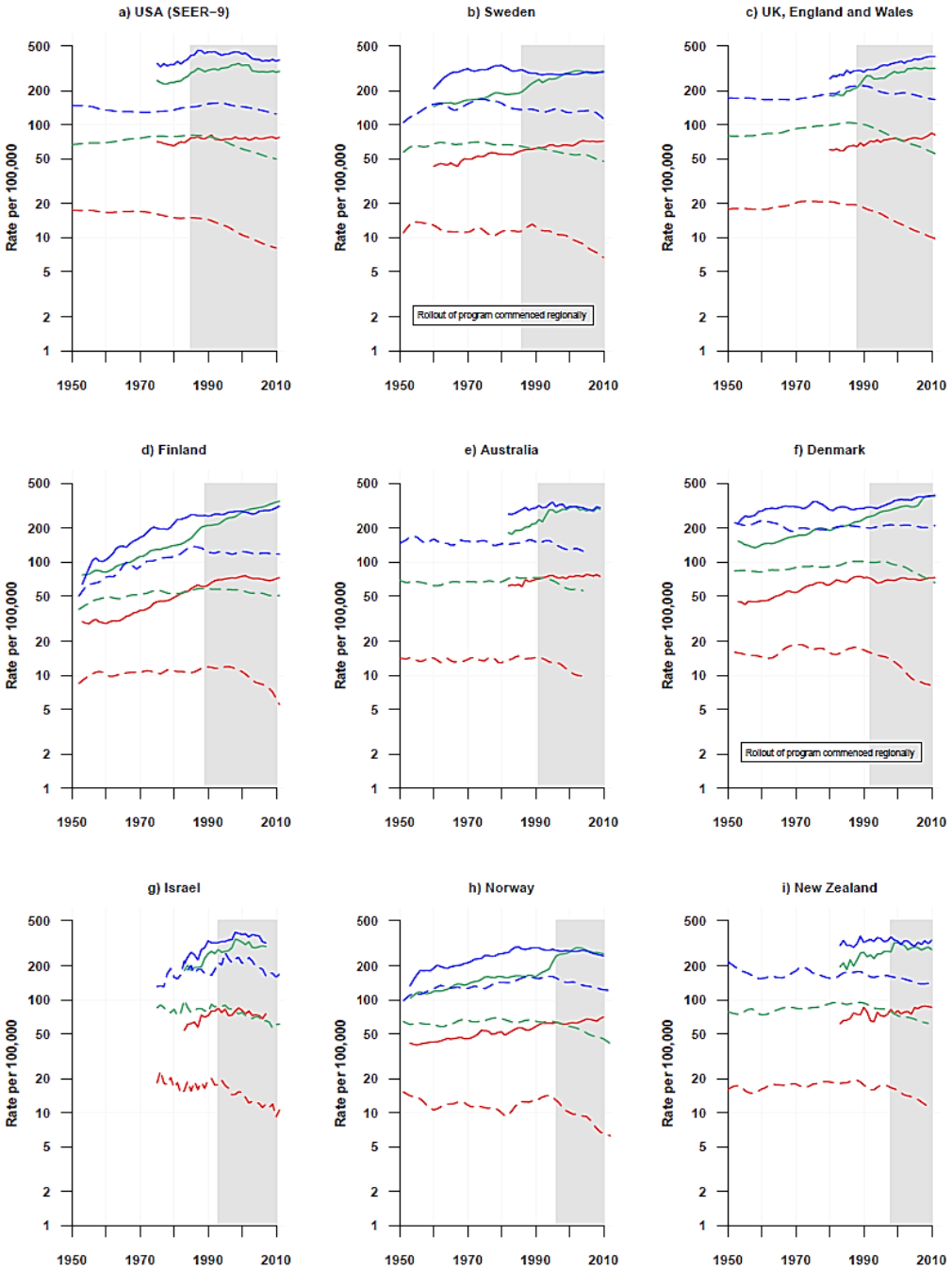
Benign papillomas are monoclonal proliferations characterized by somatic point mutations in the *PIK3CA*, *AKT1*, and *RAS* genes. Alterations of chromosome 16 have been described in both benign and malignant papillary lesions.

Lesions termed ductal adenoma (sclerosing duct papilloma) exhibit a variable appearance, similar to a certain extent to other benign breast lesions. They may resemble papillomas, although they exhibit a growth pattern that is adenomatous rather than papillary.

(v) Sclerosing adenosis

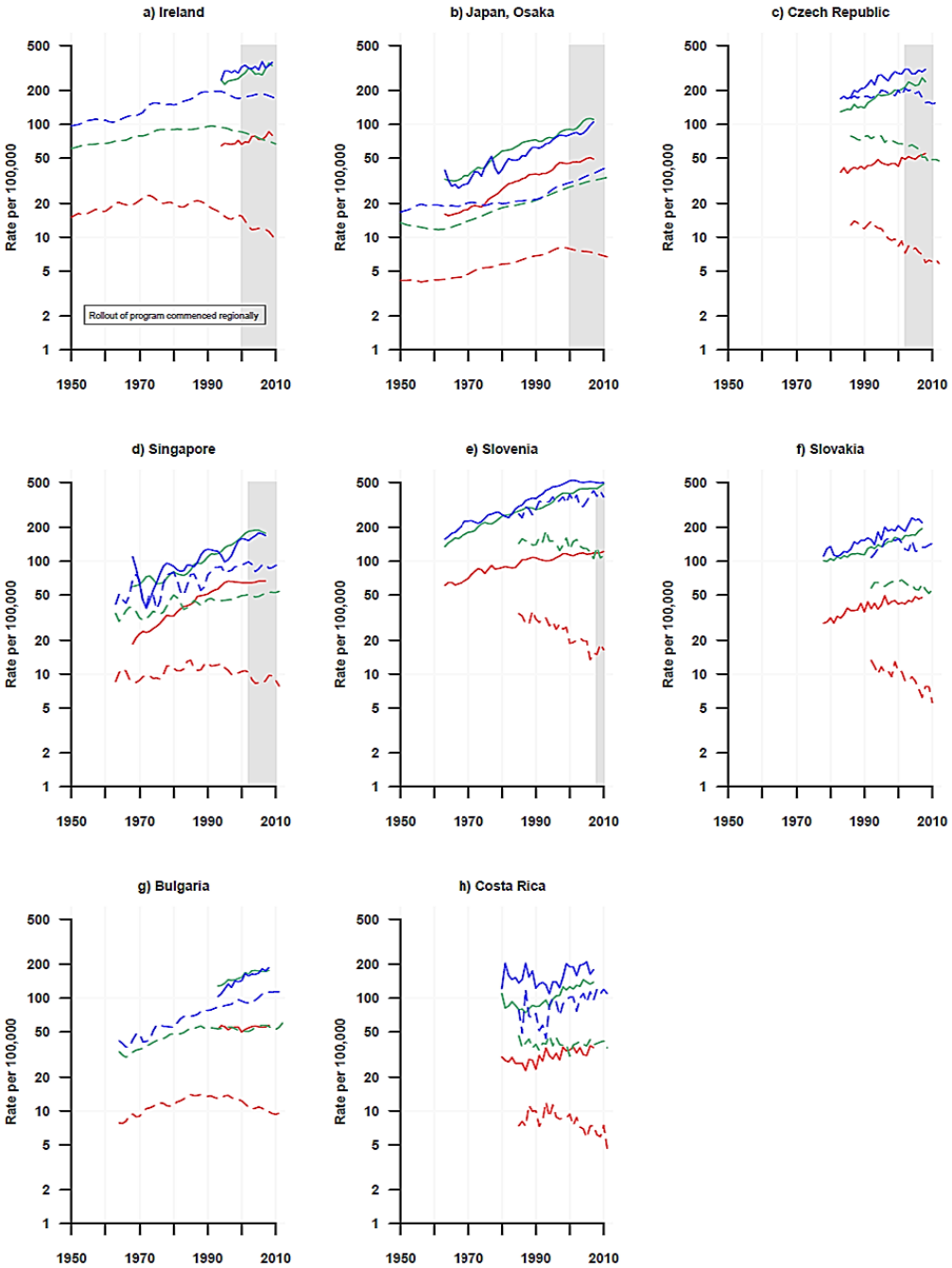
This term describes an organoid lobular enlargement in which increased numbers of acinar structures exhibit elongation and distortion. The normal two-cell lining is retained, but there is myoepithelial and stromal hyperplasia. The acinar structures may infiltrate the adjacent connective tissue and occasionally the nerves and blood vessels, thus possibly leading to an erroneous diagnosis of malignancy. Early lesions of sclerosing adenosis are more cellular-like, and later ones are more sclerotic-like. Calcification may be present. A coalescence of adjacent lobules of sclerosing adenosis may form a mass,

Fig. 1.15 Age-standardized incidence rates (solid lines) and mortality rates (dashed lines) per 100 000 by year in selected countries for breast cancer in women



25–49 years (red), 50–74 years (green), and 75 years and older (blue).
Selected countries in which population-based or opportunistic breast cancer screening programmes using mammography were initiated during the 1980s or 1990s. Shading indicates the period within which screening programmes were operational. In Sweden and Denmark, the start of the shaded period indicates the year when pilot screening programmes were implemented in a region of the country before national adoption.
Created by the Working Group using incidence data from Ferlay et al. (2014b) and mortality data from WHO (2014). All data are national, except for incidence data for the USA, which are for the SEER-9 group of cancer registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah).

Fig. 1.16 Age-standardized incidence rates (solid lines) and mortality rates (dashed lines) per 100 000 by year in selected countries for breast cancer in women



25–49 years (red), 50–74 years (green), and 75 years and older (blue).
Selected countries in which population-based or opportunistic breast cancer screening programmes using mammography were initiated after 2000 or have never been implemented. Shading indicates the period within which screening programmes were operational. In Ireland, the start of the shaded period indicates the year when a pilot screening programme was implemented in a region of the country before national adoption. Created by the Working Group using incidence data from Ferlay et al. (2014b) and mortality data from WHO (2014). All data are national, except for incidence data for Japan, which are for the Osaka Cancer Registry.

Table 1.3 Benign and malignant breast tumours recognized in the current WHO classification of tumours of the breast

EPITHELIAL TUMOURS	
Microinvasive carcinoma	
Invasive breast carcinoma	
Invasive carcinoma of no special type (NST)	8500/3
Pleomorphic carcinoma	8022/3
Carcinoma with osteoclast-like stromal giant cells	8035/3
Carcinoma with choriocarcinomatous features	—
Carcinoma with melanotic features	—
Invasive lobular carcinoma	8520/3
Tubular carcinoma	8211/3
Cribriform carcinoma	8201/3
Mucinous carcinoma	8480/3
Carcinoma with medullary features	
Medullary carcinoma	8510/3
Atypical medullary carcinoma	8513/3
Invasive carcinoma NST with medullary features	8500/3
Carcinoma with apocrine differentiation	—
Carcinoma with signet-ring-cell differentiation	—
Invasive micropapillary carcinoma	8507/3*
Metaplastic carcinoma of no special type (NST)	8575/3
Low-grade adenosquamous carcinoma	8570/3
Fibromatosis-like metaplastic carcinoma	8572/3
Squamous cell carcinoma	8070/3
Spindle cell carcinoma	8032/3
Metaplastic carcinoma with mesenchymal differentiation	8571/3
Mixed metaplastic carcinoma	8575/3
Myoepithelial carcinoma	8982/3
Rare types	
Carcinoma with neuroendocrine features	
Neuroendocrine tumour, well-differentiated	8246/3
Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)	8041/3
Carcinoma with neuroendocrine differentiation	8574/3
Secretory carcinoma	8502/3
Invasive papillary carcinoma	8503/3
Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Polymorphous carcinoma	8525/3
Oncocytic carcinoma	8290/3
Lipid-rich carcinoma	8314/3
Glycogen-rich clear cell carcinoma	8315/3
Sebaceous carcinoma	8410/3
Salivary gland/skin adnexal type tumours	
Cylindroma	8200/0
Clear cell hidradenoma	8402/0*

Table 1.3 (continued)

Epithelial–myoepithelial tumours	
Pleomorphic adenoma	8940/0
Adenomyoepithelioma	8983/0
Adenomyoepithelioma with carcinoma	8983/3*
Adenoid cystic carcinoma	8200/3
Precursor lesions	
Ductal carcinoma in situ	8500/2
Lobular neoplasia	
Lobular carcinoma in situ	
Classic lobular carcinoma in situ	8520/2
Pleomorphic lobular carcinoma in situ	8519/2*
Atypical lobular hyperplasia	—
Intraductal proliferative lesions	
Usual ductal hyperplasia	—
Columnar cell lesions including flat epithelial atypia	—
Atypical ductal hyperplasia	—
Papillary lesions	
Intraductal papilloma	8503/0
Intraductal papilloma with atypical hyperplasia	8503/0
Intraductal papilloma with ductal carcinoma in situ	8503/2*
Intraductal papilloma with lobular carcinoma in situ	8520/2
Intraductal papillary carcinoma	8503/2
Encapsulated papillary carcinoma	8504/2
Encapsulated papillary carcinoma with invasion	8504/3
Solid papillary carcinoma	
In situ	8509/2
Invasive	8509/3
Benign epithelial proliferations	
Sclerosing adenosis	—
Apocrine adenosis	—
Microglandular adenosis	—
Radial scar/complex sclerosing lesion	—
Adenomas	
Tubular adenoma	8211/0
Lactating adenoma	8204/0
Apocrine adenoma	8401/0
Ductal adenoma	8503/0
MESENCHYMAL TUMOURS	
Nodular fasciitis	8828/0*
Myofibroblastoma	8825/0
Desmoid-type fibromatosis	8821/1
Inflammatory myofibroblastic tumour	8825/1
Benign vascular lesions	
Haemangioma	9120/0
Angiomatosis	—
Atypical vascular lesions	—
Pseudoangiomatous stromal hyperplasia	—

Table 1.3 (continued)

Granular cell tumour	9580/0
Benign peripheral nerve-sheath tumours	
Neurofibroma	9540/0
Schwannoma	9560/0
Lipoma	8850/0
Angiolipoma	8861/0
Liposarcoma	8850/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
FIBROEPITHELIAL TUMOURS	
Fibroadenoma	9010/0
Phyllodes tumour	9020/1
Benign	9020/0
Borderline	9020/1
Malignant	9020/3
Periductal stromal tumour, low grade	9020/3
Hamartoma	
TUMOURS OF THE NIPPLE	
Nipple adenoma	8506/0
Syringomatous tumour	8407/0
Paget disease of the nipple	8540/3
MALIGNANT LYMPHOMA	
Diffuse large B-cell lymphoma	9680/3
Burkitt lymphoma	9687/3
T-cell lymphoma	
Anaplastic large cell lymphoma, ALK-negative	9702/3
Extranodal marginal-zone B-cell lymphoma of MALT type	9699/3
Follicular lymphoma	9690/3
METASTATIC TUMOURS	
TUMOURS OF THE MALE BREAST	
Gynaecomastia	
Carcinoma	
Invasive carcinoma	8500/3
In situ carcinoma	8500/2
CLINICAL PATTERNS	
Inflammatory carcinoma	8530/3
Bilateral breast carcinoma	

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline, or uncertain behaviour, /2 for carcinoma in situ and grade 3 intraepithelial neoplasia, and /3 for malignant tumours.

[b] The classification is modified from the previous WHO histological classification of tumours (2003), taking into account changes in our understanding of these lesions. In the case of neuroendocrine neoplasms, the classification has been simplified to be of more practical utility in morphological classification.

* These new codes were approved by the IARC/WHO Committee for ICD-O in 2013.

Source: Adapted from Lakhani et al. (2012).

detectable by mammography or by macroscopic examination, which is termed "nodular sclerosing adenosis" or "adenosis tumour". Occasionally, apocrine metaplasia is seen in areas of sclerosing adenosis (termed "apocrine adenosis"), with or without cytological atypia. Rarely, the epithelium in sclerosing adenosis may show atypical hyperplasia or carcinoma in situ. No specific molecular genetic changes are associated with this pathology.

(vi) Complex sclerosing lesions and radial scars

This term describes sclerosing lesions with a pseudo-infiltrative growth pattern. A radial scar is characterized by a diameter of 10 mm or less and by a central fibro-elastic zone from which radiate out tubular bilayered structures, which may exhibit intraluminal proliferation. Lesions larger than 10 mm are generally termed complex sclerosing lesions; they have the same features as radial scars but a larger size and more disturbance of structure, often with nodular masses around the periphery. Changes such as papilloma formation, apocrine metaplasia, and sclerosing adenosis may be superimposed on the main lesion, thus giving rise to complex sclerosing lesions. Atypia or a noticeable quantity of carcinoma in situ may also be present. No specific molecular genetic changes are associated with this pathology.

(vii) Periductal mastitis/duct ectasia

This process involves larger and intermediate-size ducts, generally in a subareolar location. The ducts are lined by normal or attenuated epithelium, are filled with amorphous, eosinophilic material and/or foam cells, and exhibit marked periductal chronic inflammation, often with large numbers of plasma cells (periductal mastitis). There may be pronounced periductal fibrosis. Calcification may be present. The process may ultimately lead to obliteration of ducts (duct ectasia), leaving dense fibrous masses, often associated with nipple discharge or retraction. No specific molecular genetic changes are associated with this pathology.

(viii) Inflammatory breast conditions

This term refers to mastitis, mammary duct fistula, lymphocytic lobulitis, specific infections, and granulomatous mastitis. No specific molecular genetic changes are associated with this pathology.

(c) Pathology and molecular genetics of benign epithelial proliferations

(i) Usual epithelial hyperplasia

This term describes the proliferation of a mixed cell population comprising (luminal) epithelial cells and basal/myoepithelial cells with a streaming epithelial architecture, with formation of irregular, slit-like, and peripheral luminal spaces. Most studies have found no consistent molecular genetic alterations associated with this pathology.

(ii) Columnar cell lesions

This term describes blunt duct adenosis, columnar cell change, columnar cell hyperplasia, unfolded lobule, and columnar alteration with prominent apical snouts and secretions. In broad terms, these lesions cover a spectrum of changes, ranging from bland columnar cell change to columnar cell hyperplasia (piling up of several layers) to flat epithelial atypia (superimposed mild atypia). These lesions have become increasingly identified by clinical examination as a consequence of more rigorous investigations of radiological calcifications. Lobular acini are commonly formed and are lined by tall and snouted epithelial cells, similar to those observed in tubular carcinoma. Commonly, this is associated with luminal secretions and/or microcalcifications. As well as atypical ductal hyperplasia (ADH)/low-grade DCIS, other epithelial proliferations may merge or be associated with columnar cell hyperplasia, including atypical lobular hyperplasia (ALH), LCIS, and

invasive carcinoma, often of low-grade tubular or tubulolobular type. There is limited information about the molecular genetic alterations associated with this pathology; loss of chromosome 16q is the most frequently described (Moinfar et al., 2000; Simpson et al., 2005; Abdel-Fatah et al., 2008; Go et al., 2012).

(iii) Atypical ductal hyperplasia

ADH is a rare lesion, which is identified based on some but not all features of DCIS. Difficulties are encountered mainly in distinguishing ADH from the low-grade variants of DCIS. Areas of ADH usually do not exceed 2–3 mm in size, with less than two complete membrane-bound spaces. Loss of heterozygosity on chromosomes 16q, 17p, and 11q13 is a common feature of ADH, low-grade DCIS, and low-grade invasive breast cancer, implying that these lesions belong to a precursor progression pathway (Lopez-Garcia et al., 2010; Bombonati & Sgroi, 2011; Lakhani et al., 2012).

(iv) Atypical lobular hyperplasia

ALH and LCIS have traditionally been separated as distinct lesions, based on cytological and quantitative features relating to the extent of lobular involvement and on different risks of subsequent invasive breast cancer. However, the two lesions have similar molecular profiles. It has been suggested that ALH and LCIS should be grouped together as in situ lobular neoplasia, except when their degree and extent can be assessed to estimate the risk of subsequent invasive carcinoma. In situ lobular neoplasia is characterized by the proliferation within the terminal duct lobular units of discohesive round, cuboidal, or polygonal cells with clear or light cytoplasm. The distension of lobular units may vary from patent lumina to complete obliteration. In ALH, there is minimal extension of less than half of the acini, whereas in LCIS more than half of the acini within the terminal duct lobular unit are distended by an expansion of the typical cells (≥ 8 cells across each acinus). ALH and LCIS are clonal lesions and share the same abnormalities, indicating that they are part of a precursor progression pathway. Loss of chromosomes 11q13, 16q, and 17p and alterations of the E-Cadherin *CCND1* locus have been reported (Simpson et al., 2003; Lopez-Garcia et al., 2010; Bombonati & Sgroi, 2011; Lakhani et al., 2012).

(d) Natural history of benign lesions associated with increased risk of breast cancer

See Lakhani et al. (2012) for review.

Various forms of breast epithelial proliferation have been associated with an increased risk of invasive breast cancer (Lopez-Garcia et al., 2010; Bombonati & Sgroi, 2011; Lakhani et al., 2012), both ipsilateral and contralateral. A 1.5–2.0-fold increased risk for usual epithelial hyperplasia, a 2.5–4.0-fold increased risk for ADH, and a 4.0–5.0-fold increased risk for ALH have been reported. Other forms of benign breast disease, such as sclerosing adenosis, fibroadenoma, and papillary apocrine change, appear not to alter the risk of breast cancer or to have a risk equivalent to that for any coexisting epithelial proliferation. All of these epithelial proliferative lesions may be detected by breast screening and excised.

1.2.2 Breast carcinoma in situ

The two non-invasive forms of breast carcinoma in situ are DCIS and LCIS, each with distinctive morphological and behavioural characteristics. The neoplastic cell populations are confined within the parenchymal site of origin without stromal invasion across the basement membrane. DCIS, but rarely LCIS, may harbour calcifications that give rise to mammographic abnormalities.

(a) Pathological classification of DCIS

See NHSBSP (2005), Perry et al. (2006), and Lakhani et al. (2012) for review.

DCIS is, in most cases, a unicentric (involving a single duct system) proliferation of epithelial cells with malignant cytological features within the parenchymal structures of the breast. Most DCIS lesions arise from the terminal duct lobular units.

The classification of DCIS is evolving, and it is now considered to represent a heterogeneous group of in situ neoplastic processes. The cytonuclear features of DCIS are less frequently variable within a lesion, and lesions of high nuclear grade are more clinically aggressive. There is less heterogeneity in nuclear grade characteristics, and most of the contemporary histological classification systems are based on a three-tier grading or differentiation system with nuclear grade: high, intermediate, and low nuclear grades (NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012).

High-nuclear-grade DCIS cells have pleomorphic, irregularly spaced, and (usually) large nuclei exhibiting marked variation in size. Mitoses are usually frequent, and abnormal forms may be seen. High-grade DCIS may exhibit several growth patterns, often solid with comedo-type central necrosis, frequently containing deposits of amorphous calcification. Sometimes a solid proliferation of malignant cells fills the duct without necrosis, and is confined to nipple/lactiferous ducts in cases presenting with Paget disease of the nipple. High-nuclear-grade DCIS may also exhibit micropapillary and cribriform patterns, frequently associated with central comedo-type necrosis. A high-grade flat form of DCIS is also recognized, although it is infrequent. These lesions are usually human epidermal growth factor receptor 2 (HER2)-positive.

Intermediate-grade DCIS cells show moderate pleomorphism of the nuclei, which lack the monotony of the low-grade cell type, with nuclei that are typically larger. The growth pattern may be solid, cribriform, or micropapillary, and clear cell or apocrine types often fall into this category.

Low-nuclear-grade DCIS is composed of monomorphic, evenly spaced cells with usually, but not invariably, rounded small nuclei, and rare individual cell necrosis. These cells are generally arranged in micropapillary and cribriform patterns.

A small proportion of cases of DCIS exhibit mixed features of differing nuclear grades.

Other rare, but morphologically distinct, subtypes of DCIS are recognized, but without firm evidence of distinction from more common DCIS forms with regard to their clinical presentation and/or behaviour, with the exception of encysted papillary carcinoma. These include apocrine, clear cell, signet ring, neuroendocrine, and cystic hypersecretory forms of DCIS and variants with a papillary structure, including papillary carcinoma in situ, solid papillary carcinoma in situ, and encysted papillary carcinoma.

(b) Molecular genetic changes of breast carcinoma in situ

Several molecular alterations have been characterized, some of which are related to survival. Molecular genetic studies of low-grade DCIS and ADH have provided evidence that these lesions are clonal and therefore fulfil the basic criterion of neoplastic transformation (Lakhani et al., 1995; Lopez-Garcia et al., 2010). Early molecular studies and particularly comparative genomic hybridization studies suggested that the genetic lesions of DCIS are associated with particular morphological subtypes (Buerger et al., 1999). Well-differentiated DCIS is associated with loss of 16q and 17p, whereas tumours of intermediate and high grades often have losses of significantly more allelic chromosomal arms, frequently including 1p, 1q, 6q, 9p, 11p, 11q, 13q, and 17q (Fujii et al., 1996). High-grade DCIS is associated with gains at 17q but also at 11q and 13q (Chuaqui et al., 1997). Intermediate-grade DCIS shows a combination of lesions, such as 16q loss and gains at other chromosomes, particularly 1q, or gain at 11q or 13q but not at 17q12, which is a feature of high-grade DCIS (Buerger et al., 1999). Similarly, ALH and LCIS show the same

genetic mutations, with loss at 16p, 16q, 17p, and 22q and gain at 6q (Lu et al., 1998). Interestingly, low-grade DCIS and ADH share similar genetic alterations with LCIS and ALH but not with high-grade DCIS. These observations challenge the existing assumptions that lobular and ductal lesions are distinct and that DCIS is a homogeneous disease.

It has been shown that in situ and invasive elements of breast cancers have identical molecular alterations (Stratton et al., 1995; Hwang et al., 2004; Moelans et al., 2011) and similar morphological characteristics (Lampejo et al., 1994), thus supporting the hypothesis that low-grade carcinoma in situ gives rise to low-grade invasive carcinoma, and high-grade carcinoma in situ to high-grade invasive carcinoma.

In addition, complementary DNA (cDNA) expression studies have confirmed that the core intrinsic molecular subgroups, including the luminal, HER2-overexpressing, and basal-like subtypes, found in invasive breast cancer (Perou et al., 2000; Sørlie et al., 2001) are replicated in DCIS, although at different frequencies (Vincent-Salomon et al., 2008).

(c) Natural history of DCIS – association of DCIS with invasive carcinoma

Data on the natural history of untreated DCIS are limited, for ethical reasons. The available studies are historical and relate to symptomatic, extensive, high-grade comedo-type DCIS. In the past, DCIS was rare in clinical practice; patients typically presented with a mass lesion, nipple discharge, or Paget disease of the nipple, and were treated with mastectomy (Dean & Geshchicter, 1938).

More recent studies are virtually all examples of low-grade DCIS, with a progression rate of about 40% to invasive disease after 30 years (Page et al., 1995; Collins et al., 2005; Sanders et al., 2005), and invasive tumours occurring in the quadrant of the breast of the initial lesion (Page et al., 1995, Sanders et al., 2005). About 50% of DCIS recurrences are invasive carcinomas, and high-grade DCIS and DCIS with necrosis represent a biologically aggressive subset compared with low-grade DCIS lesions without necrosis (Solin et al., 1993; Silverstein et al., 1995, 1996; Fisher et al., 1999). One large randomized trial (Bijker et al., 2001a) showed that the margin status is the most important factor in the success of breast-conserving therapy for DCIS. The same trial suggested that local recurrence usually reflects outgrowth of residual DCIS, that progression of low-grade DCIS to high-grade DCIS or grade 3 invasive carcinoma is unusual, and that all forms of DCIS, even the lowest-grade flat/micropapillary type, have a risk of local recurrence, which is reduced by the use of adjuvant radiotherapy (Bijker et al., 2001b; Fisher et al., 2001; Donker et al., 2013).

Invasive lesions with an extensive intraductal component also show a predisposition to local recurrence after breast-conserving therapy (van Dongen et al., 1989). The grade of DCIS associated with invasive carcinoma has been shown to correlate with both disease-free interval and survival (Lampejo et al., 1994). It has been also reported that high-grade DCIS is associated with high-grade invasive carcinoma, and low-grade DCIS with low-grade invasive carcinoma (Lampejo et al., 1994; Douglas-Jones et al., 1996; Cadman et al., 1997). An association between grade 3 invasive carcinoma and poorly differentiated DCIS is seen whatever grading system is used (Douglas-Jones et al., 1996).

(d) LCIS in the context of DCIS

Particularly in some more extensive lesions, making a distinction between in situ lobular neoplasia and DCIS may be difficult, and this may lead to misclassification (Fisher et al., 2004), as in the case of a regular, evenly spaced monotonous population within both ducts and lobules. In such cases, E-cadherin membrane reactivity may be useful in distinguishing between the two pathologies. However, if both ducts and lobules contain

epithelial proliferation of this type, particularly if E-cadherin is heterogeneous, categorization as both LCIS and DCIS is currently recommended, to imply the precursor risk of DCIS and the bilateral cancer risk of in situ lobular neoplasia.

There is evidence that some forms of LCIS that have similarities to DCIS will behave in a similar fashion to DCIS and should be managed as an established form of carcinoma in situ. Such types of LCIS are described below.

(i) Pleomorphic variant of LCIS

See Lakhani et al. (2012) for review.

This LCIS subtype has larger cells of pleomorphic type (cytonuclear grade 3), with more abundant cytoplasm than the classic type. Pleomorphic LCIS is less frequently estrogen receptor (ER)-positive and more often HER2-positive than the classic forms. Based on abundant evidence, pleomorphic LCIS is widely regarded as a more aggressive form of the disease, and it is currently recommended that it should be managed similarly to DCIS rather than to classic LCIS, based on its biological and molecular profile (Masannat et al., 2013; Pieri et al., 2014).

(ii) Extensive and mass-forming LCIS with necrosis

See Lakhani et al. (2012) for review.

This variant of LCIS has classic cytology with central necrosis in distended acini. The degree of atypia is not sufficient for a diagnosis of pleomorphic LCIS. This variant is uncommon, and its clinical behaviour is not well established, but it can behave like DCIS (Fisher et al., 2004). This entity is usually regarded as an established form of carcinoma in situ, requiring therapeutic excision, equivalent to DCIS.

1.2.3 Invasive breast carcinoma

Invasive carcinoma of the breast is a malignant tumour, commonly adenocarcinoma, part or all of which penetrates the basement membrane of the mammary epithelial site of origin, particularly from the terminal duct lobular unit (NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012). The morphological appearance of these tumours varies widely, and they show different prognostic or clinical characteristics. More recently, specific genetic alterations have been identified in some types.

(a) Histopathological characteristics and classification

The prognosis of a patient with breast cancer relies on two distinct groups of variables. The first are time-dependant variables that influence tumour stage, such as the histological size of the tumour, the presence and extent of lymph-node metastatic disease, and the presence of systemic metastatic disease. The second group of variables, sometimes referred to as intrinsic characteristics, are related to the inherent biology of the individual tumour and include the histological grade, tumour type, growth fraction, hormone and growth factor receptor status, and molecular genetic characteristics.

(i) Histological type and prognosis

A wide range of morphological patterns can be seen in invasive carcinomas, usually with distinct prognostic characteristics (Table 1.3; NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012). The favourable prognosis of certain histological types of invasive carcinoma of the breast is well established (Ellis et al., 1992; Pereira et al., 1995; NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012). These "special" or "specific" forms of invasive carcinoma have also been found at higher frequency in the prevalence round of mammographic breast screening programmes (Anderson et al., 1991; Ellis et al., 1993) and have been found more frequently at screening than as interval cancers found between screening rounds (Porter et al., 1999). The recent revision of the WHO classification, after consideration of clinical relevance and diagnostic reproducibility issues, has revised the requirements for absolute

purity of features and suggested the designation of "medullary-like carcinoma" for tumours that exhibit some or all medullary characteristics and have a moderate prognosis (Lakhani et al., 2012). This contrasts with tubular carcinoma, which has recently been shown to have an exceptionally favourable long-term prognosis (Rakha et al., 2010b). Overall, patients with infiltrating lobular carcinoma have a slightly better prognosis than those with invasive ductal carcinoma, not otherwise specified (Haagensen, 1986; Ellis et al., 1992), although recent longer-term follow-up studies have shown that patients with lobular carcinoma may experience very late recurrence.

Invasive tumours are classified based on the purity of special type characteristics, if present, and are broadly categorized as follows (NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012).

Pure special type

For an invasive tumour to be characterized as pure special type, at least 90% of the tumour should have the characteristic features of that particular type (e.g. a tumour showing 90% mucinous features is classified as being of pure mucinous carcinoma type). In general, tumours of special type show favourable clinical prognostic characteristics.

Invasive carcinoma of no special type

This is the most common category of invasive breast carcinoma, showing none, or less than 50%, of the characteristic morphology of the special type tumour. It is often described as invasive ductal carcinoma, although the term "invasive carcinoma of no special type" or "invasive carcinoma of no specific type" is preferred.

Mixed invasive carcinoma

This is a relatively common pattern of invasive breast carcinoma. The tumour may be heterogeneous in morphology, with more than 50% but less than 90% of special type areas, showing areas of pure tubular differentiation within a tumour otherwise showing no special type features.

Other primary breast carcinomas

This category includes rare variants such as carcinoma with apocrine differentiation, carcinoma with neuroendocrine differentiation, and salivary gland-type tumours (e.g. adenoid cystic carcinoma and secretory carcinoma).

Other malignant carcinomas

Non-epithelial tumours and secondary malignancies are included in this category.

(ii) Histological characteristics

Histological grade is a powerful prognostic method for grading invasive breast carcinomas based on the assessment of multiple cellular and architectural variables or nuclear variables. The early systems, in addition to a subjective histological assessment, were lacking strictly defined written criteria (Patey & Scarff, 1928; Bloom & Richardson, 1957). The method of Elston & Ellis (1991) was found to be reproducible (Dalton et al., 1994; Frierson et al., 1995; Robbins et al., 1995) and has been adopted internationally as the standard method (NHSBSP, 2005; Perry et al., 2006; Lakhani et al., 2012). It evaluates three main tumour characteristics: tubule formation as an expression of glandular differentiation, nuclear pleomorphism, and mitotic counts. After each factor is assessed individually, a numerical scoring system assigns an overall grade as follows:

- Grade 1: well differentiated; 3–5 points
- Grade 2: moderately differentiated; 6–7 points
- Grade 3: poorly differentiated; 8–9 points.

(b) Biological and molecular genetic characteristics

Several molecular alterations characterize invasive breast carcinomas. Some are related to survival and also represent tumour-specific molecular signatures, suggesting the possibility of developing targeted therapy.

(i) Estrogen and progesterone receptors

Estrogen is an important mitogen, and its expression is associated with response to hormone therapy, such as adjuvant tamoxifen (Osborne, 1998; Bundred, 2001; Isaacs et al., 2001; Ali & Coombes, 2002; Davies et al., 2011); thus, ER-positive tumours have a more favourable initial prognosis than ER-negative tumours (Ali & Coombes, 2002). ER is expressed in approximately 80% of invasive breast tumours. Progesterone receptors (PRs) serve as an indicator of an intact ER pathway and have been shown to also predict which patients will respond to hormone therapy (Bardou et al., 2003; Andre & Pusztai, 2006).

(ii) HER2

The *ERBB2/HER2* oncogene, located on 17q21, is amplified in approximately 20% of invasive breast carcinomas, leading to overexpression of the coded HER2 protein, a transmembrane receptor with tyrosine kinase activity. HER2 overexpression, measured by immunohistochemistry (Wolff et al., 2013), is a weak to moderate independent predictor of survival (Slamon et al., 1987). HER2 is targeted by the humanized anti-HER2 monoclonal antibody, the anticancer drug trastuzumab (Cobleigh et al., 1999), in combination with chemotherapy for efficacy in both the metastatic and adjuvant settings (Slamon et al., 2001; Perez et al., 2011).

(iii) Proliferation

Several markers of proliferation have been extensively investigated for their prognostic value (Stuart-Harris et al., 2008), including mitotic count, DNA flow cytometric measurement of the S-phase fraction, and immunohistochemistry with antibodies to Ki-67, which is strongly expressed in proliferating cells (Cheang et al., 2009; Yerushalmi et al., 2010; Dowsett et al., 2011). However, the widespread use of such molecular changes has been limited by the lack of methodological standardization, the lack of consensus on appropriate cut-off points for clinical use, and interobserver variability in scoring.

(iv) Gene expression and sequencing

A tumour classification system based on gene expression profiles is more informative than the morphology-based one (NICE, 2013). Variations in gene expression classify breast cancers into the following types: basal epithelial-like, luminal epithelial/ER-positive, HER2-overexpressing, and normal breast-like (Perou et al., 2000; Sørlie et al., 2001; Sotiriou & Pusztai, 2009). The luminal/ER-positive group might be further subdivided (Sotiriou & Pusztai, 2009), although the characterization of these subgroups is still controversial (Ades et al., 2014). The basal intrinsic subclass includes a high proportion of cancers that are triple-negative (ER-, PR-, and HER2-negative) (Andre & Pusztai, 2006). However, gene expression profiling has some limitations (Norum et al., 2014), and no established clinical relevance, although several commercial assays have emerged (Sinn et al., 2013). The most widely adopted to date is the 21-gene assay, which is used as a prognostic factor of recurrence in patients with ER-positive breast cancer treated with hormone therapy, but its cost–effectiveness has not been demonstrated (Isola et al., 2013). Combined genomic and transcriptomic studies have enabled the identification of a broader range of molecular subtypes (Curtis et al., 2012), and next-generation sequencing (Cancer Genome Atlas Network, 2012; Stephens et al., 2012) is improving our understanding of the biology and molecular genetics of breast cancer. Although at present the translation of this knowledge into the clinical setting is limited, there is considerable evidence that the molecular genetic signatures of breast cancer will play an increasing role in its clinical management (Balko et al., 2013).

(c) *Natural history of invasive breast carcinoma*

A very low 15-year survival rate of 5% for untreated breast cancer has been reported historically (Baum, 2013). Survival rates are higher in a modern screening setting, in which disease is detected early.

Historically, radical mastectomy was the treatment of choice, based on the assumption that breast cancer spread exclusively to and from the regional lymph nodes (Halsted, 1894). This approach has been proven ineffective, with high rates of metastatic development (Brinkley & Haybrittle, 1975). It has been demonstrated that breast cancer could also spread via the bloodstream, early and before symptomatic presentation, and may thus require systemic adjuvant treatment (Fisher et al., 2002). A strong and highly significant correlation exists between the tumour size at initiation of distant metastasis and involvement of the first lymph node, since the capacity for lymph-node metastatic spread is, on average, acquired much earlier than the capacity for systemic metastatic spread (Tubiana & Koscielny, 1991; Tabár et al., 1992). Further observations have led to the understanding that breast cancer has a long natural history and a propensity for late recurrence, compared with most other types of cancer (Brewster et al., 2008).

It has been shown that some clinically undetectable, small breast tumours can shed malignant cells with similar characteristics to the primary tumour but also with a relatively normal karyotype and few chromosomal aberrations in common (Schmidt-Kittler et al., 2003), supporting the hypothesis of cancer heterogeneity and Darwinian biological evolution (Klein, 2009; Burrell et al., 2013). These observations may shed light on the observed interindividual variability of apparently similar forms of breast cancer, as well as on the mechanisms of acquired resistance to treatment. Events at the time of surgery may have an impact on long-term survival, and a bimodal distribution of early and late recurrence is seen, possibly due to dormancy (Retsky et al., 2008) or surgical dissemination/autonomy (Badwe et al., 1999). For example, patients with ER-positive tumours have an annual recurrence rate of 2% for at least 15 years, even after 5 years of adjuvant tamoxifen therapy (Saphner et al., 1996). Currently, women who have a history of invasive breast cancer and who have been treated for 5 years with aromatase inhibitors have a risk of recurrence in the following 5 years (Early Breast Cancer Trialists' Collaborative Group, 2001; Cuzick et al., 2010). For this reason, adjuvant treatment has been extended to 10 years for women at high risk of recurrence (Sledge et al., 2014).

Spontaneous regression of breast cancer is exceptionally rare (Larsen & Rose, 1999), and although some studies suggest this possibility (Kaplan & Porzsolt, 2008; Zahl et al., 2008), their conclusions are not widely accepted as valid, given multiple methodological issues. The issue of overdiagnosis, indolence, and/or regression appears more compelling for in situ lesions, particularly non-high-grade DCIS and ADH. Hospital-based and forensic autopsy series of women not known to have had breast cancer during their lifetime have shown a frequency of 9% of DCIS (Welch & Black, 1997; Erbas et al., 2006). However, lesions identified in these studies are usually very small, low-nuclear-grade lesions and possibly ADH rather than established forms of DCIS. Also, a high proportion of these occult lesions identified histologically during postmortem examinations are not diagnosable by mammography and have been interpreted as being of questionable clinical relevance.

Pathologists use the term "overdiagnosis" to mean the incorrect pathological diagnosis of cancer, i.e. misdiagnosis or diagnostic error (Ellis et al., 2006). Epidemiologists and radiologists define "overdiagnosis" as the diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if

screening had not taken place. Under certain circumstances, the rate of overdiagnosis can be estimated by the excess proportion of cancers detected in women undergoing screening, compared with women in the non-screened control arm of a clinical trial (Kopans et al., 2011; Puliti et al., 2012). This definition implies that a proportion of breast cancers remain static, have a very indolent long-term course, or regress (Berlin, 2014). As discussed above, the evidence for regression remains highly controversial. There is compelling evidence that some cancers, particularly in situ and invasive low-grade hormone receptor-positive lesions, may remain indolent and do not progress to clinically relevant disease in a woman's lifetime. With respect to screening, these cancers would more correctly be described as "overdetected". However, in most cases it is not currently possible, based on mammographic signs, pathological features, or biological features, to determine which lesions are likely to progress or regress. The question of progression versus regression for non-high-grade forms of DCIS was investigated in two randomized trials currently under way: the Low Risk DCIS (LORIS) trial (Soumian et al., 2013; ISRCTN registry, 2014) and the Low-Risk DCIS (LORD) trial (Elshof et al., 2015).

1.2.4 Breast cancer with hereditary and somatic mutations

Two high-penetrance genes have been identified (*BRCA1* and *BRCA2*) that greatly increase the risk of developing breast cancer. Among age-matched cases, *BRCA1* mutation-related tumours are significantly different from sporadic breast tumours in their histopathological appearance and molecular characteristics (Lakhani et al., 1998, 2002; Honrado et al., 2006; Palacios et al., 2008; van der Groep et al., 2011; Vargas et al., 2011), possibly due to the expression of the basal-like phenotype. Invasive ductal carcinoma, not otherwise specified, is the most common histological type in both hereditary and sporadic breast cancers, although certain subtypes do occur more frequently in hereditary breast tumours than in sporadic breast tumours. *BRCA1* mutation-related tumours are frequently of histological grade 3 and of medullary-like type, characterized by syncytial architecture, absence of tubular or glandular structures, pushing or circumscribed margins, high nuclear grade, and a marked lymphoplasmacytic stromal infiltrate. *BRCA1*-related breast cancers are typically triple-negative and of basal phenotype or basal molecular gene expression class (Lakhani et al., 1998, 2002; Vargas et al., 2011; Mavaddat et al., 2012). In premenopausal patients with tumours of medullary and triple-negative histology, *BRCA1* mutation analysis is frequently performed regardless of the family history of breast and/or ovarian cancer. The specific biological origin of mammary tumours in *BRCA1* mutation carriers has been revealed by messenger RNA (mRNA) expression analyses and next-generation sequencing of breast cancer tissues (Sørlie, 2004; Stephens et al., 2012).

No consistently defined phenotype has been described for patients with *BRCA2* familial breast cancer, although some reports indicate a more frequent occurrence of tubular, lobular, and pleomorphic lobular carcinomas (Lakhani et al., 1998, 2002; Honrado et al., 2006; Palacios et al., 2008; van der Groep et al., 2011; Vargas et al., 2011). *BRCA2* mutation-related tumours show a high frequency of ER positivity, similar to sporadic cases, and they are usually HER2-negative. *BRCA2*-related tumours are of higher grade (grades 2 and 3) than sporadic tumours and may show more prominent lymphocytic infiltration, foci of necrosis, and pushing margins than sporadic tumours do. However, these features are exhibited less consistently by *BRCA2*-related tumours than are the medullary-like features by *BRCA1*-related tumours.

Both BRCA1-deficient cells and BRCA2-deficient cells display genomic instability due

to impaired DNA repair, but cancers arising in *BRCA1/2* mutation carriers differ in their characteristics. The pathology and behaviour of *BRCA1/2*-related cancers have been extensively studied, and comprehensive review articles are available (Lakhani et al., 1998, 2002; Honrado et al., 2006; Atchley et al., 2008; Palacios et al., 2008; van der Groep et al., 2011; Vargas et al., 2011; Goodwin et al., 2012).

Breast cancers caused by other breast cancer susceptibility genes do not seem to differ significantly from sporadic breast cancers, but the numbers studied so far are small (van der Groep et al., 2011).

Other reported somatic point mutations, such as indels (insertions or deletions of bases), may be the consequence of the intrinsic infidelity of the DNA replication machinery, of exogenous or endogenous mutagen exposures, of enzymatic DNA modification, or of defective DNA repair. Somatically acquired mutations in triple-negative cancers vary extensively among breast tumours (Stephens et al., 2012). Integrative pathway analyses, comparing basal-like and luminal tumours, have identified hyperactivated FOXM1 as a transcriptional driver of proliferation and have found increased MYC and HIF1α/ARNT as key regulators (Kristensen et al., 2012). Integrative pathway analysis has also confirmed that loss of RB1 and BRCA1 expression are basal-like features.

Combined copy number aberrations and gene expression analyses have been used to classify and categorize breast cancer, and 10 integrative cluster groups have been defined (Curtis et al., 2012). Most of the triple-negative cancers were classified in integrative cluster 10, representing the core basal subgroup in this new classification. The highest rate of *TP53* mutations was found in integrative cluster 10, combined with intermediate levels of genomic instability, loss of 5q, and gains at 8q, 10p, and 12p (Jain et al., 2001; Curtis et al., 2012). Loss of 5q has been associated with the presence of a *TP53* mutation (Jain et al., 2001), and a basal-specific gene expression pattern has been linked with cell-cycle checkpoint control, DNA damage repair, and apoptosis (Dawson et al., 2013). Also, triple-negative cancers are characterized by increased lymphocytic infiltration (Chappuis et al., 2000).

1.2.5 Summary

(a) Benign breast disease

The vast majority of benign breast lesions, which can present symptomatically or be detected using breast screening methods including BSE, do not appear to develop to breast cancers. They are therefore clinically innocent and merit treatment by excision only if causing symptoms, otherwise requiring no intervention. In contrast, various forms of breast epithelial proliferation have been associated with an increased average risk of subsequent breast cancer (1.5–2.0-fold for usual epithelial hyperplasia and 2.5–4.0-fold for atypical hyperplasia).

(b) DCIS

The two forms of non-invasive breast carcinoma in situ are DCIS and LCIS, each with distinctive morphological and behavioural characteristics. The neoplastic cell populations are confined within the parenchymal site of origin, and the cells do not infiltrate beyond the limiting basement membrane. Nuclear grading is the recommended method for subclassification of DCIS into the categories of high, intermediate, and low nuclear grade, but mixed and rare subtypes are also recognized.

Both DCIS and LCIS harbour molecular alterations and intrinsic molecular subtype characteristics that are similar to those of their related forms of invasive breast cancer; thus, no distinct biological or molecular hallmarks of invasive potential have been identified.

The available data on low-grade DCIS show that at least 40% of cases progress to invasive cancer on long-term follow-up. For ethical reasons, only historical data are available for

high-grade DCIS, and high rates of progression to invasive breast cancer are reported. There are no methods available to reliably distinguish between cases that will progress and those that will not.

DCIS is identified more frequently by mammography screening than by clinical examination, as small radiodense deposits of microcalcification.

(c) Invasive breast carcinoma

Invasive carcinoma of the breast is a malignant tumour, part or all of which penetrates the basement membrane of the epithelial site of origin (i.e. the duct or lobule).

The vast majority of these tumours are adenocarcinomas derived from mammary epithelial cells. The morphological appearance of these tumours varies widely, and many of the recognized morphological types have specific behavioural, prognostic, and clinical characteristics.

The morphological diversity of invasive breast cancer is directly related to the underlying molecular genetics. Distinct molecular intrinsic subtypes have been identified, including the luminal, HER2-overexpressing, and basal-like (often triple-negative) classes. Continued developments in molecular biology techniques will provide greater insights into the molecular pathology of breast cancer.

Invasive breast cancer may spread via both the blood and the lymphatic systems, and may progress via regional lymph nodes and systemic metastatic spread. The probability that metastatic spread has occurred is highly correlated with tumour size, and the capacity for lymph-node metastatic spread is, on average, acquired earlier than the capacity for systemic metastatic spread.

Historical studies of untreated invasive breast cancer show poor survival, with progression through the development of metastatic disease. Reviews of the medical literature indicate that confirmed examples of spontaneous regression of breast cancer are exceptionally infrequent.

(d) Related issues

When assessed by external quality assurance systems, the misclassification of cancer cases by pathologists as a cause of overdiagnosis is very rare.

In breast screening, overdiagnosis is defined as the diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if screening had not taken place. The biological explanation for this theoretical concept remains unclear, but it is widely believed to relate to potential indolence of a low proportion of breast cancers.

1.3 Risk factors

Although it would be ideal to identify a subset of the population from which most cases would arise on the basis of established breast cancer risk factors, simulations of risk-based screening have not confirmed the validity of this approach. Screening of 17 543 women led to the conclusion that more than 50% of the cases would not have been detected if only women with either a previous breast biopsy or a family history of breast cancer had been screened, and that more than 40% of the cases would have been missed if women had been selected for screening on the basis of other established breast cancer risk factors (Solin et al., 1984). An analysis of the Edinburgh randomized trial similarly reported that if women had been selected for screening based on a previous biopsy or on a history of breast cancer in a mother or sister, only 19.8% of the first-round cancers would have been detected (Alexander et al., 1987). When menopausal status and nulliparity or first birth after age 30 years were included as high-risk factors, the proportion of first-round cases that would have been detected increased to 55.6%. Consequently, restricting screening

to women with the most established risk factors would fail to identify the majority of prevalent cancers in an asymptomatic population. Madigan et al. reported population attributable risk estimates for breast cancer derived using data from the United States National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (Madigan et al., 1995). Well-established risk factors, such as later age at first live birth, nulliparity, higher family income, and family history of breast cancer in first-degree relatives, were associated with approximately 41% of the breast cancer cases in the USA. In the Netherlands, retrospective evaluation of a breast cancer screening programme showed that only 63% of the breast cancer cases would have been identified if the programme had screened only women with at least one established risk factor, representing only 37% of the study group (De Waard et al., 1988). The authors concluded that the "relevance of the high-risk group concept in screening for breast cancer is small". Finally, data from a large multicentre case–control study in Italy indicated that it would be necessary to screen 87% of the population in order to detect 95% of the cases (Paci et al., 1988). The authors concluded that breast cancer risk factors discriminated poorly for selective screening.

In each of these studies, the overall conclusion was that breast screening on the basis of selected breast cancer risk factors, individually or in combination, fails to identify a subset of women from which the majority of cases of breast cancer are expected to arise. It should also be stressed that the greater the complexity of the risk-based strategy, the greater the need for a regular risk assessment programme to ensure that as risk profiles change, women are cycled in and out of the programme. This necessity not only adds complexity and costs but also adds the potential for misspecification. From a public health standpoint, it appears that the single best strategy for breast cancer screening is a simple one, based on age-related invitation.

Breast cancer in women, as is the case for most cancers, is a multifactorial disease. Its risk factors strongly reflect the hormonal etiology; among the relevant biological exposures are levels of sex steroids, other hormones, and growth factors, including estrogens, androgens, prolactin, and insulin-like growth factors. Life-course reproductive, anthropometric, and lifestyle factors, many of which are prevalent in high-incidence countries, are well-established risk factors: early menarche, late menopause, later age at first pregnancy, nulliparity and low parity, little or no breastfeeding, higher body mass index (BMI) at postmenopausal ages, and tall stature. Lifestyle factors associated with increased risk include low physical activity levels, alcohol consumption, certain exogenous hormone therapies, and exposure to ionizing radiation. Breast density, history of benign breast disease, and family history of cancer are also linked to an increased risk of breast cancer. Also, a small proportion of breast cancers are hereditary, and specific genetic mutations have been identified.

In the following sections, breast cancer risk factors are broadly grouped into: hormonal and reproductive factors (Section 1.3.1), lifestyle factors and environmental exposures (Section 1.3.2), and risk factors that are not modifiable (Section 1.3.3). Exposure to ionizing radiation is described in Section 1.3.4, and genetic factors are described in Section 1.3.5. Population attributable fractions to known risk factors in different settings are summarized in Section 1.3.6. Table 1.4 presents the magnitude of relative risks for breast cancer associated with these risk factors.

1.3.1 Hormonal and reproductive factors

(a) Age at menarche

Women who have had an early menarche have higher breast cancer incidence rates. This association has been consistently observed across ethnic groups and countries. A collaborative

Table 1.4 Magnitude of relative risk for breast cancer associated with established risk factors

Risk factor	Categories	RR (95% confidence interval)	Reference
Hormonal and reproductive factors			
Age at menarche (years)	11	1.0 (reference)	Colditz et al. (2000)
	15	0.69 (0.65–0.74)	
Parity	Nulliparous	1.0 (reference)	
	Parous	1.26 (1.10–1.44)	
Age at first full-term pregnancy (years)	20	0.73 (0.63–0.86)	
	30	1.16 (0.96–1.41)	
Breastfeeding	Per 12 months of total breastfeeding	0.96 (0.94–0.97)	Collaborative Group on Hormonal Factors in Breast Cancer (2002)
Age at menopause (years)	45	1.0 (reference)	Colditz et al. (2000)
	55	1.44 (1.26–1.64)	
Type of menopause	Natural	1.0 (reference)	
	Bilateral oophorectomy	0.89 (0.80–0.98)	
Postmenopausal hormone use	None	1.0 (reference)	IARC (2012a)
	Estrogen only[a]	1.18 (1.08–1.30)	
	Combined estrogen–progestogen[a] for > 5 years	1.63 (1.22–2.18)	
Lifestyle factors			
Alcohol consumption	Per 12 g/day	1.12 (1.09–1.14)	Allen et al. (2009), WCRF/AICR (2010), IARC (2012b)
	Premenopausal	1.09 (1.01–1.17)	
	Postmenopausal	1.08 (1.05–1.10)	
Tobacco smoking (pack–years)	≥ 20	1.28 (1.17–1.39)	IARC (2012b), Warren et al. (2014)
Weight increase (per 5 kg/m^2 increase in BMI)	Postmenopausal	1.12 (1.08–1.16)	WCRF/AICR (2010)
	Premenopausal	0.92 (0.88–0.97)	
Physical activity, high vs low (METs)	Premenopausal	0.87 (0.84–0.92)	WCRF/AICR (2010), Chlebowski (2013), Wu et al. (2013)
	Postmenopausal	0.77 (0.72–0.84)	
	Moderate physical activity (3–5.9 METs)	0.81 (0.72–0.92)	
Non-modifiable factors			
Height (per 5 cm increase)	Premenopausal	1.09 (1.05–1.14)	WCRF/AICR (2010)
	Postmenopausal	1.11 (1.09–1.13)	
	Any age	1.03 (1.01–1.04)	
Age (years)	< 50	1.0 (reference)	Anderson et al. (2006)
	50–59	6.6 (6.5–6.7)	
	60–69	9.2 (9.1–9.3)	
	70–79	11.1 (10.9–11.2)	
	≥ 80	10.1 (10.0–10.3)	
Benign breast disease	No	1.0 (reference)	Colditz et al. (2000), Lakhani et al. (2012)
	Non-epithelial proliferative hyperplasia	1.57 (1.43–1.73)	

Table 1.4 (continued)

Risk factor	Categories	RR (95% confidence interval)	Reference
	Common epithelial hyperplasia	1.5–2.0	
	Atypical epithelial hyperplasia	2.5–4.0	
Breast density	Dense area, mean: 59.92–201.49 cm^2	1.57 (1.18–1.67)	Chiu et al. (2010)
Ionizing radiation			
Radiation exposure			See Table 1.6
Family and personal history of breast cancer			See also Section 1.3.5
Mother's age (years) at breast cancer	< 50	2.69 (2.29–3.15)	Anderson et al. (2000)
	≥ 50	1.88 (1.73–2.03)	

[a] Used continuously from age 50–60 years.
BMI, body mass index; CI, confidence interval; METs, metabolic equivalents; RR, relative risk.

pooled analysis demonstrated that each 1-year delay in menarche is associated with a reduction of approximately 5.0% (95% confidence interval [CI], 4.4–5.7%) in risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2012).

(b) Parity

In general, nulliparous women have a higher risk of breast cancer (up to 2-fold increase) compared with parous women. It has been observed that parous women have a temporarily increased risk of breast cancer up to 15 years after childbirth; thereafter, the risk declines to below that of nulliparous women (Lambe et al., 1994). Each birth is associated with an average long-term reduction of 7% in the relative risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

(c) Age at first full-term pregnancy

Women who have their first full-term pregnancy at a younger age have a lower risk of breast cancer. Women aged 30 years or older at their first full-term pregnancy have consistently been shown to have a short-term increased risk of breast cancer, with relative risks ranging between 1.2 and 2.3, compared with women younger than 20 years at their first full-term pregnancy (MacMahon et al., 1973; Trichopoulos et al., 1983; Bruzzi et al., 1985; Gail et al., 1989; Ewertz et al., 1990; Harris et al., 1992; Madigan et al., 1995; Nagata et al., 1995; Byrne & Harris, 1996; Colditz et al., 2000; Wohlfahrt & Melbye, 2001; Tamakoshi et al., 2005; Washbrook, 2006; Iwasaki et al., 2007; Pike et al., 2007; Iwasaki & Tsugane, 2011; Kobayashi et al., 2012).

(d) Breastfeeding

Women who have breastfed their children have a reduced risk of breast cancer at both premenopausal and postmenopausal ages. At an equal number of full-term pregnancies, breast cancer risk decreases by approximately 4.3% (95% CI, 2.9–5.8%) for every 12 months of breastfeeding, whether consecutive or not, compared with women who never breastfed (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). This protective effect cumulates with the effect of parity. The meta-analysis performed by the World Cancer Research Fund estimated the decreased breast cancer risk per 5 months of total breastfeeding to be 2% (pooled odds ratio, 0.98; 95% CI, 0.97–0.98) (WCRF/AICR, 2010).

(e) Age at menopause

Later age at menopause (≥55 years vs ≤45 years) is associated with an increased risk of breast cancer (1.9-fold vs 1.1-fold increased risk). Among women with natural menopause at age 55 years, the incidence is twice that among women with natural menopause at age 45 years (typically, relative risk [RR], 1.5 vs 0.7) and 3 times that among women with bilateral oophorectomy and menopause at age 35 years (RR, 0.4) (Harris et al., 1992; Kelsey & Bernstein, 1996; Colditz & Rosner, 2000; Iwasaki et al., 2007; Pike et al., 2007; Iwasaki & Tsugane, 2011). Each 1-year delay in the onset of menopause corresponds to an increase of approximately 3% in risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Cuzick, 2003; Washbrook, 2006), and each 5-year delay corresponds to an increase of 17% (95% CI, 1.11–1.22) in risk of breast cancer (Hsieh et al., 1990).

(f) Endogenous hormones

Among postmenopausal women, those with high blood levels of both estrogens and androgens have almost double the risk of breast cancer compared with those with low blood levels (Key et al., 2002; Missmer et al., 2004; Kaaks et al., 2005). The major known determinant of endogenous estrogen levels in postmenopausal women is BMI (estrogen levels in obese postmenopausal women are more than twice those in slender postmenopausal women), and this appears to largely explain the observed association (Key et al., 2003). Among premenopausal women, it is more difficult to estimate the breast cancer risk related to the levels of endogenous sex hormones, mainly because of the large variations in hormone levels across the menstrual cycle. However, high blood estrogen levels in premenopausal women have been reported to be associated with an increase of approximately 40% in breast cancer risk (Key et al., 2013). High blood levels of insulin-like growth factor 1 (IGF-1) are associated with an increase of approximately 30% in breast cancer risk in both premenopausal and postmenopausal women (Key et al., 2010), and high blood levels of prolactin are associated with an increase of approximately 30% in breast cancer risk in postmenopausal women (Tworoger et al., 2013; Tikk et al., 2014).

(g) Use of oral contraceptives

The use of combined estrogen–progestogen oral contraceptives causes breast cancer (IARC, 2012a). After 10 years of use of oral contraceptives, the relative risk is 1.24 (95% CI, 1.15–1.33) among current users, and it decreases with time since stopping the use of oral contraceptives. No significant excess risk of breast cancer has been observed 10 years or more after stopping the use of oral contraceptives. In general, the duration of use, the age at first use, and the dose and type of hormone within the oral contraceptives have not shown any additional effect on breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). The risk is particularly increased among current users with benign breast disease, or among users younger than 20 years (RR, 1.63; 95% CI, 1.02–2.62) (IARC, 2012a).

(h) Use of hormonal menopausal therapy

The use of estrogen–progestogen hormone replacement therapy (HRT) increases the risk of developing breast cancer. The relative risk is less than 2 for long-term users (≥ 5 years) or high-dose users (IARC, 2012a; Chlebowski et al., 2013; de Villiers et al., 2013b), but is already significantly increased (odds ratio [OR], 1.35; 95% CI, 1.16–1.57) after less than 5 years of use (Shah et al., 2005). In long-term users (> 5 years), the risk is still increased several years after stopping the use of HRT (hazard ratio for 5–10 years after stopping, 1.34; 95% CI, 1.04–1.73) (Fournier et al., 2014). Overall, the increase in risk is estimated to be 2% for each additional year of use. The association is clearer in slender women

than in obese women (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Beral et al., 2005; Pike et al., 2007). A decreased breast cancer risk with estrogen-only menopausal therapy was observed among women who had undergone a hysterectomy (Stefanick et al., 2006). The trend for decreased breast cancer incidence among women aged 50 years and older observed in some countries (see Section 1.1) may be related to a reduction in use of HRT (Antoine et al., 2014), although this remains a complex issue (de Villiers et al., 2013a).

It appears that the effects of HRT on a woman's risk of breast cancer depend greatly on her BMI. Treatment with estrogen (conjugated equine estrogen at 0.625 mg/day) for 5 years has an estimated effect of increasing breast cancer risk by 30% in women with a BMI of 20 kg/m^2 and by 8% in women with a BMI of 30 kg/m^2. In contrast, use of combined estrogen–progestin therapy (medroxyprogesterone acetate at 2.5 mg/day) for 5 years is estimated to increase risk of breast cancer by 50% in women with a BMI of 20 kg/m^2 and by 26% in women with a BMI of 30 kg/m^2. With use at a higher dose (medroxyprogesterone acetate at 10 mg/day) for 5 years, the estimated increase in breast cancer risk is 59% and 34%, respectively (Pike et al., 2007).

When comparing continuous versus sequential combined therapy, the risk estimates per 5-year use are of 1.20 (95% CI, 1.01–1.44) for continuous therapy and of 1.32 (95% CI, 1.11–1.56) for sequential therapy in women in the USA; for women in Europe, the breast cancer risk increases by 88% for continuous therapy (RR, 1.88; 95% CI, 1.61–2.21) and by 40% for sequential therapy (RR, 1.40; 95% CI, 1.19–1.64) (Lee et al., 2005). The observed differences in risk between women in the USA and Europe may be explained by different treatment regimens and differences in women's BMI (Pike et al., 2007).

Whereas using percutaneous estradiol with or without micronized progesterone did not seem to increase breast cancer risk, a combination of estrogens with synthetic progestogens seemed to increase it by 40–50% (RR, 1.4; 95% CI, 1.2–1.7) (Fournier et al., 2005), except with dydrogesterone (Fournier et al., 2009).

(i) Other hormonal treatment

Women exposed to diethylstilbestrol while pregnant have an increased risk of breast cancer (IARC, 2012a).

1.3.2 Lifestyle factors and environmental exposures

(a) Alcohol consumption

Alcohol consumption is carcinogenic to humans (Group 1) and causes cancer of the female breast (IARC, 2012b). There is convincing evidence that the consumption of alcoholic beverages increases the incidence of breast cancer in both premenopausal and postmenopausal women, irrespective of the type of alcoholic beverage. Compared with not consuming any alcohol, the consumption of three or more alcoholic drinks per day is associated with an increase of 40–50% in breast cancer risk (Seitz et al., 2012). A linear exposure–response relationship is apparent, and the risk increases by 10% (RR, 1.10; 95% CI, 1.06–1.14) for each 10 g/day (WCRF/AICR, 2007). Even at low levels of alcohol consumption (1 drink/day, ~12.5 g of ethanol/drink, ~0.8 g of ethanol/mL), a significant association with breast cancer risk is seen (RR, 1.05; 95% CI, 1.02–1.08) (Bagnardi et al., 2013; Scoccianti et al., 2014). No threshold of consumption has been identified, and there is robust evidence for mechanisms of alcohol-associated carcinogenesis in humans (WCRF/AICR, 2007).

(b) Tobacco smoking

Although the evidence that tobacco smoking increases breast cancer risk is limited, several subgroup analyses support that smoking at early

ages (before the first full-term pregnancy) and smoking for several decades do increase the risk (Secretan et al., 2009; IARC, 2012b). The 2014 United States Surgeon General's report concluded that "the evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer" (Warren et al., 2014). The report noted that several epidemiological issues may prevent the assessment of an association between active smoking and breast cancer risk, including: (i) timing of exposure at early ages and/or long duration of smoking, (ii) potential confounding or effect modification, and (iii) the exact definition of the outcome (e.g. ER-positive breast cancer).

(c) Overweight, obesity, and change in body weight

There are consistent epidemiological data that support an inverse exposure–response relationship (protective effect) between high body fat and risk of breast cancer in premenopausal women, with a clear exposure–response relationship (IARC, 2002; WCRF/AICR, 2007, 2010). In contrast, increased abdominal fat and weight gain in adulthood are associated with an increased risk of developing postmenopausal breast cancer (RR, 1.19; 95% CI, 1.10–1.28 per 0.1 increment in waist-to-hip ratio; RR, 1.05; 95% CI, 1.04–1.07 per 5 kg weight gain), whereas higher birth weight is associated with an increased risk of premenopausal breast cancer (RR, 1.08; 95% CI, 1.04–1.13) (WCRF/AICR, 2007). The global burden of postmenopausal breast and corpus uteri cancers attributed to excess BMI is estimated at 221 000 cases and is concentrated in countries with very high and high HDI compared with countries with medium and low HDI (Arnold et al., 2015).

(d) Physical activity

Overall, results from prospective studies suggest that increased physical activity has a protective effect for both premenopausal and postmenopausal breast cancer. The evidence for postmenopausal breast cancer appears to be stronger than that for premenopausal breast cancer, but there is some heterogeneity in the exposure–response relationship depending on the study design. There are few data regarding the effects of frequency, duration, or intensity of activity on breast cancer risk (WCRF/AICR, 2007, 2010; Chlebowski, 2013; Wu et al., 2013).

1.3.3 Non-modifiable risk factors

(a) Height

Overall, there is abundant and consistent evidence of a clear exposure–response relationship and of plausible mechanisms in humans of the association between height and breast cancer risk. The World Cancer Research Fund reported that factors leading to greater adult attained height are associated with an increased risk of breast cancer in both premenopausal and postmenopausal women (RR, 1.03; 95% CI, 1.01–1.04 per 5 cm increase in height) (WCRF/AICR, 2010).

(b) Age

In many populations, breast cancer incidence rates appear to increase rapidly before age 50 years and generally flatten in later years (see Section 1.1). Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute show that at postmenopausal ages, incidence rates of ER-positive breast cancer continue to increase, whereas those for more-aggressive, earlier-onset ER-negative breast cancer reach a plateau or decline (Anderson et al., 2006). Breast cancer shows an age–incidence pattern for ER expression, and relative risks compared with women younger than 50 years increase 6-fold at ages 50–59 years and up to 10-fold at ages 70 years and older (Anderson et al., 2006).

Table 1.5 Distribution of breast density on first and last screening mammography, by age group, for women without and with breast cancer diagnosed after the most recent or last screening mammography

Age (years)	BI-RADS category	No breast cancer (%)		Breast cancer patients (%)	
		First screen	Last screen	First screen	Last screen
40–49	1	4.9	4.8	0.9	1.3
	2	36.1	35.6	27.2	24.7
	3	44.6	47.6	49.6	57.1
	4	14.5	12.1	22.3	16.8
50–59	1	10.5	10.4	4.3	3.6
	2	49.1	49.8	45.8	47.3
	3	34.5	35.3	44.0	43.4
	4	6.0	4.5	5.9	5.7
60–69	1	16.8	14.4	11.5	7.6
	2	57.2	56.4	58.2	56.8
	3	23.5	26.8	27.2	33.5
	4	2.5	2.4	3.2	2.1

BI-RADS, American College of Radiology Breast Imaging Reporting and Data System.
Adapted from Kerlikowske et al. (2007). Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk, *Journal of the National Cancer Institute*, volume 99, issue 5, pages 386–395, by permission of Oxford University Press.

(c) Benign breast disease

The majority of benign breast conditions are non-proliferative lesions with no associated increased risk of subsequent development to breast cancer. However, usual epithelial hyperplasia is associated with a 1.5–2.0-fold increased risk, and atypical hyperplasia, both ductal and lobular, with a 2.5–4.0-fold increased risk (London et al., 1992; Dupont et al., 1993; Fitzgibbons et al., 1998; Colditz et al., 2000; Lakhani et al., 2012).

(d) Breast density

Breast density, commonly referred to as "mammographic density", is the relative composition of mammary collagen-rich stromal tissues in the breast, as opposed to the lower-density adipose tissue. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) has visually estimated and classified breast density into the following categories of increasing area density: category 1, < 25% (almost entirely fatty); category 2, 25–50% (scattered fibroglandular densities); category 3, 51–75% (heterogeneously dense); category 4, > 75% (extremely dense) (see Table 1.5 for the distribution of breast density by age group and cancer status; Lazarus et al., 2006; Kerlikowske et al., 2007). These categories serve during the routine interpretation of mammography and are measured on a mammogram as the percentage of the projected breast area that is radiodense (radiopaque), known as "percent mammographic density" (Boyd et al., 2005; McCormack & dos Santos Silva, 2006; Boyd et al., 2007; Chiu et al., 2010; Pike & Pearce, 2013).

Mammographic density appears to be correlated with several other breast cancer risk factors, including genetic predisposition (Becker & Kaaks, 2009; Boyd et al., 2009) and genetic polymorphisms (Dumas & Diorio, 2010; Lindström et al., 2011; Peng et al., 2011). Although after adjusting for other risk factors, mammographic density appears to remain independently associated with breast cancer risk (Pettersson et al., 2014), at present it has not proven to be a valuable

component for modelling and predicting breast cancer risk (Barlow et al., 2006; Tice et al., 2008).

An important effect of mammographic density is the risk of a false-negative mammography finding due to the masking effect of dense tissue (Boyd et al., 2007). The effect of density on the sensitivity of mammographic screening is discussed and quantified in Section 2.1.9.

1.3.4 Ionizing radiation

Exposure to ionizing radiation is a well-established risk factor for breast cancer, as concluded by several international committees (National Research Council, 2006; INSERM, 2008; UNSCEAR, 2010, 2013; IARC, 2012c). Knowledge about radiation-related risk of breast cancer in women is derived mainly from studies of atomic bomb survivors, women exposed to diagnostic radiation, and patients exposed during therapy for benign disease or for cancer, mainly during childhood. Other useful information about the radiation-related risk of the general population derives from studies of occupationally exposed workers, such as medical workers (Table 1.6). The huge amount of evidence of an exposure–risk relationship comes from epidemiological studies of various populations, age groups, and exposure conditions (Ronckers et al., 2005; Telle-Lamberton, 2008). In summary, the majority of studies indicate that breast cancer may be induced after radiation exposure of women younger than 40 years. Studies of atomic bomb survivors or of patients medically exposed show very low or no risk from exposure after that age.

(a) Atomic bomb survivors

Regularly updated analyses of incidence and mortality in the Life Span Study of Japanese atomic bomb survivors have enabled detailed studies of the consequences of exposure received at one time and at a high exposure rate over a population exposed at various ages (Land et al., 2003; Preston et al., 2007; Ozasa et al., 2012). The dose–response for breast cancer risk is significant, is among the highest compared with other cancer sites, and is consistent with a statistical model in which the excess risk of breast cancer is proportional to the radiation dose received (the so-called linear, no-threshold model). An important and significant effect of age at exposure is observed, with a higher risk for women exposed before age 20 years, a less-increased risk for women exposed after age 40 years, and a not measurably increased risk for women exposed after age 50 years. Although it is challenging to separate the role of age at exposure from the role of attained age (or age at observation for risk), it is necessary to calculate the radiation-associated breast cancer risk, and this has enabled the identification of an early-onset group of women at high risk (before age 35 years). The general conclusions are similar whether based on incidence or on mortality studies.

(b) Women exposed for medical monitoring

Other informative studies are from women exposed for diagnostic purposes, as during fluoroscopic examinations of pulmonary tuberculosis. An incidence study was conducted in the USA (Boice et al., 1991) and a mortality study was conducted in Canada (Howe & McLaughlin, 1996). The doses to the breast were moderate but fractionated at a high dose rate and received at a mean age of 25 years, resulting in significant dose–response relationships. The estimated excess risks observed in studies of women undergoing multiple radiological examinations for spine deformities were similarly high and suggested a higher carcinogenic effect of radiation among women with a family history of breast cancer (Doody et al., 2000; Ronckers et al., 2008, 2010). The modifying effect of stage of reproductive development at exposure was not found to be significant. Overall, the excess risk of fractionated exposure is similar to the excess risk of acute exposure, such as that received by atomic bomb survivors.

Table 1.6 Epidemiological studies on radiation exposure and risk of breast cancer in women

Reference	Exposed population (size; number of breast cancer cases/ deaths)	Country	Exposure type	Exposure rate	Average dose (Gy)	ERR/Gy (95% CI) Main conclusion
Atomic bomb survivors						
Land et al. (2003), Preston et al. (2007)	Female atomic bomb survivors (70 000; 1060)	Japan	Gamma, neutron	Acute exposure at low doses	0.28	0.87 (0.55–1.30) at age 30 years. Linear dose–response relationship; –19% (–33% to 4%) change by 10-year increment of age at exposure
Ozasa et al. (2012)	Atomic bomb survivors (51 000; 320)	Japan	Gamma, neutron	Acute exposure at low doses	0.28	1.50 (0.93–2.30) –45% (–67% to –17%) change by 10-year increment of age at exposure
Medical monitoring						
Boice et al. (1991)	Women monitored for tuberculosis (2500; 150)	USA	X-rays (radiography, fluoroscopy)	Fractionated moderate dose rate	0.79	0.61 (0.30–1.01) Included in Preston et al. (2002)
Howe & McLaughlin (1996)	Women monitored for tuberculosis (32 000; 680)	Canada	X-rays (radiography, fluoroscopy)	Fractionated moderate dose rate	0.89 Sv	0.90 (0.55–1.39) ERR/Sv at age 15 years Strong dose–response relationship Modification by age at exposure
Doody et al. (2000), Ronckers et al. (2010)	Children and adolescents monitored for scoliosis (5000; 110)	USA	Chest X-rays	Various low dose rates	0.26	3.90 (1.00–9.30)
Ronckers et al. (2008)	Children and adolescents monitored for scoliosis (3000; 80)	USA	Chest X-rays	Various low dose rates	0.13	2.86 (–0.07 to 8.62) Excess only in group with family history of breast cancer No modification by stage of reproductive development at exposure
Radiotherapy for benign disease						
Shore et al. (1986)	Women with postpartum mastitis (600; 50)	USA	X-rays	Fractionated high dose rate	3.8	3.20 (2.30–4.30)
Mattsson et al. (1993, 1995)	Women with breast disease (1200; 280)	Sweden	X-rays	Fractionated high dose rate	5.8	1.63 (0.77–2.89)
Hildreth et al. (1989), Adams et al. (2010)	Infants irradiated for treatment of thymus hypertrophy (1200; 100)	USA	X-rays	Fractionated moderate dose rate	0.71	1.10 (0.61–1.86)
Lundell et al. (1999), Eidemüller et al. (2009)	Children irradiated for treatment of skin haemangioma (17 000; 680)	Sweden	Gamma	Protracted low dose rate	0.29	0.25 (0.14–0.37)

Table 1.6 (continued)

Reference	Exposed population (size; number of breast cancer cases/ deaths)	Country	Exposure type	Exposure rate	Average dose (Gy)	ERR/Gy (95% CI) Main conclusion
Radiotherapy for breast cancer						
Storm et al. (1992)	Women treated by radiotherapy, mainly at or after menopause (56 500; 529)	Denmark	X-rays	High dose rate	2.51	1.04 (0.74–1.46)
Boice et al. (1992)	Women treated by radiotherapy, mainly at or after menopause (41 000; 650)	USA	X-rays	High dose rate	2.82	1.59 (1.07–2.36) at age < 45 years Significant exposure–response only for women treated at age < 45 years
Survivors of childhood cancer						
van Leeuwen et al. (2000, 2003)	Children treated for Hodgkin lymphoma (1200; 50)	Netherlands	Mantle chest radiotherapy	Several fractions of very high dose rate	38	0.06 (0.01–0.45) Further risk reduction for women treated after age 30 years, and for women also receiving chemotherapy
Travis et al. (2003), Hill et al. (2005)	Children treated for Hodgkin lymphoma (3800; 105)	Denmark, Finland, Netherlands, Sweden, USA	Mantle chest radiotherapy	Several fractions of very high dose rate	25	0.15 (0.04–0.73) Higher risk for higher doses No modifying effect of time since radiotherapy No strong conclusion on modifying factors
Guibout et al. (2005)	Children treated for cancer at different sites (1300; 16)	France, United Kingdom	External beam radiotherapy	Several fractions of high dose rate	5.1	0.13 (< 0–0.75) High risk for survivors of Hodgkin lymphoma No effect of age at first cancer
Reulen et al. (2011)	Children treated for cancer at different sites (18 000; 100)	United Kingdom	External beam radiotherapy	Several fractions of moderate to high dose rate	NA	SIR, 2.2 (1.8–2.7)
Kenney et al. (2004), Friedman et al. (2010)	Children treated for cancer at different sites (6000; 200)	USA	External beam radiotherapy	Several fractions of moderate to high dose rate	NA	SIR, 9.8 (8.4–11.5) Larger excess of breast cancer for survivors of Hodgkin lymphoma Increased risk when family history of breast cancer No modifying effect of reproductive and menstrual histories

Table 1.6 (continued)

Reference	Exposed population (size; number of breast cancer cases/ deaths)	Country	Exposure type	Exposure rate	Average dose (Gy)	ERR/Gy (95% CI) Main conclusion
Moskowitz et al. (2014)	Children treated for cancer at different sites (1200; 170)	Canada, USA	External beam radiotherapy	Several fractions of high to very high dose rate	14	SIR, 30.6 (18.4–50.7) for radiation to chest Large excess risks of breast cancer whatever type of radiotherapy Higher risk for mantle field and whole-lung field therapies
Lange et al. (2014)	Children treated for Wilms tumour (2500, 28)	Canada, USA	Chest radiotherapy	Several fractions of high dose rate	12	14.8% (8.7–24.5%) at age 40 years Large excess of breast cancer
Pooled analysis						
Preston et al. (2002)	Atomic bomb survivors, women with tuberculosis, women with postpartum mastitis, women with benign breast disease, children with thymus hypertrophy, and children with skin haemangioma (77 500; 1500)	Japan, Sweden, USA	X-rays, gamma, neutron	Acute and fractionated low to high dose rate	0.2–5.8	0.86 (0.7–1.04) Linear dose–response relationship, flattening at high doses −45% change by 10-year increase of age at exposure Similar risks for acute and fractionated rate
Occupational exposure – medical and radiation workers						
Sigurdson et al. (2003), Doody et al. (2006)	Radiologists and radiological technologists (56 600; 1050)	USA	X-rays	Protracted very low dose rate	~100 mSv/ yr before 1940	2.9 (1.3–6.2) for women exposed before 1935 2.6 (1.3–5.1) for women exposed before age 17 years
Mohan et al. (2002), Liu et al. (2014)	Radiologists and radiological technologists (69 500; 520)	USA	X-rays	Protracted low to moderate dose rate	NA	HR, 2.51 (1.24–5.05) for women exposed before the 1940s Decline in breast cancer mortality with increasing number of times technologists held patient for X-ray
Muirhead et al. (2009)	Radiation workers (17 500; 150 cases/60 deaths)	United Kingdom	X-rays, gamma	Protracted very low dose rate	0.02 Sv	ERR/Sv Mortality, 2.28 (< 0–38.2) Incidence, −0.23 (< 0–18.1)

Table 1.6 (continued)

Reference	Exposed population (size; number of breast cancer cases/ deaths)	Country	Exposure type	Exposure rate	Average dose (Gy)	ERR/Gy (95% CI) Main conclusion
Buitenhuis et al. (2013)	Workers occupationally exposed to radiation (3000; 1200)	Australia	Occupational external radiation	Protracted very low dose rate	NA	OR, 1.16 (0.86–1.57)
Hammer et al. (2014)	Airline flight crews (44 700; 200)	Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, Sweden, United Kingdom, USA	Cosmic radiation	Protracted very low dose rate	~2–6 mSv/ yr	SMR, 1.06 (0.89–1.27)

CI, confidence interval; ERR/Gy (Sv), dose-specific excess relative risk per Gy (per Sv); Gy, gray; HR, hazard ratio; NA, not applicable; OR, odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; Sv, Sievert; yr, year or years.

(c) Women irradiated for benign disease

The risk of breast cancer after radiotherapy for treatment of benign diseases has been estimated mainly among women treated for postpartum mastitis (Shore et al., 1986) or for benign breast disease (Mattsson et al., 1993, 1995), and among children treated for thymus hypertrophy (Hildreth et al., 1989; Adams et al., 2010) or for skin haemangioma (Lundell et al., 1999; Eidemüller et al., 2009). The doses were low to moderate but were received at a fractionated high dose rate, except for the skin haemangioma study. All these studies overall reported significant excess risks of breast cancer. The mean age at exposure of women treated for postpartum mastitis was 26 years and for benign breast disease was 40 years, but in these two studies no effect of age at exposure was observed. Infants treated for thymus hypertrophy were exposed mainly before age 1 year, and an excess risk of breast cancer was still observed after a mean follow-up of 57 years (Adams et al., 2010). In children treated for haemangioma, who were exposed at low doses and at a low dose rate, the estimated dose–response was lower but significant (Eidemüller et al., 2009).

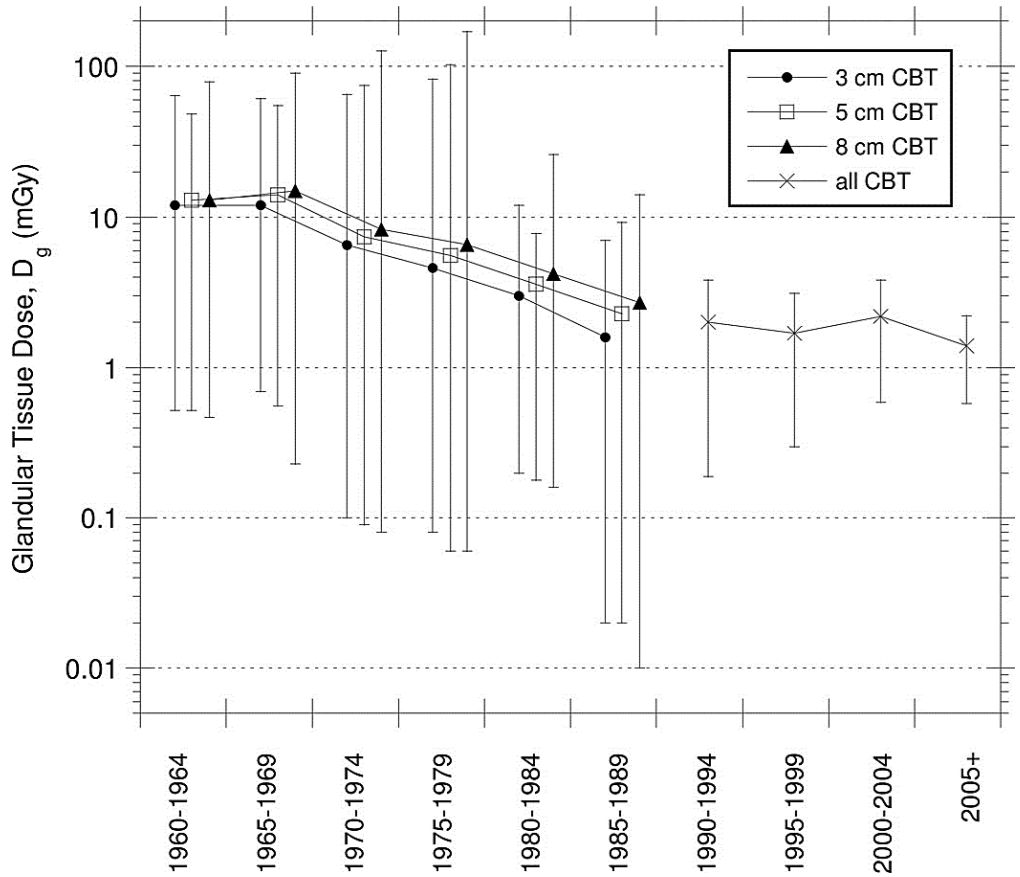
(d) Women irradiated for breast cancer

Two studies were conducted on the risk of contralateral cancer associated with radiotherapy for breast cancer (Boice et al., 1992; Storm et al., 1992). The study in Denmark was mostly of perimenopausal or postmenopausal women and reported little evidence of radiation-induced contralateral breast cancer at low doses (Storm et al., 1992). The study in the USA reported an excess risk that was significant only for women treated before age 45 years (Boice et al., 1992). These two studies concluded that radiotherapy for breast cancer, at average radiation doses of 2.8 Gy and after age 45 years, contributes little, if at all, to the risk of a second cancer in the opposite breast.

(e) Survivors of childhood cancer

Cohorts of survivors of childhood cancer in the United Kingdom and the USA who were treated by X-ray radiotherapy with moderate to very high doses of chest radiation, targeted to mantle and modified mantle fields, mediastinum, lung, and chest (Henderson et al., 2010) exhibit a much higher risk of developing breast cancer compared with the general population (Kenney et al., 2004; Friedman et al., 2010; Reulen et al., 2011). The excess risk of breast cancer was consistently higher among survivors of Hodgkin lymphoma, mainly because they received higher exposure (Henderson et al., 2010). Two pooled studies (Guibout et al., 2005; Moskowitz et al., 2014) reported similar increased risks and gave detailed results either by radiation field or by radiation dose. A significant increase in risk of breast cancer was observed in the pooled cohort from France and the United Kingdom, with each Gray unit received by any breast increasing the excess relative risk by 0.13 (95% CI, < 0.0–0.75) (Guibout et al., 2005). Higher risks for mantle-field therapy (very high doses) and whole-lung-field therapy (large volume of radiation) were reported among women in Canada and the USA treated for cancer during childhood (Moskowitz et al., 2014). Female survivors of Wilms tumour who had been treated with chest radiotherapy had a high risk of developing early breast cancer (Lange et al., 2014). A study of women treated for Hodgkin lymphoma during childhood focused on a good reconstruction of radiation dosimetry and reported a significant dose–response relationship that still increased at very high doses and remained significant with increasing time since therapy (Travis et al., 2003). An analysis of modifying factors in that study was not conclusive (Hill et al., 2005). Similarly, in another study, in the Netherlands, the risk of breast cancer increased significantly with radiation dose, and the relationship was still observed at high doses (van Leeuwen et al., 2000, 2003). In that study,

Fig. 1.17 Population estimates (mean, minimum, maximum) of glandular tissue dose (mGy) from mammography, by time period and CBT



CBT, compressed breast thickness; D_g, glandular tissue dose; mGy, milligray.
From Thierry-Chef et al. (2012). Reconstruction of absorbed doses to fibroglandular tissue of the breast of women undergoing mammography (1960 to the present). *Radiat Res*, 177(1):92–108.

the risk seemed to decrease in women treated after age 30 years (compared with ≤ 20 years) and in women who received additional chemotherapy, partly due to the effect of chemotherapy on an earlier age at menopause.

(f) Women undergoing mammography

The risk of breast cancer induced by mammography is dependent on the dose received by the glandular tissue, as well as many other parameters, including age at exposure, dose rate, type of radiation, and dose–response relationship at low or high dose. Historical estimated doses to glandular breast tissue received from a single mammography view are presented in Fig. 1.17 (Thierry-Chef et al., 2012). Since the late 1990s, the dose received is about 2 mGy, about one sixth of the dose level in the 1960s and well below the dose level of most other exposures, apart from that received by radiation workers (see Table 1.6). Nevertheless, the detailed screening modalities (age range, frequency of screening, number of examinations at each screening, etc.) are necessary to accurately estimate the cumulative dose received by women during their entire participation in a screening programme. The risk of mammography-induced breast cancer is discussed in more detail in Section 5.3.4.

(g) *Pooled analysis of non-occupational exposures*

A very informative pooled analysis of eight cohort studies, of atomic bomb survivors, women with tuberculosis, women with post-partum mastitis, women with benign breast disease, infants treated for thymus hypertrophy, and children treated for skin hemangioma, included women from Japan, Sweden, and the USA exposed to a wide range of radiation doses at different ages (Preston et al., 2002). This study supports the linearity of the dose–response relationship for breast cancer, with evidence of a flattening at high doses. It highlights the independent modifying effect of age at exposure and attained age. Some heterogeneity of the dose–response relationship was observed across studies; this is partly explained by modifying factors such as family history of breast cancer. The study also suggests a similarity in dose–response for acute and fractionated high-dose-rate exposure.

(h) *Women exposed occupationally*

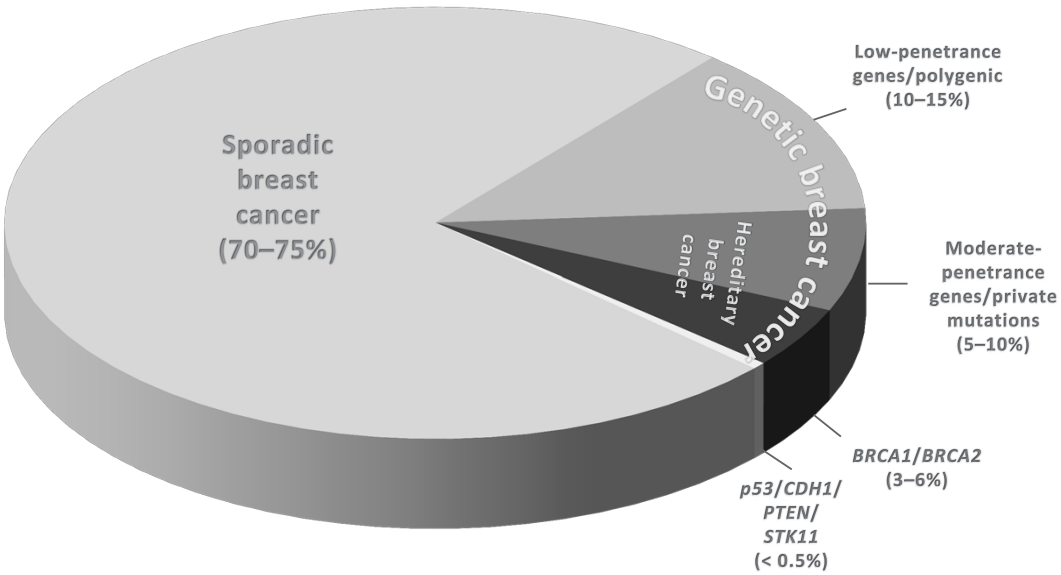
Incidence and mortality data on radiological technologists are available from large cohorts in Canada, the USA, Europe, and China (Mohan et al., 2002; Sigurdson et al., 2003; Doody et al., 2006). Doses received were elevated before 1940 and then decreased gradually; accordingly, current results show higher risks of breast cancer for women in their earlier years of employment. Other cohort studies of medical workers occupationally exposed to radiation are currently under way and may provide interesting results on breast cancer risk among women in the general population. Studies of nuclear workers are another important source of information on cancer risk at low doses and low-dose-rate exposure, but to date they have included too few women to be informative (Cardis et al., 2007). An incidence and mortality study from the United Kingdom National Registry for Radiation Workers showed no significant dose–response relationship for breast cancer (Muirhead et al., 2009). A case–control study in Australia found a low and non-significant excess risk of breast cancer among exposed women (Buitenhuis et al., 2013). Airline flight crews, composed mainly of women, are exposed to doses of cosmic radiation of up to 6 mSv per year. The most recent updated mortality study of an international joint analysis of cohorts of flight crews from 10 countries showed a breast cancer mortality rate similar to that of the general population, whereas a deficit was observed for almost all other cancer sites (Hammer et al., 2010).

(i) *Increased radiosensitivity*

Due to the involvement of *BRCA1/2* in the repair of DNA double-strand breaks, which can be caused by radiation, *BRCA1/2* mutation carriers show increased radiosensitivity (Nieuwenhuis et al., 2002; Venkitaraman, 2002; Powell & Kachnic, 2003; Yoshida & Miki, 2004; Boulton, 2006). In addition to the DNA repair mechanisms described in the above-mentioned studies, very recently a DNA damage-induced BRCA1 protein complex was described as part of the mRNA-splicing machinery. Mutations in BRCA1 and several proteins found within this complex lead to increased sensitivity to DNA damage (Savage et al., 2014).

It has been shown that female *BRCA1/2* mutation carriers have a higher risk of developing a radiation-induced breast cancer compared with non-carriers, and particularly before age 40 years (Broeks et al., 2007). A meta-analysis based on six case–control studies and one cohort study showed a non-significantly increased risk of breast cancer due to exposure to low-dose radiation (OR, 1.3; 95% CI, 0.9–1.8) among women with a familial or genetic predisposition (Jansen-van der Weide et al., 2010). The risk became significant at increasing cumulative doses compared with no or minimal radiation exposure (OR, 1.8; 95% CI, 1.1–3.0) and for exposure occurring before age 20 years (OR, 2.0; 95% CI, 1.3–3.1) (Jansen-van

Fig. 1.18 Schematic distribution of breast cancer incidence according to genetic risk



Created by the Working Group.

der Weide et al., 2010). Similarly, female *BRCA1/2* mutation carriers showed an increased risk of breast cancer before age 20–30 years associated with increasing cumulative doses of (low-dose) diagnostic radiation, and sensitivity analysis showed that this was not confounded by family history in this population (Pijpe et al., 2012).

1.3.5 Women at high genetic risk of breast cancer

Among the established risk factors for breast cancer (Mahoney et al., 2008), genetic factors are of particular importance. The current implementation of high-throughput technology has enabled the detection of hereditary alterations and related oncogenic pathways and of driver somatic mutations in mammary tumours, to characterize the phenotypic subtypes of pathologically heterogeneous breast tumours (Stephens et al., 2012).

As in other malignant tumours, the development of breast cancer is driven predominantly by the gradual and lifelong accumulation of acquired (somatic) mutations, but also by epigenetic changes in mammary cells and their progenitors (Polyak, 2007). Breast cancer is a highly pleomorphic disease, and numerous driver mutations (guiding the process of tumorigenesis) (Stratton et al., 2009) have been described by next-generation sequencing studies (Stephens et al., 2012). These mutations usually affect genes that code for key proteins regulating the maintenance of normal tissue homeostasis. A schematic distribution of breast cancer incidence according to genetic risk is given in Fig. 1.18. (See Section 5.6 for a discussion of the screening of women at an increased risk.)

(a) Hereditary breast cancer

Hereditary breast cancer is caused by germline mutations in highly penetrant breast cancer susceptibility genes, most commonly the *BRCA1/2* genes (Lichtenstein et al., 2000; Rahman, 2014a). Breast cancers attributable to heritable factors represent 5–10% of all breast cancer cases, which is a small but important proportion. Overall, the presence of breast

cancer in any first-degree female relative nearly doubles the risk for a proband, and the inherited risk increases gradually with the number of affected relatives (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). When risk is conferred through the mother, it increases gradually if the mother was diagnosed at a young age or had multiple diagnoses of breast or ovarian cancer (Anderson et al., 2000). For example, the presence of breast cancer in at least one first-degree relative accounts for 13% of cases (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). Also, the early onset of breast cancer and other cancers in mutation carriers increases the probability of recurrence.

Other high- or moderate-penetrance breast cancer susceptibility genes that contribute to the hereditary breast cancer spectrum include *CHEK2*, *PTEN*, *TP53*, *ATM*, *STK11/LKB1*, *CDH1*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2*, although none of them is comparable in frequency and clinical importance to *BRCA1/2* (Antoniou et al., 2014; Couch et al., 2014). Several common features of hereditary breast cancer, documented in both affected families and individuals, characterize this high-risk population.

(b) Penetrance of breast cancer susceptibility genes

Breast cancer susceptibility genes are usually categorized as high-penetrance, moderate-penetrance, or low-penetrance genes, reflecting the relative risk of breast cancer development in mutation carriers.

Mutations in high-penetrance genes (*BRCA1*, *BRCA2*, *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*) increase breast cancer risk more than 5-fold (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). Within this group, the major breast cancer susceptibility genes *BRCA1* and *BRCA2* account for approximately 3–5% of all breast cancer cases and approximately 20–50% of all hereditary breast cancer cases (Rahman, 2014b).

Mutations in moderate- or intermediate-penetrance genes (such as *CHEK2*, *ATM*, *BRIP1*, *NBS1*, *RAD51C*, and *XRCC2*) increase breast cancer risk 2–5-fold. The identification of breast cancer-predisposing mutations in genes is of great clinical importance for both patients and unaffected relatives carrying a pathogenic variant. Analysis of these moderate-penetrance genes has been recommended in individuals with a high familial risk who are found to be negative for the presence of mutations in the major breast cancer susceptibility genes. Signs suggesting the presence of a germline mutation in a breast cancer susceptibility gene are: (i) unusual breast cancer appearance (early disease onset; tumour recurrence; bilateral tumour development; male breast cancer development; presence of rare or minor histopathological diagnoses [triple-negative, medullary, or atypical medullary type]; ER-negative); (ii) clustering of breast cancer in affected families; and (iii) cancer multiplicity (development of breast and other cancer types, including ovarian cancer, colorectal cancer, and melanoma).

Mutations in low-penetrance genes increase breast cancer risk less than 2-fold and have no clinical utility at present (Michailidou et al., 2013). However, the categorization of penetrance is not optimal and sometimes could be rather misleading, due to a limited understanding of the true phenotypic characteristics. Even the major breast cancer susceptibility genes exhibit polymorphisms that increase breast cancer risk only mildly (although with high statistical significance); examples are the *BRCA1* missense mutation R1699Q and the *BRCA2* truncating mutation c.K3326* (Michailidou et al., 2013). Deep sequencing analyses revealed that approximately 20% of triple-negative cancers have potentially druggable aberrations, which include *BRAF* V600E, *EGFR* amplifications, and *ERBB2/ERBB3* mutations (Shah et al., 2012). The incomplete knowledge of the disease characteristics and response to treatment in patients harbouring

mutations in breast cancer susceptibility genes limits the clinical potential of dozens of recently characterized variants, making the assessment of cancer risk in this high-risk population uncertain (Kean, 2014).

The clinical utility of specific variants in the breast cancer susceptibility genes depends not only on their penetrance but also on the population-specific prevalence, which is inversely correlated with the risk of breast cancer development (John et al., 2007; Karami & Mehdipour, 2013). Mutations in breast cancer-predisposing genes other than *BRCA1/2* are usually not frequent and have large population variability. For example, the most common pathogenic variant in the *CHEK2* gene, c.1100delC (Bell et al., 1999), has a frequency of more than 1% in populations in northern Europe, whereas its frequency is lower in central Europe, extremely low in southern Europe, and practically null in Asian populations (Kleibl et al., 2005).

The large majority of breast cancer susceptibility genes code for tumour suppressor proteins that are involved in key DNA repair pathways (except for *PTEN*, *STK11*, and *CDH1*) and could thus represent a critical anticancer barrier; however, the molecular mechanisms through which hereditary alterations trigger the development of breast cancer remain to be elucidated (Bartek et al., 2007).

(c) BRCA1 *and* BRCA2 *mutation carriers*

The BRCA1 and BRCA2 proteins are coded by the most important breast cancer susceptibility genes responsible for the development of familial breast and ovarian cancer syndromes 1 and 2 (Online Mendelian Inheritance in Man [OMIM] #604370 and #612555; OMIM, 2015). The BRCA1 and BRCA2 proteins are structurally unrelated and form part of large multiprotein complexes involved in the repair of DNA double-strand breaks (Li & Greenberg, 2012). Currently, the Breast Cancer Information Core database (BIC, 2015) describes more than 1700 distinct variants in the *BRCA1* gene and more than 1900 in the *BRCA2* gene. The mutation frequency in both genes varies worldwide; it is highest in the Ashkenazi Jewish population, in which 2.5% of women are carriers (Warner et al., 1999; Karami & Mehdipour, 2013).

Among *BRCA1* and *BRCA2* mutation carriers, the cumulative risk to age 80 years was shown to reach 90% and 41%, respectively, for breast cancer and 24% and 8.4%, respectively, for ovarian cancer (Offit, 2006). Overall, the risk of mutations in either gene is comparable in patients from hereditary breast cancer-only families, is particularly increased in families with breast and/or ovarian cancer cases, and is inversely correlated with the age at onset (see above).

Carriers of mutations in either gene are also at increased risk of cancer at other anatomical sites. *BRCA1* mutations in women predispose to the development of fallopian tube and peritoneal cancers, and to a 5-fold increased risk of early-onset colorectal cancer in women younger than 50 years (Sopik et al., 2014).

It has been suggested that several lifestyle factors may modulate the risk of breast cancer in *BRCA1/2* mutation carriers, including breast-feeding, the use of oral contraceptives (associated with a reduced risk in *BRCA1/2* mutation carriers), and smoking (associated with an increased risk in *BRCA2* mutation carriers) (Friebel et al., 2014).

(d) Putative BRCA3 *candidate:* PALB2

The *PALB2* (partner and localizer of *BRCA2*) gene codes for a protein that serves as a scaffold for the BRCA1/2 proteins during the DNA double-strand break repair process. *PALB2* mutations have been associated with an increased risk of hereditary breast cancer and pancreatic cancer. A recent study estimated the cumulative risk to age 70 years of developing breast cancer to be 47.5% for carriers of *PALB2* loss-of-function mutations (Antoniou et al., 2014). Therefore, the risk is similar to that ascertained in *BRCA2*

mutation carriers, although *PALB2* mutations are less frequent. The clinical management of *PALB2* mutation carriers should be similar to that of *BRCA2* mutation carriers.

(e) Other high-penetrance breast cancer susceptibility genes

Hereditary mutations in other high-penetrance genes conferring a high risk of breast cancer are very rare. Previously, they were usually analysed in cases with the clinical and histopathological characteristics of the associated genetic syndromes (Walsh et al., 2006). This practice has changed with the implementation of next-generation sequencing analyses in high-risk individuals (Couch et al., 2014; Tung et al., 2014). Interestingly, somatic mutations in these genes represent frequent driver mutations in sporadic breast cancer (Stephens et al., 2012).

Breast cancer is the most common cancer diagnosed in women affected by Li–Fraumeni syndrome (LFS; OMIM #151623; OMIM, 2015), mostly as ductal carcinoma or DCIS with ER and PR positivity and/or HER2/neu positivity (Masciari et al., 2012). LFS is a hereditary cancer predisposition syndrome caused by a *TP53* mutation (Gonzalez et al., 2009), which confers a cumulative risk of 49% of developing breast cancer by age 60 years. The probability of carrying a *TP53* mutation is increased in breast cancer patients younger than 30 years with a first- or second-degree relative with typical LFS-associated cancers at any age, and is almost null in patients diagnosed with breast cancer at age 30–49 years and with no family history of LFS-associated cancers (Gonzalez et al., 2009).

Female carriers of *CDH1* (human epithelial cadherin) mutations have a cumulative breast cancer risk to age 75 years of 52% (Kaurah et al., 2007), and the breast cancer is frequently of lobular type in patients older than 45 years (Schrader et al., 2011).

Hereditary heterozygous mutations in the *PTEN* (phosphatase and tensin homologue) gene, which codes for a phosphatase targeting phosphatidylinositol (3,4,5)-triphosphate, were characterized in individuals with Cowden syndrome (OMIM #158350; OMIM, 2015). Cowden syndrome is a rare, multisystem disease with an increased lifetime risk of developing breast cancer of 25–50% (Pilarski et al., 2013); higher lifetime risks of breast cancer (67%) and development of other cancer types (e.g. dysplastic cerebellar gangliocytoma) are also reported (Nieuwenhuis et al., 2014).

Mutations in the *STK11* (serine/threonine-protein kinase) gene have been associated with Peutz–Jeghers syndrome (OMIM #175200; OMIM, 2015), a rare disorder characterized by an increased risk of various neoplasms, including an increased risk of 45% of developing ductal breast cancer by age 70 years (Hearle et al., 2006).

(f) Moderate-penetrance breast cancer susceptibility genes

A representative of this group is the *CHEK2* (checkpoint kinase 2) gene, which codes for a regulatory serine/threonine kinase that phosphorylates various protein substrates (including p53 and BRCA1) in response to DNA damage. Mutations in *CHEK2* variants could be dispersed over the entire coding sequence, but only a few studies have analysed these in breast cancer patients (Desrichard et al., 2011). The most common variant, c.1100delC, increases breast cancer risk, with odds ratios of 2.7 for unselected breast cancer, 2.6 for early-onset breast cancer, and 4.8 for familial breast cancer (Weischer et al., 2008) and a hazard ratio of 3.5 and worsened survival for contralateral breast cancer (Weischer et al., 2012), in high-risk individuals not carrying *BRCA1/2* mutations (Meijers-Heijboer et al., 2002). The cumulative risk for patients with familial breast cancer and who are heterozygous carriers was estimated at 37% (Weischer et al., 2008). Breast tumours arising in c.1100delC mutation carriers are frequently of luminal type and express ER and/or PR (Nagel et

al., 2012; Kriege et al., 2014), and do not occur at a particularly young age (Narod, 2010). *CHEK2* variants are highly population-specific, and four other variants were found to be associated with increased risk of multiple cancers, including cancers of the breast, colorectum, prostate, and thyroid (Cybulski et al., 2004). The p.I157T variant has been associated with a significantly increased breast cancer risk (OR, 4.2 for lobular breast cancer) (Liu et al., 2012a, b).

The upstream signalling activator of the CHEK2 protein is the large ATM (ataxia telangiectasia mutated) kinase. The frequency of hereditary variants of the *ATM* gene is estimated to be 0.3–1% in the general population (Prokopcova et al., 2007), and these variants have been associated with an increased relative risk of breast cancer of 2.4 (Renwick et al., 2006). Several studies led to the identification of only a limited number of mutation carriers in high-risk patients, characterized by a 2–3-fold increased breast cancer risk (Damiola et al., 2014).

Several other breast cancer susceptibility genes have been reported. *BRIP1* (also known as *BACH1*) is a BRCA1-binding helicase associated with breast cancer. Three genes – *MRE11*, *RAD50*, and *NBN* (*NBS1*) – that code for a protein complex (MRE11–RAD50–NBS1) required for DNA strand processing during the repair of DNA double-strand breaks have also been identified in breast cancer patients. Recent studies also indicate that mutations in non-canonical breast cancer susceptibility genes (e.g. mismatch repair genes, including *MLH1*, *MLH2*, and *PMS6*, which are associated with hereditary colorectal cancer) may contribute to the increased risk in patients with hereditary breast cancer (Castéra et al., 2014; Tung et al., 2014).

1.3.6 Attributable burden to known risk factors

Overall, established breast cancer risk factors are common across female populations worldwide and explain a large proportion of the 10-fold international variations in breast cancer incidence rates, as well as the increases seen in migrant studies. It has been estimated that the cumulative incidence of breast cancer to age 70 years in developed countries would drop from 6.3% to 2.7% if women had just two reproductive factors (parity and lifetime breastfeeding) similar to those of women in less-developed countries at the time (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; see Table 1.7); in lower-incidence countries, such as those in Africa and Asia, the cumulative risks to age 70 years were 1–2%. International differences in age at first full-term pregnancy and age at menarche are likely to contribute further. Similarly, in the Million Women Study in the United Kingdom, lower breast cancer incidence rates in South Asian women (unadjusted RR, 0.82) and Black women (RR, 0.85) compared with White women were almost entirely attributed to eight reproductive and lifestyle risk factors (Gathani et al., 2014).

Within the same population, non-modifiable risk factors and family history appear to account for population attributable fractions of 40–50%, but most results are from higher-incidence countries. In terms of immediately modifiable risk factors, the 2005 Global Burden of Disease study estimated that 5% of deaths from breast cancer worldwide were attributable to alcohol consumption, 9% to overweight/obesity, and 10% to physical inactivity (with 21% attributable to their joint hazard) (Danaei et al., 2005). Joint population attributable fractions were considerably lower (18%) in low- and middle-income countries (LMICs) than in high-income countries (27%), largely due to lower alcohol consumption and lower prevalence of overweight/obesity in LMICs. [Note that this analysis did not include breastfeeding.]

Table 1.7 Population attributable fraction for breast cancer incidence associated with lifestyle factors in selected populations

Setting	Menopausal status	Risk factor	PAF (%)	References
High-income countries/countries with higher breast cancer incidence rates				
Worldwide		Alcohol consumption	9	Danaei et al. (2005), Arnold et al. (2015)
	Postmenopausal	Overweight/obesity	12.5	
Europe		Physical inactivity	9	
		Insufficiently active	20	Friedenreich et al. (2010)
		Sedentary lifestyle	10	
China		Number of children	4.7	Li et al. (2012)
		OC use	0.7	
		HRT use (1–5 years)	0.3	
Japan		Alcohol consumption, overweight/obesity, physical inactivity, and exogenous hormone use (including HRT and OC use)	10.5	Inoue et al. (2012)
Republic of Korea		Obesity (BMI ≥ 30 kg/m^2)	8.2	Park et al. (2014)
		Low leisure-time physical activity	8.8	
Brazil		Overweight/obesity	14	WCRF/AICR (2009)
Low- and middle-income countries/countries with lower breast cancer incidence rates				
Worldwide		Alcohol consumption	4	
	Postmenopausal	Overweight/obesity	4.4	Danaei et al. (2005), Arnold et al. (2015)
		Physical inactivity	10	
Islamic Republic of Iran	Postmenopausal	Parity < 7	52.6	Ghiasvand et al. (2012)
		BMI > 25 kg/m^2	24.8	
		Family history of breast cancer	15.7	
		OC use	13.7	
		Parity + BMI > 25 kg/m^3 + family history + OC use	71.3	

BMI, body mass index; HRT, hormone replacement therapy; OC, oral contraceptive; PAF, population attributable fraction.
The results collected may reflect some heterogeneity among the methods of the different source publications.

1.4 Stage at diagnosis, survival, and management

The diagnosis and management of breast cancer developed significantly during the late 1990s and early 2000s. Staging describes the size of a carcinoma and whether it has spread regionally to lymph nodes or metastasized to distant organs. Accurate staging provides key prognostic information, helps to tailor treatment protocols, and contributes to the planning and implementation of specific public health interventions, such as screening programmes, aiming to improve the detection of lesions at an early stage and to decrease overall cancer mortality rates.

The staging system routinely used for breast cancer is the tumour–node–metastasis (TNM) classification. It describes localized disease as stages I and II, regional disease as stage III, and distant disease as stage IV, mostly based on the anatomical extent of the primary tumour and the

presence of spread to regional lymph nodes and of distant metastases (Table 1.8 and Table 1.9; UICC, 2010). This classification was first developed in 1940 and is periodically revised and updated by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (Edge et al., 2010). Although the coding schema has evolved considerably over time, a good correlation has always been maintained between old and new classifications, especially for stages 0, I, II, and IV (Kwan et al., 2012; Walters et al., 2013b). The sixth edition of the TNM staging system was officially adopted by tumour registries in January 2003. The heterogeneity of small tumours was reflected in more subcategories in the lower levels of the staging system, and additional issues were assessed, including metastatic lesions detected by molecular biology techniques and/or immunohistochemical staining of sentinel node specimens and the clinical importance of the total number of positive axillary lymph nodes (Singletary & Greene, 2003). The most recent, seventh edition (Table 1.8 and Table 1.9) was published in 2010 and includes the use of specific imaging modalities and of circulating tumour cells detectable in blood or bone marrow to better estimate clinical tumour size (Edge et al., 2010; Murthy & Chamberlain, 2011). The eighth edition will be published in late 2016 and will incorporate further advances in cancer research, staging, diagnosis, and treatment (AJCC, 2014).

Although the TNM classification system is accepted worldwide, there is great variability in the process of stage recording, due to different technological advances in diagnostic procedures across the globe. Therefore, estimates of survival based on stage at diagnosis may be misleading, and survival by stage at diagnosis may appear to have improved while overall survival does not change (Feinstein et al., 1985). International comparisons of survival by stage at diagnosis should take into consideration the variations in clinical classification and coding among cancer registries, which reflect the source of stage data, the time frame after the diagnosis within which the stage was recorded, whether the classification was defined clinically or pathologically, and whether tumour size was recorded before or after neo-adjuvant therapy (Walters et al., 2013a). The TNM system has become extremely complex and may be too complicated for use in developing countries. A much simpler system, such as the one used by the United States National Cancer Institute, could be a better option. The SEER staging, based on the widely accepted theory of cancer development, is the most basic staging system applicable to all anatomical sites (solid tumours). The five main categories of summary staging (in situ, localized, regional, distant, and unknown) are developed based on information available in the medical, clinical, and pathological records. However, although this system is frequently used by tumour registries, is not always properly understood by physicians (SEER, 2014b).

1.4.1 Stage at diagnosis and survival

Population-based cancer registries (PBCRs) provide information on the cancer burden in communities around the world, including incidence, mortality, stage at diagnosis, and survival. Currently, there are more than 700 PBCRs worldwide, although the quality and data coverage of registries differ substantially between developed and developing countries. PBCRs are especially valuable in LMICs, where the available population-based cancer data are few; poorly developed and inaccessible health services result in inconsistencies in early diagnosis, adequate treatment, and follow-up care, with a profound negative effect on cancer survival (Sankaranarayanan et al., 2010; Bray et al., 2014). A standardized minimum data set of variables with coding based on international systems like the TNM classification is required to facilitate the analysis of data

Table 1.8 Tumour–node–metastasis (TNM) clinical classification of breast cancer

T – Primary tumour
TX – Primary tumour cannot be assessed
T0 – No evidence of primary tumour
Tis – Carcinoma in situ
Tis (DCIS) – Ductal carcinoma in situ
Tis (LCIS) – Lobular carcinoma in situ
Tis (Paget) – Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma
T1 – Tumour 2 cm or less in greatest dimension
T1mi – Microinvasion 0.1 cm or less in greatest dimension
T1a – More than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b – More than 0.5 cm but not more than 1 cm in greatest dimension
T1c – More than 1 cm but not more than 2 cm in greatest dimension
T2 – Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3 – Tumour more than 5 cm in greatest dimension
T4 – Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)
T4a – Extension to chest wall (does not include pectoralis muscle invasion only)
T4b – Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
T4c – Both 4a and 4b, above
T4d – Inflammatory carcinoma
N – Regional lymph nodes
NX – Regional lymph nodes cannot be assessed (e.g. previously removed)
N0 – No regional lymph-node metastasis
N1 – Metastasis in movable ipsilateral level I, II axillary lymph node(s)
N2 – Metastasis in ipsilateral level I, II axillary lymph node(s) that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph-node metastasis
N2a – Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
N2b – Metastasis only in clinically detected internal mammary lymph node(s) and in the absence of clinically detected axillary lymph-node metastasis
N3 – Metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph-node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph-node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a – Metastasis in infraclavicular lymph node(s)
N3b – Metastasis in internal mammary and axillary lymph nodes
N3c – Metastasis in supraclavicular lymph node(s)
M – Distant metastasis
M0 – No distant metastasis
M1 – Distant metastasis

Adapted from UICC (2010).

Table 1.9 Tumour–node–metastasis (TNM) stage grouping of breast cancer

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1[a]	N0	M0
Stage IB	T0, T1[a]	N1mi[b]	M0
Stage IIA	T0, T1[a]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0,T1[a],T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[a] T1 includes T1mic.

[b] N1mi, micrometastases > 0.2 mm and ≤ 2 mm.

Used with the permission of the Union for International Cancer Control (UICC, 2010), Geneva, Switzerland. The original source for this material is TNM Classification of Malignant Tumours, 7th Edition, Sobin LH, Gospodarowicz MK, Wittekind C (editors), published by Wiley-Blackwell, 2009.

and to enable comparison of results among registries (Bray et al., 2014).

(a) Stage at diagnosis

In developing countries, an estimated 75% (range, 30–98%) of breast cancer cases are diagnosed at late clinical stages, such as stage III or IV (Sloan & Gelband, 2007; Coughlin & Ekwueme, 2009).

In African countries, retrospective studies have reported that 70–90% of breast cancers are diagnosed at stage III or IV (Fregene & Newman, 2005). A PBCR that covers the Gharbiah Governorate in Egypt reported an increase in the percentage of localized breast tumours from 14.8% in 1999 to 21.4% in 2008 (Hirko et al., 2013).

In India, more than 70% of patients are diagnosed with clinically advanced disease (stage III or IV) (Okonkwo et al., 2008).

In China, findings from a multicentre nationwide screening study showed a tendency towards higher cancer stages for disadvantaged women, with the majority of cases diagnosed at stage II (44.9% of cases) or stage III (18.7% of cases) (Li et al., 2011; Fan et al., 2014).

The proportion of breast cancer cases that are clinically advanced at diagnosis (stages III and IV) is reported as approximately 30–40% in Mexico and less than 20% in Uruguay, although in Uruguay the data come from a single institution. In Brazil, women are diagnosed earlier in the wealthier regions of the country; generally percentages of advanced disease (25–40%) are similar to those in Chile (30%) in 2003 (Justo et al., 2013).

Data from high-income countries for 2000–2007 reported the proportion of stage III or IV disease to be 8% in Sweden and 22% in Denmark and the proportion of localized disease to be 61–62% in Australia, Canada, Denmark, Norway, Sweden, and the United Kingdom (Walters et al., 2013a). For Norway in 2008–2012, the proportion was 0.7% for stage 0, 40.8% for stage I, 38.0% for stage II, 5.9% for stage III, and 3.5% for stage IV (Cancer Registry of Norway, 2014).

In British Columbia, Canada, a population-based cohort study of participants in the Screening Mammography Program reported that the majority of cases were detected at localized stages (38% at stage I and 32% at stage II)

Table 1.10 5-Year age-standardized breast cancer relative survival, by country/region

Country/region (type of registry)	5-Year relative survival (%)
The Gambia[b]	12
Uganda[b]	46
Philippines[b]	47 (40–55)
India[b]	52 (31–54)
Brazil (Brazilian registries)[a]	58.4 (52.7–64.6)
Thailand[b]	63
United Kingdom[a]	69.7 (69.4–70.1)
Europe (European registries)[a]	73.1 (72.9–73.4)
Singapore[b]	76
Costa Rica[b]	77
Turkey[b]	77
Republic of Korea[b]	79 (78–81)
Australia (national registry)[a]	80.7 (80.1–81.3)
Japan (Japanese registries)[a]	81.6 (79.7–83.5)
China[b]	82 (58–90)
Sweden[a]	82.0 (81.2–82.7)
Canada (Canadian registries)[a]	82.5 (81.9–83.0)
USA (North American registries)[a]	83.9 (83.7–84.1)

[a] International Cancer Survival Standard data (with 95% confidence interval) are for adults (aged 15–99 years) diagnosed during 1990–1994 and followed up until 1999. Adapted from Coleman et al. (2008).

[b] Data are the median percentage of an individual registry (and range, minimum–maximum, if more than one registry) for adults diagnosed during 1990–2001 and followed up until 2003. Adapted from Sankaranarayanan et al. (2010).

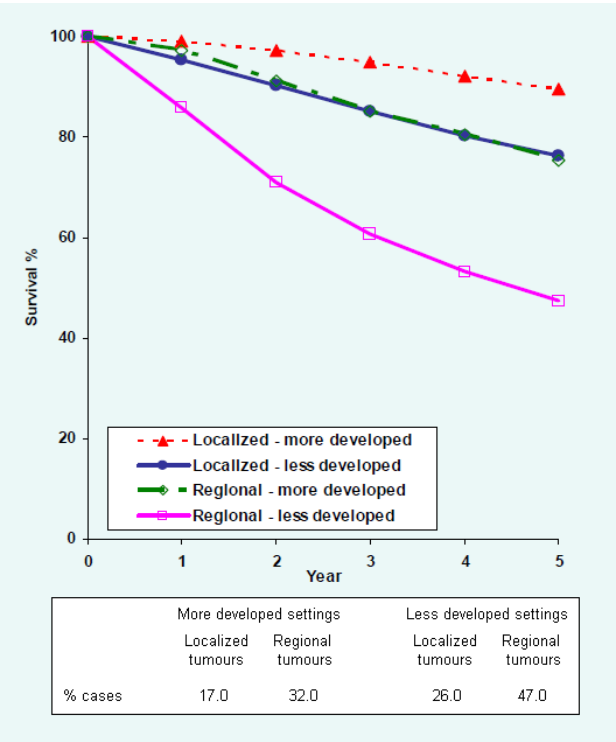
(Davidson et al., 2013). Similarly, in the USA in 1999–2005, 61% of cases were detected at localized stages (stages I and II), 32% at a regionally advanced stage (stage III), and only 5% at a distant-metastatic stage (stage IV) (Shulman et al., 2010). However, the proportion of cases diagnosed beyond the local stage and the 5-year cause-specific probability of death were higher among Black women than among White women (Harper et al., 2009). Data for 2003–2009 for all races showed that 61% of breast cancers were localized (among African-American women, only 52%), 32% were regional, and 5% were distant (Siegel et al., 2014).

(b) Survival

Worldwide, survival differences that persist after adjustment for tumour stage at diagnosis are likely to reflect differences in treatment, accuracy of staging, or tumour biology (Sant et al., 2003; Walters et al., 2013a). Overall, 5-year survival rates are consistently lower in LMICs compared with upper-middle- and high-income countries (Table 1.10; Anderson et al., 2011). Differences in 5-year survival between more- and less-developed health services for both localized and regional breast cancer are shown in Fig. 1.19.

A population-based study on breast cancer survival in countries in Africa, Asia, and Central America reported 5-year relative survival rates of 12% in The Gambia, 46% in Uganda, 52% in India, 82% in China, and 63% in Thailand. Rates in upper-middle- and high-income countries were 70% in Costa Rica, 77% in Turkey, 79% in the Republic of Korea, and 76% in Singapore (Sankaranarayanan et al., 2010). In Latin America, reported 5-year survival rates were 79% in Suriname, 72% in Chile, and 75% in Brazil (Mendonça et al., 2004; Navarrete Montalvo et al., 2008; van Leeuwaarde et al., 2011). In the

Fig. 1.19 Absolute survival for breast cancer, localized and regional extent of disease, by level of development of health services



	More developed settings		Less developed settings	
	Localized tumours	Regional tumours	Localized tumours	Regional tumours
% cases	17.0	32.0	26.0	47.0

From Sankaranarayanan & Swaminathan (2011).

industrialized city of Shanghai, China, 5-year survival was 78% in 1992–1995, whereas in a rural neighbouring area, Qidong, it was only 58% in 1992–2000 (Fan et al., 2014).

Data from PBCRs in Canada (Alberta, British Columbia, Ontario, and Manitoba) showed a slight increase in 5-year survival rates over time, from 85.3% in 1995–2000 to 86.3% in 2005–2007 (Coleman et al., 2011) and to 88% in 2006–2008 (Canadian Cancer Society, 2014).

In the USA, the 5-year survival increased from 75% in 1975 to 89% in 2010, and was 98% for localized disease, 85% for regional disease, and 25% for distant disease (SEER, 2014a). A meta-analysis among African-American and White American breast cancer patients revealed that African-American ethnicity was associated with a 20% excess of mortality in 1980–2005 (Newman et al., 2006).

In Finland, the 5-year survival for breast cancer (all malignant neoplasms) of patients diagnosed in 2005–2010 and observed in 2010–2012 was 90% (Finnish Cancer Registry, 2015).

The largest cooperative study of population-based cancer survival in Europe (EUROCARE) shows a mean breast cancer survival rate of about 82% for breast cancer diagnosed in 2000–2007 (De Angelis et al., 2014). Geographical differences were reported, with higher survival in northern (84.7%), southern (83.6%), and central Europe (83.9%) and lower survival in the United Kingdom and Ireland (79.2%) and eastern Europe (73.7%). For most countries, the 5-year survival rate for breast cancer was fairly close to the European mean. Overall, survival rates in Europe increased over time, from 78.4% in 1999–2001 to 82.4% in 2005–2007. This increase was the most marked in eastern Europe and the United Kingdom and Ireland, so the survival gap between these countries and the rest of Europe decreased. Predictions of 10-year survival exceed 70% in most regions, with the highest value in northern Europe (74.9%) and the lowest in eastern Europe (54.2%), although 10-year survival is about 10% lower than 5-year survival in almost all European regions (Allemani et al., 2013). See Sections 1.5 and 1.6 and Section 4.1 for further details on the interpretation of survival findings with regard to mammographic screening.

1.4.2 Management

Breast cancer care has improved dramatically over the past 50 years, thanks to advances in multidisciplinary management, diagnosis, and treatment, including adjuvant treatments. Biological markers of prognosis have been identified, as well as biomarkers for targeted therapies, such as aromatase inhibitors for hormone receptor-positive breast cancers and anti-HER2

therapy for HER2/neu-overexpressing breast cancers.

The management of breast cancer often requires multimodality treatment involving surgery, radiotherapy, systemic treatment with chemotherapy, and/or hormone therapy and targeted therapy. Neo-adjuvant therapy may be given before surgery to shrink the tumour and after surgery to treat micrometastases.

(a) Surgery

Surgical treatment for breast cancer has been used for centuries. Radical mastectomy became the standard surgical approach towards the end of the 19th century and was popular until the 1980s, when randomized trials showed that it had a limited beneficial effect on survival. Modified radical mastectomy, simple mastectomy, and the evaluation of breast-conserving surgery were then introduced. Surgical interventions such as oophorectomies and adrenalectomies were relatively popular in the 20th century (Ahmed et al., 2011; American College of Surgeons, 2014). Nowadays, surgical treatment for the primary tumour may involve breast-conserving surgery plus radiotherapy, modified radical mastectomy, or simple mastectomy, depending on the size and location of the tumour, the suitability of breast-conserving surgery, and, in developing countries, the availability of radiotherapy.

Assessing the axillary lymph nodes is critical in staging and to determine prognosis and therapeutic options. Nowadays, axillary lymph node dissection as a staging procedure has largely been replaced by the less-invasive sentinel lymph node biopsy. Local surgical treatments have improved greatly without compromising locoregional control in breast cancer management (McWhirter, 1948; Lythgoe et al., 1978; Langlands et al., 1980; Fisher et al., 1981; Maddox et al., 1983).

(b) Radiotherapy

Radiotherapy is regularly indicated for locoregional treatment after breast-conserving surgery and in post-mastectomy patients to eradicate residual disease, thus reducing local recurrence. In women with axillary lymph node dissection and with up to three positive lymph nodes or with four or more positive nodes, radiotherapy reduced locoregional recurrence and overall recurrence (RR, 0.68; 95% CI, 0.57–0.82 versus RR, 0.79; 95% CI, 0.69–0.90) and reduced cancer mortality (RR, 0.80; 95% CI, 0.67–0.95 versus RR, 0.87; 95% CI, 0.77–0.99) (McGale et al., 2014). In women with no positive nodes, radiotherapy had no statistically significant effect on locoregional recurrence, overall recurrence, or cancer mortality, although it increased overall mortality (RR, 1.23; 95% CI, 1.02–1.49). Results were similar in the subset of trials in which women received systemic therapy (McGale et al., 2014). Women who receive breast-conserving surgery without radiotherapy have a risk of recurrence in the conserved breast of greater than 20% even when axillary lymph nodes are absent. It has been shown that radiotherapy to the conserved breast reduces the 10-year risk of any recurrence from 35.0% to 19.3% and the 15-year risk of mortality from 25.2% to 21.4%. The mortality reduction differed significantly between patients with node-positive and node-negative disease (Darby et al., 2011).

(c) Chemotherapy and adjuvant therapy

Chemotherapy was introduced into clinical cancer practice in the middle of the 20th century, and targeted therapy was introduced towards the end of the 20th century, whereas hormone therapy was already in use by the end of the 19th century (American College of Surgeons, 2014). The need for and the choice of adjuvant systemic treatment are determined by the stage and the molecular features of the disease. The side-effects must be considered before starting any treatment, as they

can be immediate (appearing during treatment) or long-term (appearing weeks, months, or years after the treatment ends) and may be associated both with the patient's clinical conditions and stage at diagnosis and with the treatment (type and intensity).

Patients with ER-positive and/or PR-positive tumours, which account for 50–80% of breast cancers, usually receive hormone therapy, and patients with HER2-overexpressing tumours receive adjuvant anti-HER2 therapy in combination with chemotherapeutic agents, which may reduce mortality by one third and the risk of recurrence by 40% (Moja et al., 2012; Pinto et al., 2013). When neither HER2 overexpression nor hormone receptors are present, adjuvant therapy relies on chemotherapeutic regimens. It has been shown that 2 years of adjuvant anti-HER2 therapy is not more effective than 1 year of treatment for patients with HER2-positive early breast cancer, and thus 1 year of treatment remains the standard of care (Gianni et al., 2011; Goldhirsch et al., 2013), although cardiac toxicity is still a concern.

The classic adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (Bonadonna et al., 1976) was shown to improve survival in both node-positive and node-negative patients. Chemotherapy regimens such as 6 months of anthracycline as well as the addition of taxanes led to an additional decline in recurrence and mortality. A few years after its introduction in routine adjuvant practice, CMF was replaced by more-effective "third-generation" regimens containing anthracyclines and taxanes (Munzone et al., 2012). A meta-analysis showed that six cycles of anthracycline-based polychemotherapy, such as combination of 5-fluorouracil, doxorubicin, and cyclophosphamide or 5-fluorouracil, epirubicin, and cyclophosphamide, reduced the annual breast cancer death rate by about 38% in women younger than 50 years and by about 20% in women aged 50–69 years, irrespective of the use of tamoxifen and of ER status, nodal status, or other tumour characteristics (EBCTCG, 2005). The addition of four separate cycles of a taxane to such anthracycline-based regimens and the extension of treatment duration further reduced breast cancer mortality (RR, 0.86) (Peto et al., 2012).

It has been clearly demonstrated that neo-adjuvant chemotherapy such as tamoxifen reduces breast cancer mortality (RR, 0.71) and recurrence (RR, 0.68) in both node-positive and node-negative ER-positive breast cancers (Davies et al., 2011). Recent findings suggest that tamoxifen treatment is more beneficial for 10 years rather than for 5 years in women at high risk of recurrence (Davies et al., 2013). Studies have shown that the aromatase inhibitors offer an incremental improvement in survival and lower toxicity for postmenopausal women requiring hormone therapy. Pooled analyses of radiotherapy and systemic treatments reported a clinically significant improvement for both local and systemic therapy and provided evidence of modest but consistent effects of treatment.

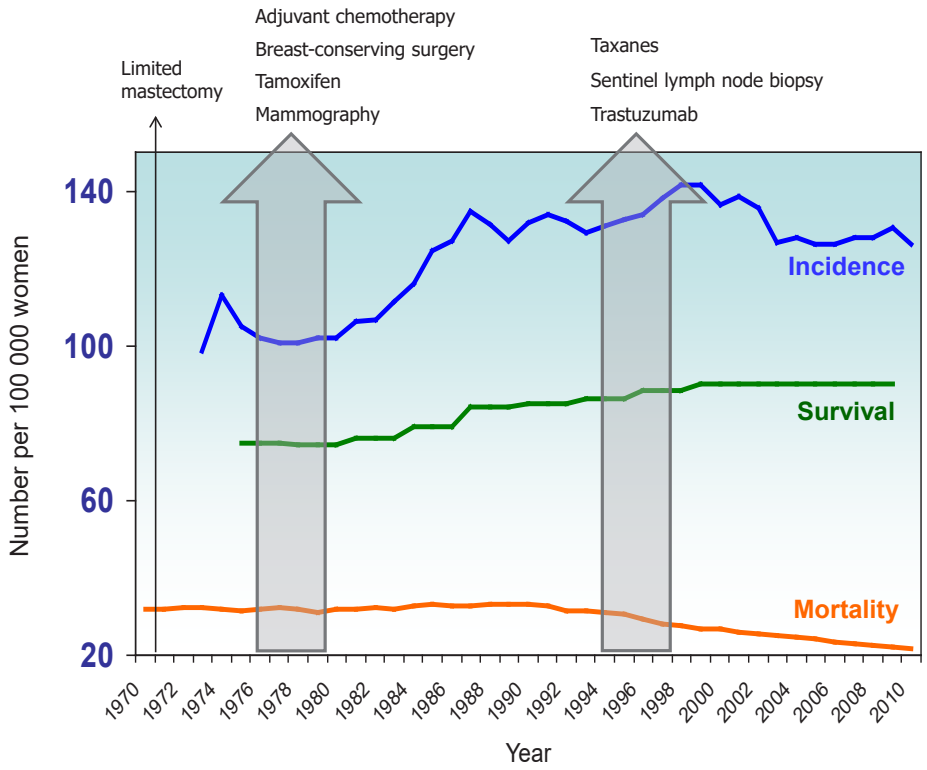
As an example, the milestones of breast cancer treatment in the USA and their relationship with time trends in incidence, survival, and mortality are shown in Fig. 1.20.

(i) Access to care and treatment in high-income countries

In high-income countries and in populations where sufficient resources are available, access to optimal cancer treatment is promoted by well-developed infrastructures, due to the spending of 6–16% of gross domestic product (GDP) on health care (Coleman, 2010). The variations observed in survival trends mainly reflect later diagnosis or differences in treatment (Coleman et al., 2011), particularly among women in eastern European countries and non-Hispanic Black women in the USA (Kingsmore et al., 2004; Mikeljevic et al., 2004).

Expenditure on cancer therapy in Europe rose from €840 million in 1993 to €6.2 billion in 2004,

Fig. 1.20 Milestones of breast cancer therapy in the USA



Courtesy of the IARC Screening Group, based on data from the American Society of Clinical Oncology (ASCO, 2014) and the SEER Program, USA (SEER, 2014a).

and is likely to increase further with the advent of targeted chemotherapy (Sullivan et al., 2011). Variations in breast cancer care across European countries are apparent (Allemani et al., 2010). Data from EUROCARE-3 show that 55% of women diagnosed with T1N0M0 breast cancers received breast-conserving surgery plus radiotherapy, ranging from 9% in Estonia to 78% in France. Of node-positive patients, chemotherapy was received by 52.1% of postmenopausal women and by 90.7% of premenopausal women, with marked variations among countries, particularly for postmenopausal women. For patients with ER-positive tumours, which constituted 45.3% of total cases, marked variations across countries in the availability of endocrine therapy were noted (Allemani et al., 2010).

Breast cancers are generally less advanced at diagnosis in the USA than in Europe, but the overall frequency of metastatic tumours is similar, at about 5–6% (Allemani et al., 2013). Currently, about 60% of cancer patients in the USA are treated with highly modern radiotherapy (Sullivan et al., 2011). Lymphadenectomy was reported in 86% of women in Europe and in 81% of women in the USA; surgical treatment was received by 91% of women in Europe and by 96% of women in the USA. Among women with early node-negative disease, 55% in Europe and 49% in the USA received breast-conserving surgery plus radiotherapy. Among women with node-positive tumours, 58% in Europe and 69% in the USA received chemotherapy. Compared with women aged 15–49 years, the proportion of women aged 50–99 years who received

chemotherapy was higher in the USA (60%) than in Europe (46%), as was access to endocrine treatment for ER-positive tumours (62% in the USA and 55% in Europe) (Allemani et al., 2013).

(ii) Access to care and treatment in low- and middle-income countries

In many LMICs, major treatments (surgery, chemotherapy, and radiotherapy) are delivered within inadequate health services infrastructures. Rural areas, in particular, lack infusion equipment or other supplies, skilled oncology surgeons, and proper equipment; radiotherapy facilities are scarce (available to about 15% of patients) or non-existent, and access to chemotherapy and hormone therapy is limited (Anderson at al., 2011; Cesario, 2012).

In Latin America, the WHO Medical Devices Database reports inadequate cancer care due to limited physical and technological resources. The supply of radiotherapy units may vary, from 6 per 100 000 people in Bolivia and Paraguay to 57 per 100 000 people in Uruguay (Goss et al., 2013). In most Latin American countries, oncology services are concentrated in major cities, whereas rural regions often lack or have limited cancer care services. In Brazil, anti-HER2 targeted therapy for HER2-positive early breast cancer became available only in 2012. The situation is similar in other Latin American countries, such as Mexico, Argentina, and Colombia (Goss et al., 2013).

In sub-Saharan Africa, delayed presentation of breast cancer is common. Although mastectomy is not always culturally accepted in this region, it is the most widely used procedure for breast cancer treatment, due to the poor availability of adjuvant radiotherapy, chemotherapy, and resources for the assessment of sentinel lymph nodes. In a hospital in Uganda in 1996–2000, 75% of patients underwent surgery (58% of surgeries were modified radical mastectomy), 76% received radiotherapy, 60% received hormone therapy, and 29% received chemotherapy (Kingham et al., 2013). Locally advanced breast cancers are frequently treated with neo-adjuvant therapy; however, the frequencies of response and positive outcomes are not as high as those in high-income countries (Kingham et al., 2013).

In China, important disparities in access and timely care for breast cancer are reported. Although breast-conserving surgery has become the recommended surgical treatment since the 1990s, mastectomy still accounts for almost 89% of primary breast cancer surgery (Li et al., 2011; Fan et al., 2014). Even in developed urban areas, breast-conserving surgeries represented only 12.1% of surgeries in 2005 and 24.3% of surgeries in 2008. In Beijing in 2008, complete axillary lymph node dissection was performed for 84.1% of the patients. There is poor availability of radiotherapy as well as linear accelerator equipment, trained radiation oncologists, and technologists. Among patients who underwent breast-conserving surgery, 16.3% did not receive radiotherapy as per standard guidelines, and only 27% of patients nationwide received radiotherapy as part of their primary treatment. Access to systemic therapy is relatively frequent in China. About 81.4% of all patients with invasive breast cancer received adjuvant chemotherapy, and 80.2% of patients with HER2-positive tumours received adjuvant targeted therapy. Unfortunately, for many drugs the costs are not reimbursed by insurance, and the lack of access to new drugs also limits systemic treatment options for metastatic disease. For example, despite the approval of anti-HER2 therapy in 2002, in Beijing only 20.6% of patients with HER2-positive disease received targeted therapy (Fan et al., 2014).

Although cancer control programmes are becoming a higher priority and adequate multidisciplinary breast cancer treatment services generally exist, socioeconomic, geographical, or ethnic barriers are reflected in the inequity of cancer treatment. As the economies of middle-resource countries strengthen, higher breast cancer

Table 1.11 Recommended breast cancer treatment resources for low-resource countries

Resource level[a]	Local-regional treatment	Radiotherapy	Chemotherapy	Endocrine therapy	Supportive therapy
Basic	Modified radical mastectomy	[b]	Preoperative chemotherapy with AC, EC, FAC, or CMF[c]	Oophorectomy in premenopausal women Tamoxifen[d]	Non-opioid and opioid analgesics and symptom management
Limited	Breast-conserving surgery[e] Sentinel lymph node biopsy with blue dye[f]	Post-mastectomy irradiation of chest and regional nodes for high-risk cases[b]	See note	See note	See note

[a] Basic-level resources are defined as core resources or fundamental services that are absolutely necessary for any breast health care system to function. Limited-level resources or services are defined as those that produce major improvements in outcome but that are attainable with limited financial means and modest infrastructure.

[b] Chest wall and regional lymph node irradiation substantially decreases the risk of post-mastectomy local recurrence. If available, it should be used as a basic-level resource.

[c] Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should also be provided.

[d] Estrogen receptor (ER) testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, IHC testing of ER status should also be provided.

[e] Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiotherapy. If breast-conserving radiation is unavailable, patients should be transferred to a higher-level facility for post-lumpectomy radiation.

[f] Use of the sentinel lymph node (SLN) biopsy requires clinical and laboratory validation of SLN technique.

Note: The table stratification scheme implies incrementally increasing resource allocation at the basic and limited levels.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide.

Adapted from *Breast*, Volume 20, Supplement 2, El Saghir NS, Adebamowo CA, Anderson BO, Carlson RW, Bird PA, Corbex M et al., Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative, pages 3–11, Copyright (2011), with permission from Elsevier (El Saghir et al., 2011); and from *Cancer*, Volume 113, issue 8, Supplement 20, Anderson BO, Yip C-H, Smith RA, Shyyan R, Sener SF, Eniu A et al., Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007, pages 2221–2243, Copyright (2008), with permission from John Wiley & Sons, Inc. (Anderson et al., 2008).

survival rates are reported, due to earlier detection and better treatment options (Anderson at al., 2011). Identifying what can be done to diagnose and treat cancers more effectively at each level of the health system will require a global public health approach (Anderson et al., 2010). Recommended breast cancer treatment resources for low-resource countries from the Breast Health Global Initiative are shown in Table 1.11.

1.5 Breast awareness, early detection and diagnosis, and screening

Early detection of breast cancer aims to reduce mortality and other serious consequences of advanced disease through the early clinical diagnosis of symptomatic breast cancer or by screening asymptomatic women (Sankaranarayanan, 2000). When earlier treatments are available for detected cases, life expectancy, locoregional control of disease, and quality of life are much improved. In turn, early detection relies on access to prompt and effective diagnostic and treatment services (von Karsa et al., 2014a).

Early cancer detection is part of a cancer control strategy, which also should include: health education; breast cancer awareness; health-care providers with sufficient clinical skills, particularly at the primary care level; availability of accessible, affordable, and efficient health services with adequate infrastructure, human resources, and information systems; prompt diagnosis, staging, and treatment; and follow-up care (Richards et al., 1999; Norsa'adah et al., 2011; Ermiah et al., 2012; Caplan, 2014; Poum et al., 2014; Unger-Saldaña, 2014).

1.5.1 Breast awareness

Breast awareness is intended to encourage women to be conscious of how their breasts normally look and feel, so that they can recognize and report any abnormality. Breast awareness programmes also provide information about the efficacy of treatment when breast cancer is detected and treated early. Breast Cancer Awareness Month is observed worldwide every October.

Breast awareness is distinguished from breast self-examination (BSE). The purpose of BSE is to detect breast cancer by performing regular, systematic palpation and inspection of the breasts. The common goal of breast awareness and BSE is to improve breast cancer survival by detecting breast cancer at an early stage. The United Kingdom National Health Service (NHS) mammography screening programme historically emphasized breast awareness over BSE (Faulder, 1992) because BSE was thought to lead to an excessive preoccupation with cancer and to anxiety, while being theoretically equivalent to breast awareness. In 1991, the NHS emphasized a five-point plan for being breast aware: (i) knowing what is normal for you; (ii) looking at your breasts and feeling them; (iii) knowing what changes to look for; (iv) reporting any changes without delay; and (v) attending breast screening if you are aged 50 years or older (NHSBSP, 2006). Nowadays, it is pointed out that the distinction between breast awareness and BSE is not clear and that there is no evidence that morbidity or mortality are reduced by taking the recommended steps to become breast aware; in addition, it is not known whether the harms, such as anxiety and excess false-positive biopsies, are associated with both breast awareness and BSE (McCready et al., 2005; Thornton & Pillarisetti, 2008; Mac Bride et al., 2012; Mark et al., 2014). It has been suggested that breast awareness should be replaced with the concept of "sensible alertness" to the possibility of finding an abnormality, with women occasionally but regularly performing quick BSE (Thornton & Pillarisetti, 2008), because breast awareness may cause more harm than good unless it is followed up by prompt and effective diagnosis and treatment. At present, it is still not clear what breast awareness means to women, how it is acquired, and whether the balance of benefits and harms is favourable. Awareness about breast cancer is especially relevant for LMICs, compared with more developed countries, which rely heavily on mammographic screening to improve earlier detection and treatment of symptomatic cases (Yip et al., 2008).

1.5.2 Early diagnosis of symptomatic breast cancer

Given the fact that most breast cancers are first recognized by patients, an important aspect of early diagnosis is encouraging women to seek medical care without delay when they notice symptoms or signs. Referral occurs mostly in health centres, in dispensaries, and in the offices of general and family practitioners. It is critical that the doctors, nurses, and health workers at these primary care levels are knowledgeable and skilled about early symptoms and signs of breast cancer and about referral. A systematic review of 23 studies worldwide reported a 7% difference in pooled survival at 5 years between patients with a short delay (< 3 months) from onset of

symptoms to initiation of treatment and those with a moderate delay (3–6 months) (Richards et al., 1999).

The common symptoms and clinical signs of breast cancer are: painless firm to hard lump in the breast; feeling of lumpiness in the breast; asymmetry of breasts; unilateral nipple retraction (as opposed to nipple inversion); unilateral bloody or serous nipple discharge; localized breast skin changes, such as tethering, oedema, puckering, or skin thickening; and eczematous changes in or around the nipple or areola. The clinical predictability of symptoms and signs should be considered together with family history of breast cancer (especially among first-degree relatives), past history of breast disease, and other risk factors, to avoid unnecessary referrals of women with normal breasts or benign lesions.

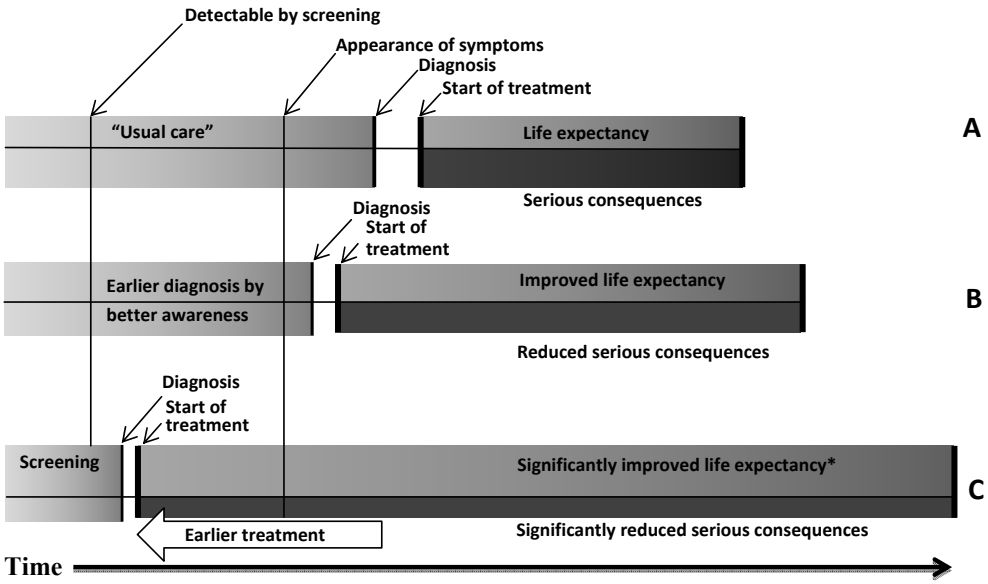
The single most important symptom of early breast cancer is the presence of a small palpable lump. The positive predictive value of a breast lump for breast cancer is reported to be about 1% or less in population-based studies (Mittra et al., 2010; Sankaranarayanan et al., 2011; Singh et al., 2015) and between 13% and 25% in hospital-based studies (Mahoney & Csima, 1982; Ohene-Yeboah & Amaning, 2008; Pradhan & Dhakal, 2008). The vast majority of breast lumps are fibroadenoma, fibroadenosis, fibrocystic mastopathy, mastitis, or solitary cysts, which are associated with benign breast disease (Mahoney & Csima, 1982; Ohene-Yeboah & Amaning, 2008; Pradhan & Dhakal, 2008; Sankaranarayanan et al., 2011). Discrete lumps with a hard consistency, lumps with skin or nipple changes, lumps associated with unilateral nipple discharge, and persistent breast lumps are associated with advanced breast cancer (Mahoney & Csima, 1982; Giess et al., 1998; Dolan et al., 2010; Chen et al., 2012). Breast pain and discomfort without a palpable breast lump is very common in menstrual and premenstrual women and is rarely, if ever, a sign of early breast cancer, whereas painless lumps should be brought to immediate medical attention (Ohene-Yeboah & Amaning, 2008).

Nipple changes are an important aspect of early detection and breast awareness. Inversion of one or both nipples is a common occurrence and is not typically associated with breast cancer. Unilateral bloody or serous nipple discharge, considered by many to be pathognomonic for breast cancer, is usually caused by benign conditions, most frequently papillomas and papillomatosis (Tabár et al., 1983). In contrast, extensive nipple retraction is associated with a tumour deep to the nipple causing retraction of the nipple towards the tumour. Serious nipple changes such as eczema and areola, with or without retraction, often accompanied by erythema and unpleasant or painful sensations, may be caused by Paget disease, which is associated with invasive or in situ breast cancer. As the disease advances, the surface of the skin breaks down, with a resulting oozing of fluid. A palpable tumour and nipple retraction are late symptoms of Paget disease. Any nipple rash or itchy, dry skin in or around the nipple should be brought to medical attention.

Early diagnosis of breast cancer can be facilitated by clinical breast examination or breast self-examination (see Sections 2.3 and 2.4, respectively).

Women referred with suspected breast cancer rarely require open surgery and usually undergo clinical assessment by a surgeon, oncologist, or radiologist, diagnostic imaging (magnetic resonance imaging or ultrasonography), and percutaneous tissue sampling (core needle biopsy provides greater sensitivity and specificity than fine-needle aspiration cytology) (Hukkinen et al., 2008). Triple assessment (comprising clinical examination, imaging, and tissue sampling) is an approach that is cost-effective, easy to perform, and time-saving but is achieved only in high-resource settings with excellent diagnostic imaging facilities and pathology services. In the lowest-resource settings, as in many countries in sub-Saharan Africa, clinical assessment is

Fig. 1.21 Early detection of breast cancer through screening asymptomatic women or early diagnosis of symptomatic women



(A) Time intervals between the appearance of symptoms, the diagnosis, and the start of breast cancer treatment can be weeks to several months, depending on access to specialized care.
(B) Earlier diagnosis and good access to treatment may increase life expectancy and reduce serious consequences of the disease. Some overdiagnosis may also occur.
(C) Screening asymptomatic women leads to even earlier detection and treatment of breast cancer, albeit with some overdiagnosis but with a significantly increased life expectancy and less serious consequences of the cancer, provided screening services are adequate. The time intervals between positive screening results or the appearance of symptoms and the diagnosis and the start of treatment should be as short as possible. Well-organized screening programmes can shorten the interval between diagnosis and the start of treatment by prompt referral to qualified clinical units. They also provide an organizational framework for implementing the quality assurance.
Adapted with permission from de Koning (2009). The mysterious mass(es). [Inaugural address, Professor of Screening Evaluation.] Rotterdam, Netherlands: Erasmus MC. Available from: http://repub.eur.nl/res/pub/30689/oratie.pdf. (Figure 1, p. 7) and from Stewart BW, Wild CP, editors (2014). World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer.

usually performed by biopsy. Improved breast cancer survival rates and reduced mortality were already observed in high-income countries before the introduction of widespread mammography screening (see Fig. 1.3; Sankaranarayanan et al., 2010; Tryggvadóttir et al., 2010). This has been attributed to increased breast awareness, improved medical assessment, early clinical diagnosis, the introduction of national universal medical insurance, and improved access to treatment (Taylor et al., 2003).

1.5.3 Screening asymptomatic women

Screening asymptomatic women, as part of early detection, includes both performing mammography screening at specified intervals and referring those women with positive screening findings for further diagnostic investigations and possibly treatment. Screening programmes may be either organized or unorganized (opportunistic) programmes (von Karsa et al., 2014a).

The main objective of screening asymptomatic women of appropriate age and average risk is to enable adequate treatment before the cancer poses a more serious threat to the individual woman (Fig. 1.21; Wilson & Jungner, 1968; Duffy

et al., 2003; Perry et al., 2006, 2008; de Koning, 2009). As in any form of early detection, access to prompt and effective diagnosis and treatment is key to achieving the potential benefit of breast cancer screening (von Karsa et al., 2014a). In practice, less than one third of the breast cancers detected by mammography screening would also be detectable by clinical examination (Friedman et al., 2013). Also, some subtypes of breast cancer are more frequently detected at a more advanced stage, irrespectively of whether through screening or symptomatically (Tabár et al., 2014).

(a) Appropriate balance of benefits and harms

In recent decades, the principles of screening established by WHO in 1968 have been extended through experience gained from the implementation of population-based cancer screening programmes (WHO, 2007, 2013a, b). The careful consideration of the harm–benefit balance associated with the implementation of a cancer screening programme is particularly important in breast cancer screening, given the large number of women potentially involved.

The principal benefits of screening are the avoidance of death due to breast cancer (IARC, 2002; see Section 5.2), or of other serious consequences, such as advanced-stage breast cancer (Taplin et al., 2004; Norman et al., 2006; Malmgren et al., 2014; Fig. 1.21). The primary harms of screening include the morbidity and mortality from the procedures for detection and diagnosis, false-positive tests, overdiagnosis, and the side-effects of treatment (Sections 5.3.1–5.3.4). Another reported harm is anxiety, particularly when further investigation is required after a mammogram (see Section 5.3.5).

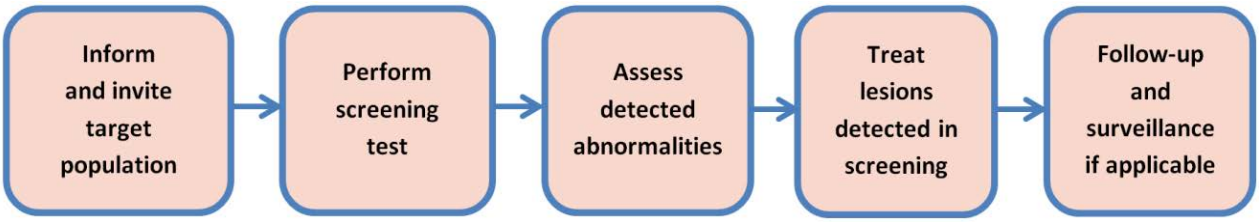
Exposure to these risks in the absence of any direct health benefit is of particular concern.

(b) Organized, population-based programmes

Organized programmes are characterized by centralized screening invitations to a well-defined target population, systematic call and recall for screening, delivery of test results, investigations, treatment and follow-up care, centralized quality assurance, and a programme database with linkages to other information systems, such as cancer registration systems and death registration systems, for monitoring and evaluation of the programme. Implementation of organized and opportunistic screening programmes is presented in Section 3.2, by WHO regions.

Most breast cancer screening programmes offer mammography to normal-risk women beginning at age 40–50 years and ending at age 69–74 years, typically at 2-year intervals (von Karsa et al., 2014b). The screening policy of an organized programme defines at least the screening protocol, the repeat interval, and the determinants of eligibility for screening. Effective communications should also be supported (Giordano et al., 2006; Webster & Austoker, 2006; Robb et al., 2010), enabling women to make an informed decision about whether to participate (Giordano et al., 2006, 2012; von Karsa et al., 2014a). In addition, organized programmes include an administrative structure, which is responsible for service delivery, including follow-up of detected lesions, quality assurance, and evaluation. Organized screening programmes generally include a national or regional implementation team, which is responsible for coordinating the delivery of the screening services, maintaining the requisite quality, reporting on performance and results, and defining standard operating procedures. In addition, information about all new cases and deaths from breast cancer occurring in the defined population served by the screening programme enables an estimate to be made of the impact of the programme on breast cancer mortality (IARC, 2002). Ideally, this can be

Fig. 1.22 The process of cancer screening



Adapted from von Karsa (1995) with permission from Deutscher Ärzte-Verlag.

achieved through linkage of individual data from a PBCR and a screening registry, if available (von Karsa & Arrossi, 2013; Anttila et al., 2014).

(c) Opportunistic programmes

Opportunistic programmes are not tailored to a predetermined eligible population and provide screening tests on request or at the time of routine health examinations. These programmes are less amenable to quality assurance than population-based screening, due, among other things, to the lack of administrative and organization infrastructure (de Gelder et al., 2009). They rely on the initiative of individual healthcare providers to offer screening or to encourage participation in a screening programme or outside the context of any programme (so-called wild screening). Organized breast screening programmes reach women who have not participated in opportunistic screening (Chamot et al., 2007; Gorini et al., 2014).

(d) Quality assurance of screening programmes

Quality assurance in breast cancer screening programmes goes beyond the need to ensure that any medical intervention is performed adequately, efficiently, and with minimum risk and maximum benefit. Screening involves a complex sequence of events and interrelated activities (see Fig. 1.22 for a summary of the process). To achieve maximum benefits with minimum risk, quality must be optimal at every step of the screening process (Perry et al., 2006, 2008; von Karsa & Arrossi, 2013). This can be achieved by a coordinated approach to programme planning and management, and by the availability of adequate human, financial, and technical resources. Overall, in Europe, the proportion of expenditure devoted to quality assurance should be no less than 10–20%, depending on the scale of the programme (Perry et al., 2013b; von Karsa et al., 2013, 2014a).

Numerous countries have adopted regulations, guidelines, and recommendations covering different aspects of quality assurance of mammography screening (Sibbering et al., 2009; Ellis, 2011; Gemeinsamen Bundesausschuss, 2011; Tonelli et al., 2011; Smith et al., 2012; BMV-Ä/EKV, 2014). The European Commission has published comprehensive multidisciplinary European guidelines for quality assurance in breast cancer screening and diagnosis (Perry et al., 2006, 2008, 2013a), and for establishing a population-based cancer screening programme (Lynge et al., 2012; Perry et al., 2013b; von Karsa & Arrossi, 2013; von Karsa et al., 2013) (see Section 3.2 for further information by country/region). In the USA, the Mammography Quality Standards Act (MQSA) made accreditation of mammography facilities mandatory (FDA, 2014). Professional and scientific societies provide additional guidance and standards, and training and technical support for the achievement of the standards, such as in preparation

for accreditation, including comprehensive audits of professional and organizational performance (D'Orsi et al., 2013; American College of Surgeons, 2014; Canadian Association of Radiologists, 2014).

It may take several years to implement a population-based cancer screening programme, from the beginning of planning to completion of roll-out across an entire country or region. Sustainable institutional capacity is useful for programme management; computerized information systems, registration of breast cancer cases in the population, in screening registries and other data repositories and institutions are needed to collaborate in monitoring and evaluation, for regular audits of programme performance, and to assure the technical quality of equipment and services.

International collaboration can compensate for a local shortage of expertise in any given country, to facilitate process evaluation and avoid unnecessary delays in establishing fully functional screening programmes (von Karsa et al., 2014a).

(e) Denominators

As pointed out in the Working Procedures of this Handbook, the evaluation of the efficacy and effectiveness of breast cancer screening should measure the impact of a specific intervention, procedure, regimen, or service (Porta, 2008). The terms "breast cancer screening" and "mammography screening" are ambiguous; they may refer either to the invitation of women intended to be screened or to their actual participation by undergoing a screening mammogram. It is crucial to properly differentiate between the two concepts in order to evaluate breast cancer screening and to accurately interpret published reports.

The number of women, invited or participating, provides the denominator when the results of a screening programme are presented as rates or proportions. Results on women invited to screening are of particular interest to public health authorities when considering the potential benefits and harms to the population served by the programme. Participation in screening is fundamental to estimate the actual benefit of breast screening programmes and make informed decisions about whether to participate. In this Handbook, mammography screening programmes are examined using the number of women invited as the denominator, and the effects of participation in the screening programme are examined using the number of women participating as the denominator. Due consideration is given to the fact that the difference between the effect of invitation and the effect of attendance will depend on the proportion of women participating and so will not be generalizable from programme to programme.

References

Abdel-Fatah TM, Powe DG, Hodi Z, Reis-Filho JS, Lee AH, Ellis IO (2008). Morphologic and molecular evolutionary pathways of low nuclear grade invasive breast cancers and their putative precursor lesions: further evidence to support the concept of low nuclear grade breast neoplasia family. *Am J Surg Pathol*, 32(4):513–23. doi:10.1097/PAS.0b013e318161d1a5 PMID:18223478

Adams MJ, Dozier A, Shore RE, Lipshultz SE, Schwartz RG, Constine LS et al. (2010). Breast cancer risk 55+ years after irradiation for an enlarged thymus and its implications for early childhood medical irradiation today. *Cancer Epidemiol Biomarkers Prev*, 19(1):48–58. doi:10.1158/1055-9965.EPI-09-0520 PMID:20056622

Ades F, Zardavas D, Bozovic-Spasojevic I, Pugliano L, Fumagalli D, de Azambuja E et al. (2014). Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. *J Clin Oncol*, 32(25):2794–803. doi:10.1200/JCO.2013.54.1870 PMID:25049332

Ahmed MI, Youssef M, Carr M (2011). Breast Cancer Care: A Historical Review. *Pak J Surg*, 27(2):135–9.

AJCC (2014). AJCC cancer staging manual, 8th edition updates. Chicago (IL), USA: American Joint Committee on Cancer. Available from: http://cancerstaging.org/About/Pages/8th-Edition.aspx.

Alexander FE, Roberts MM, Huggins A (1987). Risk factors for breast cancer with applications to selection for the

prevalence screen. *J Epidemiol Community Health*, 41(2):101–6. doi:10.1136/jech.41.2.101 PMID:3498783

Ali S, Coombes RC (2002). Endocrine-responsive breast cancer and strategies for combating resistance. *Nat Rev Cancer*, 2(2):101–12. doi:10.1038/nrc721 PMID:12635173

Allemani C, Minicozzi P, Berrino F, Bastiaannet E, Gavin A, Galceran J et al.; EUROCARE Working Group (2013). Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000–2002. *Int J Cancer*, 132(10):2404–12. doi:10.1002/ijc.27895 PMID:23047687

Allemani C, Storm H, Voogd AC, Holli K, Izarzugaza I, Torrella-Ramos A et al. (2010). Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. *Eur J Cancer*, 46(9):1528–36. doi:10.1016/j.ejca.2010.02.016 PMID:20299206

Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS et al.; CONCORD Working Group (2014). Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*, 385(9972):977–1010. doi:10.1016/S0140-6736(14)62038-9 PMID:25467588

Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A et al.; Million Women Study Collaborators (2009). Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*, 101(5):296–305. doi:10.1093/jnci/djn514 PMID:19244173

American College of Surgeons (2014). National Accreditation Program for Breast Centers. Available from: https://www.facs.org/quality%20programs/napbc.

Anderson B, Ballieu M, Bradley C, Elzawawy A, Cazap E, Enio A et al. (2010). Access to cancer treatment in low- and middle-income countries – an essential part of global cancer control. Working Paper. CanTreat International.

Anderson BO, Cazap E, El Saghir NS, Yip CH, Khaled HM, Otero IV et al. (2011). Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol*, 12(4):387–98. doi:10.1016/S1470-2045(11)70031-6 PMID:21463833

Anderson H, Bladström A, Olsson H, Möller TR (2000). Familial breast and ovarian cancer: a Swedish population-based register study. *Am J Epidemiol*, 152(12):1154–63. doi:10.1093/aje/152.12.1154 PMID:11130621

Anderson TJ, Lamb J, Donnan P, Alexander FE, Huggins A, Muir BB et al. (1991). Comparative pathology of breast cancer in a randomised trial of screening. *Br J Cancer*, 64(1):108–13. doi:10.1038/bjc.1991.251 PMID:1854609

Anderson WF, Pfeiffer RM, Dores GM, Sherman ME (2006). Comparison of age distribution patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev*, 15(10):1899–905. doi:10.1158/1055-9965.EPI-06-0191 PMID:17035397

Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A et al. (2008). Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer*, 113(8 Suppl): 2221–43. doi:10.1002/cncr.23844 PMID:18816619

Andre F, Pusztai L (2006). Molecular classification of breast cancer: implications for selection of adjuvant chemotherapy. *Nat Clin Pract Oncol*, 3(11):621–32. doi:10.1038/ncponc0636 PMID:17080180

Antoine C, Ameye L, Paesmans M, Rozenberg S (2014). Systematic review about breast cancer incidence in relation to hormone replacement therapy use. *Climacteric*, 17(2):116–32. doi:10.3109/13697137.2013.829812 PMID:23909434

Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J et al. (2014). Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*, 371(6):497–506. doi:10.1056/NEJMoa1400382 PMID:25099575

Anttila A, Lönnberg S, Ponti A, Suonio E, Villain P, Coebergh JW et al. (2014). Towards better implementation of cancer screening in Europe through improved monitoring and evaluation and greater engagement of cancer registries. *Eur J Cancer*, 51(2):241–51. doi:10.1016/j.ejca.2014.10.022 PMID:25483785

Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M et al. (2015). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol*, 16(1):36–46. doi:10.1016/S1470-2045(14)71123-4 PMID:25467404

ASCO (2014). American Society of Clinical Oncology. Available from: http://cancerprogress.net/timeline/breast-cancer, accessed May 2011.

Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM et al. (2008). Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol*, 26(26):4282–8. doi:10.1200/JCO.2008.16.6231 PMID:18779615

Badwe RA, Dikshit R, Laversanne M, Bray F (2014). Cancer incidence trends in India. *Jpn J Clin Oncol*, 44(5):401–7. doi:10.1093/jjco/hyu040 PMID:24755545

Badwe RA, Mittra I, Havaldar R (1999). Timing of surgery with regard to the menstrual cycle in women with primary breast cancer. *Surg Clin North Am*, 79(5):1047–59. doi:10.1016/S0039-6109(05)70060-8 PMID:10572550

Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V et al. (2013). Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol*, 24(2):301–8. doi:10.1093/annonc/mds337 PMID:22910838

Balko JM, Stricker TP, Arteaga CL (2013). The genomic map of breast cancer: which roads lead to better targeted therapies? *Breast Cancer Res*, 15(4):209. doi:10.1186/bcr3435 PMID:23905624

Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM (2003). Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. *J Clin Oncol*, 21(10):1973–9. doi:10.1200/JCO.2003.09.099 PMID:12743151

Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, Carney PA et al. (2006). Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst*, 98(17):1204–14. doi:10.1093/jnci/djj331 PMID:16954473

Bartek J, Bartkova J, Lukas J (2007). DNA damage signalling guards against activated oncogenes and tumour progression. *Oncogene*, 26(56):7773–9. doi:10.1038/sj.onc.1210881 PMID:18066090

Baum M (2013). Modern concepts of the natural history of breast cancer: a guide to the design and publication of trials of the treatment of breast cancer. *Eur J Cancer*, 49(1):60–4. doi:10.1016/j.ejca.2012.07.005 PMID:22884336

Becker S, Kaaks R (2009). Exogenous and endogenous hormones, mammographic density and breast cancer risk: can mammographic density be considered an intermediate marker of risk? *Recent Results Cancer Res*, 181:135–57. doi:10.1007/978-3-540-69297-3_14 PMID:19213565

Bell DW, Varley JM, Szydlo TE, Kang DH, Wahrer DC, Shannon KE et al. (1999). Heterozygous germ line *hCHK2* mutations in Li-Fraumeni syndrome. *Science*, 286(5449):2528–31. doi:10.1126/science.286.5449.2528 PMID:10617473

Beral V, Reeves G, Banks E (2005). Current evidence about the effect of hormone replacement therapy on the incidence of major conditions in postmenopausal women. *BJOG*, 112(6):692–5. doi:10.1111/j.1471-0528.2005.00541.x PMID:15924521

Berlin L (2014). Point: Mammography, breast cancer, and overdiagnosis: the truth versus the whole truth versus nothing but the truth. *J Am Coll Radiol*, 11(7):642–7. doi:10.1016/j.jacr.2014.01.015 PMID:24794764

BIC (2015). Breast Cancer Information Core database. Bethesda (MD), USA: National Human Genome Research Institute. Available from: http://research.nhgri.nih.gov/bic/.

Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C et al. (2001a). Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol*, 19(8):2263–71. PMID:11304780

Bijker N, Peterse JL, Duchateau L, Robanus-Maandag EC, Bosch CA, Duval C et al. (2001b). Histological type and marker expression of the primary tumour compared with its local recurrence after breast-conserving therapy for ductal carcinoma in situ. *Br J Cancer*, 84(4):539–44. doi:10.1054/bjoc.2000.1618 PMID:11207051

Bloom HJ, Richardson WW (1957). Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer*, 11(3):359–77. doi:10.1038/bjc.1957.43 PMID:13499785

BMV-Ä/EKV (2014). Provision of care in the Programme for Early Detection of Breast Cancer by Mammography Screening. Federal Collective Agreement – Physician fee schedule of the substitute funds, Annex 9.2, version 16 June 2014, valid from 1 July 2014 [in German]. Legal documents compendium of the German National Association of Statutory Health Insurance Physicians. Available from: http://www.kbv.de/media/sp/09.2_Mammographie.pdf.

Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT (1992). Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med*, 326(12):781–5. doi:10.1056/NEJM199203193261201 PMID:1538720

Boice JD Jr, Morin MM, Glass AG, Friedman GD, Stovall M, Hoover RN et al. (1991). Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. *JAMA*, 265(10):1290–4. doi:10.1001/jama.1991.03460100092031 PMID:2053936

Bombonati A, Sgroi DC (2011). The molecular pathology of breast cancer progression. *J Pathol*, 223(2):308–17. doi:10.1002/path.2808 PMID:21125683

Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C et al. (1976). Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med*, 294(8):405–10. doi:10.1056/NEJM197602192940801 PMID:1246307

Boulton SJ (2006). Cellular functions of the BRCA tumour-suppressor proteins. *Biochem Soc Trans*, 34(5):633–45. doi:10.1042/BST0340633 PMID:17052168

Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E et al. (2007). Mammographic density and the risk and detection of breast cancer. *N Engl J Med*, 356(3):227–36. doi:10.1056/NEJMoa062790 PMID:17229950

Boyd NF, Martin LJ, Rommens JM, Paterson AD, Minkin S, Yaffe MJ et al. (2009). Mammographic density: a heritable risk factor for breast cancer. *Methods Mol Biol*, 472:343–60. doi:10.1007/978-1-60327-492-0_15 PMID:19107441

Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ et al. (2005). Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol*, 6(10):798–808. doi:10.1016/S1470-2045(05)70390-9 PMID:16198986

Bray F, Znaor A, Cueva P, Korir A, Swaminathan R, Ullrich A et al. (2014). Planning and developing population-based cancer registration in low- and middle-income settings. Lyon: International Agency for Research on Cancer (IARC Technical Publication Series, No. 43).

Available from: http://www.iarc.fr/en/publications/pdfs-online/treport-pub/treport-pub43/index.php.

Brewster AM, Hortobagyi GN, Broglio KR, Kau SW, Santa-Maria CA, Arun B et al. (2008). Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst*, 100(16):1179–83. doi:10.1093/jnci/djn233 PMID:18695137

Brinkley D, Haybrittle JL (1975). The curability of breast cancer. *Lancet*, 306(7925):95–7. doi:10.1016/S0140-6736(75)90003-3 PMID:49738

Broeks A, Braaf LM, Huseinovic A, Nooijen A, Urbanus J, Hogervorst FB et al. (2007). Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. *Breast Cancer Res*, 9(2):R26. doi:10.1186/bcr1668 PMID:17428320

Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C (1985). Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*, 122(5):904–14. PMID:4050778

Buerger H, Otterbach F, Simon R, Poremba C, Diallo R, Decker T et al. (1999). Comparative genomic hybridization of ductal carcinoma in situ of the breast-evidence of multiple genetic pathways. *J Pathol*, 187(4):396–402. doi:10.1002/(SICI)1096-9896(199903)187:4<396::AID-PATH286>3.0.CO;2-L PMID:10398097

Buitenhuis W, Fritschi L, Thomson A, Glass D, Heyworth J, Peters S (2013). Occupational exposure to ionizing radiation and risk of breast cancer in Western Australia. *J Occup Environ Med*, 55(12):1431–5. doi:10.1097/JOM.0b013e3182a7e692 PMID:24270294

Bundred NJ (2001). Prognostic and predictive factors in breast cancer. *Cancer Treat Rev*, 27(3):137–42. doi:10.1053/ctrv.2000.0207 PMID:11417963

Burrell RA, McGranahan N, Bartek J, Swanton C (2013). The causes and consequences of genetic heterogeneity in cancer evolution. *Nature*, 501(7467):338–45. doi:10.1038/nature12625 PMID:24048066

Byrne C, Harris A (1996). Cancer rates and risks, 4th edition. Bethesda (MD), USA: US Department of Health and Human Services, National Institute of Health.

Cadman BA, Ostrowski JL, Quinn CM (1997). Invasive ductal carcinoma accompanied by ductal carcinoma in situ (DCIS): comparison of DCIS grade with grade of invasive component. *Breast*, 6(3):132–7. doi:10.1016/S0960-9776(97)90553-1

Canadian Association of Radiologists (2014). Mammography Accreditation Program (MAP). Available from: http://www.car.ca/en/accreditation/map.aspx.

Canadian Cancer Society (2014). Breast Cancer Statistics. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2014. Toronto: Canadian Cancer Society.

Cancer Genome Atlas Network (2012). Comprehensive molecular portraits of human breast tumours. *Nature*, 490(7418):61–70. doi:10.1038/nature11412 PMID:23000897

Cancer Registry of Norway (2014). Cancer in Norway 2012 – Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway. Available from: http://www.kreftregisteret.no/global/cancer_in norway/2012/cin_2012.pdf.

Caplan L (2014). Delay in breast cancer: implications for stage at diagnosis and survival. *Front Public Health*, 2:87. doi:10.3389/fpubh.2014.00087 PMID:25121080

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C et al. (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. *Radiat Res*, 167(4):396–416. doi:10.1667/RR0553.1 PMID:17388693

Castéra L, Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O et al. (2014). Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet*, 22(11):1305–13. doi:10.1038/ejhg.2014.16 PMID:24549055

Cesario SK (2012). Global inequalities in the care of women with cancer. *Nurs Womens Health*, 16(5):372–85. doi:10.1111/j.1751-486X.2012.01761.x PMID:23067282

Chamot E, Charvet AI, Perneger TV (2007). Who gets screened, and where: a comparison of organised and opportunistic mammography screening in Geneva, Switzerland. *Eur J Cancer*, 43(3):576–84. doi:10.1016/j.ejca.2006.10.017 PMID:17223542

Chappuis PO, Nethercot V, Foulkes WD (2000). Clinicopathological characteristics of *BRCA1*- and *BRCA2*-related breast cancer. *Semin Surg Oncol*, 18(4):287–95. doi:10.1002/(SICI)1098-2388(200006)18:4<287::AID-SSU3>3.0.CO;2-5 PMID:10805950

Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J et al. (2009). Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*, 101(10):736–50. doi:10.1093/jnci/djp082 PMID:19436038

Chen L, Zhou WB, Zhao Y, Liu XA, Ding Q, Zha XM et al. (2012). Bloody nipple discharge is a predictor of breast cancer risk: a meta-analysis. *Breast Cancer Res Treat*, 132(1):9–14. doi:10.1007/s10549-011-1787-5 PMID:21947751

Chiu SY, Duffy S, Yen AM, Tabár L, Smith RA, Chen HH (2010). Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev*, 19(5):1219–28. doi:10.1158/1055-9965.EPI-09-1028 PMID:20406961

Chlebowski RT (2013). Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast*, 22(Suppl 2):S30–7. doi:10.1016/j.breast.2013.07.006 PMID:24074789

Chlebowski RT, Manson JE, Anderson GL, Cauley JA, Aragaki AK, Stefanick ML et al. (2013). Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. *J Natl Cancer Inst*, 105(8):526–35. doi:10.1093/jnci/djt043 PMID:23543779

Chuaqui RF, Zhuang Z, Emmert-Buck MR, Liotta LA, Merino MJ (1997). Analysis of loss of heterozygosity on chromosome 11q13 in atypical ductal hyperplasia and in situ carcinoma of the breast. *Am J Pathol*, 150(1):297–303. PMID:9006344

Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L et al. (1999). Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol*, 17(9):2639–48. PMID:10561337

Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D et al. (2000). Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Risk Index Working Group, Harvard Center for Cancer Prevention. *Cancer Causes Control*, 11(6):477–88. doi:10.1023/A:1008984432272 PMID:10880030

Colditz GA, Rosner B (2000). Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*, 152(10):950–64. doi:10.1093/aje/152.10.950 PMID:11092437

Coleman MP (2010). Cancer survival in the developing world. *Lancet Oncol*, 11(2):110–1. doi:10.1016/S1470-2045(09)70371-7 PMID:20005176

Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C et al.; ICBP Module 1 Working Group (2011). Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet*, 377(9760):127–38. doi:10.1016/S0140-6736(10)62231-3 PMID:21183212

Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R et al.; CONCORD Working Group (2008). Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol*, 9(8):730–56. doi:10.1016/S1470-2045(08)70179-7 PMID:18639491

Collaborative Group on Hormonal Factors in Breast Cancer (1996). Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*, 347(9017):1713–27. doi:10.1016/S0140-6736(96)90806-5 PMID:8656904

Collaborative Group on Hormonal Factors in Breast Cancer (1997). Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*, 350(9084):1047–59. doi:10.1016/S0140-6736(97)08233-0 PMID:10213546

Collaborative Group on Hormonal Factors in Breast Cancer (2001). Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*, 358(9291):1389–99. doi:10.1016/S0140-6736(01)06524-2 PMID:11705483

Collaborative Group on Hormonal Factors in Breast Cancer (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*, 360(9328):187–95. doi:10.1016/S0140-6736(02)09454-0 PMID:12133652

Collaborative Group on Hormonal Factors in Breast Cancer (2012). Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*, 13(11):1141–51. doi:10.1016/S1470-2045(12)70425-4 PMID:23084519

Collins LC, Tamimi RM, Baer HJ, Connolly JL, Colditz GA, Schnitt SJ (2005). Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. *Cancer*, 103(9):1778–84. doi:10.1002/cncr.20979 PMID:15770688

Corbex M, Burton R, Sancho-Garnier H (2012). Breast cancer early detection methods for low and middle income countries, a review of the evidence. *Breast*, 21(4):428–34. doi:10.1016/j.breast.2012.01.002 PMID:22289154

Couch FJ, Nathanson KL, Offit K (2014). Two decades after BRCA: setting paradigms in personalized cancer care and prevention. *Science*, 343(6178):1466–70. doi:10.1126/science.1251827 PMID:24675953

Coughlin SS, Ekwueme DU (2009). Breast cancer as a global health concern. *Cancer Epidemiol*, 33(5):315–8. doi:10.1016/j.canep.2009.10.003 PMID:19896917

Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ et al.; METABRIC Group (2012). The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature*, 486(7403):346–52. PMID:22522925

Cuzick J (2003). Epidemiology of breast cancer – selected highlights. *Breast*, 12(6):405–11. doi:10.1016/S0960-9776(03)00144-9 PMID:14659113

Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M et al.; ATAC/LATTE investigators (2010). Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol*, 11(12):1135–41. doi:10.1016/S1470-2045(10)70257-6 PMID:21087898

Cybulski C, Górski B, Huzarski T, Masojć B, Mierzejewski M, Debniak T et al. (2004). *CHEK2* is a multiorgan cancer susceptibility gene. *Am J Hum Genet*, 75(6):1131–5. doi:10.1086/426403 PMID:15492928

D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al. (2013). ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston (VA), USA: American College of Radiology.

Dalton LW, Page DL, Dupont WD (1994). Histologic grading of breast carcinoma. A reproducibility study. *Cancer*, 73(11):2765–70. doi:10.1002/1097-0142(19940601)73:11<2765::AID-CNCR2820731119>3.0.CO;2-K PMID:8194018

Damiola F, Pertesi M, Oliver J, Le Calvez-Kelm F, Voegele C, Young EL et al. (2014). Rare key functional domain missense substitutions in *MRE11A*, *RAD50*, and *NBN* contribute to breast cancer susceptibility: results from a Breast Cancer Family Registry case-control mutation-screening study. *Breast Cancer Res*, 16(3):R58 doi:10.1186/bcr3669 PMID:24894818

Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M; Comparative Risk Assessment collaborating group (Cancers) (2005). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*, 366(9499):1784–93. doi:10.1016/S0140-6736(05)67725-2 PMID:16298215

Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*, 378(9804):1707–16. doi:10.1016/S0140-6736(11)61629-2 PMID:22019144

Davidson A, Chia S, Olson R, Nichol A, Speers C, Coldman AJ et al. (2013). Stage, treatment and outcomes for patients with breast cancer in British Columbia in 2002: a population-based cohort study. *CMAJ Open*, 1(4):E134–41. doi:10.9778/cmajo.20130017 PMID:25077115

Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*, 378(9793):771–84. doi:10.1016/S0140-6736(11)60993-8 PMID:21802721

Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V et al.; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group (2013). Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*, 381(9869):805–16. doi:10.1016/S0140-6736(12)61963-1 PMID:23219286

Dawson SJ, Rueda OM, Aparicio S, Caldas C (2013). A new genome-driven integrated classification of breast cancer and its implications. *EMBO J*, 32(5):617–28. doi:10.1038/emboj.2013.19 PMID:23395906

De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D et al.; EUROCARE-5 Working Group (2014). Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5 – a population-based study. *Lancet Oncol*, 15(1):23–34. doi:10.1016/S1470-2045(13)70546-1 PMID:24314615

de Gelder R, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D et al. (2009). Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. *Eur J Cancer*, 45(1):127–38. doi:10.1016/j.ejca.2008.09.015 PMID:19038540

de Koning HJ (2009). The mysterious mass(es). [Inaugural address, Professor of Screening Evaluation.] Rotterdam, Netherlands: Erasmus MC. Available from: http://repub.eur.nl/res/pub/30689/oratie.pdf.

de Villiers TJ, Gass ML, Haines CJ, Hall JE, Lobo RA, Pierroz DD et al. (2013a). Global consensus statement on menopausal hormone therapy. *Climacteric*, 16(2):203–4. doi:10.3109/13697137.2013.771520 PMID:23488524

de Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ et al.; International Menopause Society (2013b). Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric*, 16(3):316–37. doi:10.3109/13697137.2013.795683 PMID:23672656

De Waard F, Collette HJ, Rombach JJ, Collette C (1988). Breast cancer screening, with particular reference to the concept of 'high risk' groups. *Breast Cancer Res Treat*, 11(2):125–32. doi:10.1007/BF01805836 PMID:3401604

Dean L, Geshchicter CF (1938). Comedo carcinoma of the breast. *Arch Surg*, 36(2):225–34. doi:10.1001/archsurg.1938.01190200057003

Desrichard A, Bidet Y, Uhrhammer N, Bignon YJ (2011). *CHEK2* contribution to hereditary breast cancer in non-*BRCA* families. *Breast Cancer Res*, 13(6):R119. doi:10.1186/bcr3062 PMID:22114986

Dixon JM, Sainsbury JRC (1998). Handbook of diseases of the breast, 2nd edition. Edinburgh, UK: Churchill Livingstone.

Dolan RT, Butler JS, Kell MR, Gorey TF, Stokes MA (2010). Nipple discharge and the efficacy of duct cytology in evaluating breast cancer risk. *Surgeon*, 8(5):252–8. doi:10.1016/j.surge.2010.03.005 PMID:20709281

Donker M, Litière S, Werutsky G, Julien JP, Fentiman IS, Agresti R et al. (2013). Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol*, 31(32):4054–9. doi:10.1200/JCO.2013.49.5077 PMID:24043739

Doody MM, Freedman DM, Alexander BH, Hauptmann M, Miller JS, Rao RS et al. (2006). Breast cancer incidence in U.S. radiologic technologists. *Cancer*, 106(12):2707–15. doi:10.1002/cncr.21876 PMID:16639729

Doody MM, Lonstein JE, Stovall M, Hacker DG, Luckyanov N, Land CE (2000). Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. *Spine*, 25(16):2052–63. doi:10.1097/00007632-200008150-00009 PMID:10954636

Douglas-Jones AG, Gupta SK, Attanoos RL, Morgan JM, Mansel RE (1996). A critical appraisal of six modern classifications of ductal carcinoma in situ of the breast (DCIS): correlation with grade of associated invasive carcinoma. *Histopathology*, 29(5):397–409. doi:10.1046/j.1365-2559.1996.d01-513.x PMID:8951484

Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J et al.; International Ki-67 in Breast Cancer Working Group (2011). Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst*, 103(22):1656–64. doi:10.1093/jnci/djr393 PMID:21960707

Duffy SW, Tabár L, Vitak B, Day NE, Smith RA, Chen HH et al. (2003). The relative contributions of screen-detected in situ and invasive breast carcinomas in reducing mortality from the disease. *Eur J Cancer*, 39(12):1755–60. doi:10.1016/S0959-8049(03)00259-4 PMID:12888371

Dumas I, Diorio C (2010). Polymorphisms in genes involved in the estrogen pathway and mammographic density. *BMC Cancer*, 10(1):636. doi:10.1186/1471-2407-10-636 PMID:21092186

Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA et al. (1993). Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer*, 71(4):1258–65. doi:10.1002/1097-0142(19930215)71:4<1258::AID-CNCR2820710415>3.0.CO;2-I PMID:8435803

EBCTCG; Early Breast Cancer Trialists' Collaborative Group (2001). Tamoxifen for early breast cancer. *Cochrane Database Syst Rev*, (1):CD000486. PMID:11279694

EBCTCG; Early Breast Cancer Trialists' Collaborative Group (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, 365(9472):1687–717. doi:10.1016/S0140-6736(05)66544-0 PMID:15894097

Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors (2010). AJCC cancer staging manuals. Preface, 7th edition. With CD-ROM.

Eidemüller M, Holmberg E, Jacob P, Lundell M, Karlsson P (2009). Breast cancer risk among Swedish hemangioma patients and possible consequences of radiation-induced genomic instability. *Mutat Res*, 669(1–2):48–55. doi:10.1016/j.mrfmmm.2009.04.009 PMID:19416732

El Saghir NS, Adebamowo CA, Anderson BO, Carlson RW, Bird PA, Corbex M et al. (2011). Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. *Breast*, 20(Suppl 2):S3–11. doi:10.1016/j.breast.2011.02.006 PMID:21392996

Ellis I, editor (2011). Quality assurance guidelines for breast pathology services, 2nd edition. NHSBSP Publication No. 2. Sheffield, UK: NHS Cancer Screening Programmes.

Ellis IO, Coleman D, Wells C, Kodikara S, Paish EM, Moss S et al. (2006). Impact of a national external quality assessment scheme for breast pathology in the UK. *J Clin Pathol*, 59(2):138–45. doi:10.1136/jcp.2004.025551 PMID:16443727

Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW (1992). Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. *Histopathology*, 20(6):479–89. doi:10.1111/j.1365-2559.1992.tb01032.x PMID:1607149

Ellis IO, Galea MH, Locker A, Roebuck EJ, Elston CW, Blamey RW et al. (1993). Early experience in breast cancer screening: emphasis on development of protocols for triple assessment. *Breast*, 2(3):148–53. doi:10.1016/0960-9776(93)90058-N

Elshof LE, Tryfonidis K, Slaets L, van Leeuwen-Stok AE, Skinner VP, Dif N et al. (2015). Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study. *Eur J Cancer*, 51(12):1497–510. doi:10.1016/j.ejca.2015.05.008 PMID:26025767

Elston CW, Ellis IO (1991). Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*, 19(5):403–10. doi:10.1111/j.1365-2559.1991.tb00229.x PMID:1757079

Engholm G, Ferlay J, Christensen N, Kejs AMT, Johannesen TB, Khan S et al. (2014). NORDCAN: Cancer incidence, mortality, prevalence and survival in the Nordic countries, Version 7.0 (17.12.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from: http://www.ancr.nu, accessed 5 December 2014.

Erbas B, Provenzano E, Armes J, Gertig D (2006). The natural history of ductal carcinoma in situ of the breast: a review. *Breast Cancer Res Treat*, 97(2):135–44. doi:10.1007/s10549-005-9101-z PMID:16319971

Ermiah E, Abdalla F, Buhmeida A, Larbesh E, Pyrhönen S, Collan Y (2012). Diagnosis delay in Libyan female breast cancer. *BMC Res Notes*, 5(1):452. doi:10.1186/1756-0500-5-452 PMID:22909280

Ewertz M, Duffy SW, Adami HO, Kvåle G, Lund E, Meirik O et al. (1990). Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. *Int J Cancer*, 46(4):597–603. doi:10.1002/ijc.2910460408 PMID:2145231

Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD et al. (2014). Breast cancer in China. *Lancet Oncol*, 15(7):e279–89. doi:10.1016/S1470-2045(13)70567-9 PMID:24872111

Faulder C (1992). Breast awareness: what do we really mean? *Eur J Cancer*, 28(10):1595–6. doi:10.1016/0959-8049(92)90048-7 PMID:1389471

FDA (2014). Mammography Quality Standards Act and Program. US Food and Drug Administration. Available from: http://www.fda.gov/Radiation-EmittingProducts/MammographyQualityStandardsActandProgram/default.htm.

Feinstein AR, Sosin DM, Wells CK (1985). The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*, 312(25):1604–8. doi:10.1056/NEJM198506203122504 PMID:4000199

Ferlay J, Bray F, Steliarova-Foucher E, Forman D (2014b). Cancer Incidence in Five Continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. (2014a). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 136(5):E359–86. doi:10.1002/ijc.29210 PMID:25220842

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://globocan.iarc.fr, accessed 15 September 2014.

Finnish Cancer Registry (2015). Survival ratios of cancer patients in Finland. Institute for Statistical and Epidemiological Cancer Research. Available from: http://www.cancer.fi/syoparekisteri/en/statistics/survival-ratios-of-cancer-patien/.

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER et al. (2002). Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*, 347(16):1233–41. doi:10.1056/NEJMoa022152 PMID:12393820

Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N (2001). Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol*, 28(4):400–18. doi:10.1016/S0093-7754(01)90133-2 PMID:11498833

Fisher B, Wolmark N, Redmond C, Deutsch M, Fisher ER (1981). Findings from NSABP Protocol No. B-04: comparison of radical mastectomy with alternative treatments. II. The clinical and biologic significance of medial-central breast cancers. *Cancer*, 48(8):1863–72. doi:10.1002/1097-0142(19811015)48:8<1863::AID-CNCR2820480825>3.0.CO;2-U PMID:7284980

Fisher ER, Dignam J, Tan-Chiu E, Costantino J, Fisher B, Paik S et al. (1999). Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. *Cancer*, 86(3):429–38. doi:10.1002/(SICI)1097-0142(19990801)86:3<429::AID-CNCR11>3.0.CO;2-Y PMID:10430251

Fisher ER, Land SR, Fisher B, Mamounas E, Gilarski L, Wolmark N (2004). Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma in situ. *Cancer*, 100(2):238–44. doi:10.1002/cncr.11883 PMID:14716756

Fitzgibbons PL, Henson DE, Hutter RV; Cancer Committee of the College of American Pathologists (1998). Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. *Arch Pathol Lab Med*, 122(12):1053–5. PMID:9870852

Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M et al. (2013). Cancer Incidence in Five Continents, Volume X (electronic version). Lyon, France: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr.

Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F (2005). Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*, 114(3):448–54. doi:10.1002/ijc.20710 PMID:15551359

Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F (2009). Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol*, 27(31):5138–43. doi:10.1200/JCO.2008.21.6432 PMID:19752341

Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F, Chabbert-Buffet N (2014). Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. *Breast Cancer Res Treat*, 145(2):535–43. doi:10.1007/s10549-014-2934-6 PMID:24781971

Fregene A, Newman LA (2005). Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in African-American women? *Cancer*, 103(8):1540–50. doi:10.1002/cncr.20978 PMID:15768434

Friebel TM, Domchek SM, Rebbeck TR (2014). Modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers: systematic review and meta-analysis. *J Natl Cancer Inst*, 106(6):dju091. doi:10.1093/jnci/dju091 PMID:24824314

Friedenreich CM, Neilson HK, Lynch BM (2010). State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer*, 46(14):2593–604. doi:10.1016/j.ejca.2010.07.028 PMID:20843488

Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M et al. (2010). Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*, 102(14):1083–95. doi:10.1093/jnci/djq238 PMID:20634481

Friedman EB, Chun J, Schnabel F, Schwartz S, Law S, Billig J et al. (2013). Screening prior to breast cancer diagnosis: the more things change, the more they stay the same. *Int J Breast Cancer*, 2013:1. doi:10.1155/2013/327567 PMID:24159387

Frierson HF Jr, Wolber RA, Berean KW, Franquemont DW, Gaffey MJ, Boyd JC et al. (1995). Interobserver reproducibility of the Nottingham modification of the Bloom and Richardson histologic grading scheme for infiltrating ductal carcinoma. *Am J Clin Pathol*, 103(2):195–8. PMID:7856562

Fujii H, Szumel R, Marsh C, Zhou W, Gabrielson E (1996). Genetic progression, histological grade, and allelic loss in ductal carcinoma in situ of the breast. *Cancer Res*, 56(22):5260–5. PMID:8912866

Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C et al. (1989). Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*, 81(24):1879–86. doi:10.1093/jnci/81.24.1879 PMID:2593165

Gathani T, Ali R, Balkwill A, Green J, Reeves G, Beral V et al.; Million Women Study Collaborators (2014). Ethnic differences in breast cancer incidence in England are due to differences in known risk factors for the disease: prospective study. *Br J Cancer*, 110(1):224–9. doi:10.1038/bjc.2013.632 PMID:24169349

Gemeinsamen Bundesausschuss (2011). Regulation of the Joint Committee on Cancer Screening (cancer screening regulation/KFE-RL) [in German]. *Bundesanzeiger*, 34(S.864):1–5.

Ghiasvand R, Bahmanyar S, Zendehdel K, Tahmasebi S, Talei A, Adami HO et al. (2012). Postmenopausal breast cancer in Iran; risk factors and their population attributable fractions. *BMC Cancer*, 12(1):414. doi:10.1186/1471-2407-12-414 PMID:22992276

Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team (2011). Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol*, 12(3):236–44. doi:10.1016/S1470-2045(11)70033-X PMID:21354370

Giess CS, Keating DM, Osborne MP, Ng YY, Rosenblatt R (1998). Retroareolar breast carcinoma: clinical, imaging, and histopathologic features. *Radiology*, 207(3):669–73. doi:10.1148/radiology.207.3.9609889 PMID:9609889

Giordano L, Cogo C, Patnick J, Paci E; Euroscreen Working Group (2012). Communicating the balance sheet in breast cancer screening. *J Med Screen*, 19(Suppl 1): 67–71. doi:10.1258/jms.2012.012084 PMID:22972812

Giordano L, Webster P, Segnan N, Austoker J (2006). Guidance on breast screening communication. In: Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L et al., editors. European guidelines for quality assurance in breast cancer screening and diagnosis. 4th ed. Luxembourg: European Commission, Office for Official Publications of the European Communities; pp. 379–94.

Go EM, Tsang JY, Ni YB, Yu AM, Mendoza P, Chan SK et al. (2012). Relationship between columnar cell changes and low-grade carcinoma in situ of the breast–a cytogenetic study. *Hum Pathol*, 43(11):1924–31. doi:10.1016/j.humpath.2012.02.001 PMID:22542249

Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM et al.; Herceptin Adjuvant (HERA) Trial Study Team (2013). 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*, 382(9897):1021–8. doi:10.1016/S0140-6736(13)61094-6 PMID:23871490

Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ et al. (2009). Beyond Li Fraumeni syndrome: clinical characteristics of families with *p53* germline mutations. *J Clin Oncol*, 27(8):1250–6. doi:10.1200/JCO.2008.16.6959 PMID:19204208

Goodwin PJ, Phillips KA, West DW, Ennis M, Hopper JL, John EM et al. (2012). Breast cancer prognosis in *BRCA1* and *BRCA2* mutation carriers: an International Prospective Breast Cancer Family Registry population-based cohort study. *J Clin Oncol*, 30(1):19–26. doi:10.1200/JCO.2010.33.0068 PMID:22147742

Gorini G, Zappa M, Cortini B, Martini A, Mantellini P, Ventura L et al. (2014). Breast cancer mortality trends in Italy by region and screening programme, 1980–2008. *J Med Screen*, 21(4):189–93. doi:10.1177/0969141314549368 PMID:25186117

Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, Chavarri-Guerra Y, St Louis J et al. (2013). Planning cancer control in Latin America and the Caribbean. *Lancet Oncol*, 14(5):391–436. doi:10.1016/S1470-2045(13)70048-2 PMID:23628188

Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M et al. (2005). Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*, 23(1):197–204. doi:10.1200/JCO.2005.06.225 PMID:15625374

Haagensen CD (1986). Diseases of the breast. Philadelphia (PA), USA: Saunders.

Halsted WS (1894). The results of operations for the cure of cancer of the breast performed at The Johns Hopkins Hospital from June 1889 to January 1894. *Ann Surg*, 20(5):497–555. doi:10.1097/00000658-189407000-00075 PMID:17860107

Hammer GP, Auvinen A, De Stavola BL, Grajewski B, Gundestrup M, Haldorsen T et al. (2014). Mortality from cancer and other causes in commercial airline crews: a joint analysis of cohorts from 10 countries. *Occup Environ Med*, 71(5):313–22. doi:10.1136/oemed-2013-101395 PMID:24389960

Hammer GP, Seidenbusch MC, Schneider K, Regulla D, Zeeb H, Spix C et al. (2010). Cancer incidence rate after diagnostic X-ray exposure in 1976–2003 among patients of a university children's hospital [in German]. *Rofo*, 182(5):404–14. doi:10.1055/s-0029-1245235 PMID:20234999

Harford JB (2011). Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all. *Lancet Oncol*, 12(3):306–12. doi:10.1016/S1470-2045(10)70273-4 PMID:21376292

Harper S, Lynch J, Meersman SC, Breen N, Davis WW, Reichman MC (2009). Trends in area-socioeconomic and race-ethnic disparities in breast cancer incidence, stage at diagnosis, screening, mortality, and survival among women ages 50 years and over (1987–2005). *Cancer Epidemiol Biomarkers Prev*, 18(1):121–31. doi:10.1158/1055-9965.EPI-08-0679 PMID:19124489

Harris JR, Lippman ME, Veronesi U, Willett W (1992). Breast cancer. *N Engl J Med*, 327(5):319–28. doi:10.1056/NEJM199207303270505 PMID:1620171

Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ et al. (2006). Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res*, 12(10):3209–15. doi:10.1158/1078-0432.CCR-06-0083 PMID:16707622

Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP et al. (2010). Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med*, 152(7):444–55, W144–54. doi:10.7326/0003-4819-152-7-201004060-00009 PMID:20368650

Hildreth NG, Shore RE, Dvoretsky PM (1989). The risk of breast cancer after irradiation of the thymus in infancy. *N Engl J Med*, 321(19):1281–4. doi:10.1056/NEJM198911093211901 PMID:2797100

Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E et al. (2005). Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood*, 106(10):3358–65. doi:10.1182/blood-2005-04-1535 PMID:16051739

Hirko KA, Soliman AS, Hablas A, Seifeldin IA, Ramadan M, Banerjee M et al. (2013). Trends in breast cancer incidence rates by age and stage at diagnosis in Gharbiah, Egypt, over 10 years (1999–2008). *J Cancer Epidemiol*, 2013:1. doi:10.1155/2013/916394 PMID:24282410

Honrado E, Benítez J, Palacios J (2006). Histopathology of *BRCA1*- and *BRCA2*-associated breast cancer. *Crit Rev Oncol Hematol*, 59(1):27–39. doi:10.1016/j.critrevonc.2006.01.006 PMID:16530420

Howe GR, McLaughlin J (1996). Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res*, 145(6):694–707. doi:10.2307/3579360 PMID:8643829

Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S (1990). Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer*, 46(5):796–800. doi:10.1002/ijc.2910460508 PMID:2228308

Hukkinen K, Kivisaari L, Heikkilä PS, Von Smitten K, Leidenius M (2008). Unsuccessful preoperative biopsies, fine needle aspiration cytology or core needle biopsy, lead to increased costs in the diagnostic workup in breast cancer. *Acta Oncol*, 47(6):1037–45. doi:10.1080/02841860802001442 PMID:18607862

Hwang ES, DeVries S, Chew KL, Moore DH 2nd, Kerlikowske K, Thor A et al. (2004). Patterns of chromosomal alterations in breast ductal carcinoma in situ. *Clin Cancer Res*, 10(15):5160–7. doi:10.1158/1078-0432.CCR-04-0165 PMID:15297420

IARC (2002). Breast cancer screening. *IARC Handb Cancer Prev*, 7:1–229. Available from: http://www.iarc.fr/en/publications/pdfs-online/prev/handbook7/Handbook7_Breast.pdf.

IARC (2012a). Pharmaceuticals. *IARC Monogr Eval Carcinog Risks Hum*. 100A:1–437. PMID:23189749 Available from: http://monographs.iarc.fr/ENG/Monographs/vol100A/index.php.

IARC (2012b). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*. 100E:1–575. PMID:23193840 Available from: http://monographs.iarc.fr/ENG/Monographs/vol100E/index.php.

IARC (2012c). Radiation. *IARC Monogr Eval Carcinog Risks Hum*. 100D:1–437. PMID:23189752 Available from: http://monographs.iarc.fr/ENG/Monographs/vol100D/index.php.

Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T et al. (2012). Attributable causes of cancer in Japan in 2005 – systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. *Ann Oncol*, 23(5):1362–9. doi:10.1093/annonc/mdr437 PMID:22048150

INSERM (2008). Cancer et environnement. Rapport. Institut national de la santé et de la recherche médicale. Paris, France: Les éditions INSERM.

Isaacs C, Stearns V, Hayes DF (2001). New prognostic factors for breast cancer recurrence. *Semin Oncol*, 28(1):53–67. doi:10.1016/S0093-7754(01)90045-4 PMID:11254867

Isola J, Saijonkari M, Kataja V, Lundin J, Hytönen M, Isojärvi J et al. (2013). Gene profiling assays for planning breast cancer treatment [in Finnish]. *Suomen Lääkärilehti*, 68(50–52):3321–7ö. English summary available from: http://www.thl.fi/attachments/halo/summaries/SLL_2013_GeeniprofilointitestienMerkitysRintasyovanHoidonValinnassa_eng.pdf.

ISRCTN registry (2014). Surgery versus active monitoring for low risk ductal carcinoma in situ (DCIS). Available from: http://www.isrctn.com/ISRCTN27544579.

Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S; Japan Public Health Center-based Prospective Study Group (2007). Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev*, 16(2):116–23. doi:10.1097/01.cej.0000228410.14095.2d PMID:17297387

Iwasaki M, Tsugane S (2011). Risk factors for breast cancer: epidemiological evidence from Japanese studies. *Cancer Sci*, 102(9):1607–14. doi:10.1111/j.1349-7006.2011.01996.x PMID:21624009

Jain AN, Chin K, Børresen-Dale AL, Erikstein BK, Eynstein Lonning P, Kaaresen R et al. (2001). Quantitative analysis of chromosomal CGH in human breast tumors associates copy number abnormalities with p53 status and patient survival. *Proc Natl Acad Sci USA*, 98(14):7952–7. doi:10.1073/pnas.151241198 PMID:11438741

Jansen-van der Weide MC, Greuter MJ, Jansen L, Oosterwijk JCW, Pijnappel RM, de Bock GH (2010). Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. *Eur Radiol*, 20(11):2547–56. doi:10.1007/s00330-010-1839-y PMID:20582702

John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP et al. (2007). Prevalence of pathogenic *BRCA1* mutation carriers in 5 US racial/ethnic groups. *JAMA*, 298(24):2869–76. doi:10.1001/jama.298.24.2869 PMID:18159056

Justo N, Wilking N, Jönsson B, Luciani S, Cazap E (2013). A review of breast cancer care and outcomes in Latin America. *Oncologist*, 18(3):248–56. doi:10.1634/theoncologist.2012-0373 PMID:23442305

Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C et al. (2005). Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer*, 12(4):1071–82. doi:10.1677/erc.1.01038 PMID:16322344

Kaplan RM, Porzsolt F (2008). The natural history of breast cancer. *Arch Intern Med*, 168(21):2302–3. doi:10.1001/archinte.168.21.2302 PMID:19029491

Karami F, Mehdipour P (2013). A comprehensive focus on global spectrum of *BRCA1* and *BRCA2* mutations in breast cancer. *BioMed Res Int*, 2013:1. doi:10.1155/2013/928562 PMID:24312913

Kaurah P, MacMillan A, Boyd N, Senz J, De Luca A, Chun N et al. (2007). Founder and recurrent *CDH1* mutations in families with hereditary diffuse gastric cancer. *JAMA*, 297(21):2360–72. doi:10.1001/jama.297.21.2360 PMID:17545690

Kean S (2014). Breast cancer. The 'other' breast cancer genes. *Science*, 343(6178):1457–9. doi:10.1126/science.343.6178.1457 PMID:24675950

Kelsey JL, Bernstein L (1996). Epidemiology and prevention of breast cancer. *Annu Rev Public Health*, 17(1):47–67. doi:10.1146/annurev.pu.17.050196.000403 PMID:8724215

Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC et al. (2004). Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med*, 141(8):590–7. doi:10.7326/0003-4819-141-8-200410190-00006 PMID:15492338

Kerlikowske K, Ichikawa L, Miglioretti DL, Buist DS, Vacek PM, Smith-Bindman R et al.; National Institutes of Health Breast Cancer Surveillance Consortium (2007). Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J Natl Cancer Inst*, 99(5):386–95. doi:10.1093/jnci/djk066 PMID:17341730

Key T, Appleby P, Barnes I, Reeves G; Endogenous Hormones and Breast Cancer Collaborative Group (2002). Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*, 94(8):606–16. doi:10.1093/jnci/94.8.606 PMID:11959894

Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C et al.; Endogenous Hormones Breast Cancer Collaborative Group (2003). Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*, 95(16):1218–26. doi:10.1093/jnci/djg022 PMID:12928347

Key TJ, Appleby PN, Reeves GK, Roddam AW; Endogenous Hormones and Breast Cancer Collaborative Group (2010). Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol*, 11(6):530–42. doi:10.1016/S1470-2045(10)70095-4 PMID:20472501

Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A et al.; Endogenous Hormones and Breast Cancer Collaborative Group (2013). Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol*, 14(10):1009–19. doi:10.1016/S1470-2045(13)70301-2 PMID:23890780

Kingham TP, Alatise OI, Vanderpuye V, Casper C, Abantanga FA, Kamara TB et al. (2013). Treatment of cancer in sub-Saharan Africa. *Lancet Oncol*, 14(4):e158–67. doi:10.1016/S1470-2045(12)70472-2 PMID:23561747

Kingsmore D, Hole D, Gillis C (2004). Why does specialist treatment of breast cancer improve survival? The role of surgical management. *Br J Cancer*, 90(10):1920–5. doi:10.1038/sj.bjc.6601846 PMID:15138472

Kleibl Z, Novotny J, Bezdickova D, Malik R, Kleiblova P, Foretova L et al. (2005). The *CHEK2* c.1100delC germline mutation rarely contributes to breast cancer development in the Czech Republic. *Breast Cancer Res Treat*, 90(2):165–7. doi:10.1007/s10549-004-4023-8 PMID:15803363

Klein CA (2009). Parallel progression of primary tumours and metastases. *Nat Rev Cancer*, 9(4):302–12. doi:10.1038/nrc2627 PMID:19308069

Kobayashi S, Sugiura H, Ando Y, Shiraki N, Yanagi T, Yamashita H et al. (2012). Reproductive history and breast cancer risk. *Breast Cancer*, 19(4):302–8. doi:10.1007/s12282-012-0384-8 PMID:22711317

Kopans DB, Smith RA, Duffy SW (2011). Mammographic screening and "overdiagnosis". *Radiology*, 260(3):616–20. doi:10.1148/radiol.11110716 PMID:21846757

Kriege M, Hollestelle A, Jager A, Huijts PE, Berns EM, Sieuwerts AM et al. (2014). Survival and contralateral breast cancer in *CHEK2* 1100delC breast cancer patients: impact of adjuvant chemotherapy. *Br J Cancer*, 111(5):1004–13. doi:10.1038/bjc.2014.306 PMID:24918820

Kristensen VN, Vaske CJ, Ursini-Siegel J, Van Loo P, Nordgard SH, Sachidanandam R et al. (2012). Integrated molecular profiles of invasive breast tumors and ductal carcinoma in situ (DCIS) reveal differential vascular and interleukin signaling. *Proc Natl Acad Sci USA*, 109(8):2802–7. doi:10.1073/pnas.1108781108 PMID:21908711

Kwan ML, Haque R, Lee VS, Joanie Chung WL, Avila CC, Clancy HA et al. (2012). Validation of AJCC TNM staging for breast tumors diagnosed before 2004 in cancer registries. *Cancer Causes Control*, 23(9):1587–91. doi:10.1007/s10552-012-0026-7 PMID:22798182

Lakhani SR, Collins N, Stratton MR, Sloane JP (1995). Atypical ductal hyperplasia of the breast: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. *J Clin Pathol*, 48(7):611–5. doi:10.1136/jcp.48.7.611 PMID:7560165

Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors (2012). WHO classification of tumours of the breast. 4th ed. Lyon, France: International Agency for Research on Cancer.

Lakhani SR, Jacquemier J, Sloane JP, Gusterson BA, Anderson TJ, van de Vijver MJ et al. (1998). Multifactorial analysis of differences between sporadic breast cancers and cancers involving *BRCA1* and *BRCA2* mutations. *J Natl Cancer Inst*, 90(15):1138–45. doi:10.1093/jnci/90.15.1138 PMID:9701363

Lakhani SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, McGuffog L et al. (2002). The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in *BRCA1* and *BRCA2*. *J Clin Oncol*, 20(9):2310–8. doi:10.1200/JCO.2002.09.023 PMID:11981002

Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO (1994). Transient increase in the risk of breast cancer after giving birth. *N Engl J Med*, 331(1):5–9. doi:10.1056/NEJM199407073310102 PMID:8202106

Lampejo OT, Barnes DM, Smith P, Millis RR (1994). Evaluation of infiltrating ductal carcinomas with a DCIS component: correlation of the histologic type of the in situ component with grade of the infiltrating component. *Semin Diagn Pathol*, 11(3):215–22. PMID:7831533

Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I et al. (2003). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. *Radiat Res*, 160(6):707–17. doi:10.1667/RR3082 PMID:14640793

Lange JM, Takashima JR, Peterson SM, Kalapurakal JA, Green DM, Breslow NE (2014). Breast cancer in female survivors of Wilms tumor: a report from the national Wilms tumor late effects study. *Cancer*, 120(23):3722–30. doi:10.1002/cncr.28908 PMID:25348097

Langlands AO, Prescott RJ, Hamilton T (1980). A clinical trial in the management of operable cancer of the breast. *Br J Surg*, 67(3):170–4. doi:10.1002/bjs.1800670304 PMID:6988032

Larsen SU, Rose C (1999). Spontaneous remission of breast cancer. A literature review [in Danish]. *Ugeskr Laeger*, 161(26):4001–4. PMID:10402936

Lazarus E, Mainiero MB, Schepps B, Koelliker SL, Livingston LS (2006). BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value. *Radiology*, 239(2):385–91. doi:10.1148/radiol.2392042127 PMID:16569780

Lee SA, Ross RK, Pike MC (2005). An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. *Br J Cancer*, 92(11):2049–58. doi:10.1038/sj.bjc.6602617 PMID:15900297

Li J, Zhang BN, Fan JH, Pang Y, Zhang P, Wang SL et al. (2011). A nation-wide multicenter 10-year (1999–2008) retrospective clinical epidemiological study of female breast cancer in China. *BMC Cancer*, 11(1):364. doi:10.1186/1471-2407-11-364 PMID:21859480

Li L, Ji J, Wang JB, Niyazi M, Qiao YL, Boffetta P (2012). Attributable causes of breast cancer and ovarian cancer in China: reproductive factors, oral contraceptives and hormone replacement therapy. *Chin J Cancer Res*, 24(1):9–17. doi:10.1007/s11670-012-0009-y PMID:23359757

Li ML, Greenberg RA (2012). Links between genome integrity and *BRCA1* tumor suppression. *Trends Biochem Sci*, 37(10):418–24. doi:10.1016/j.tibs.2012.06.007 PMID:22836122

Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M et al. (2000). Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*, 343(2):78–85. doi:10.1056/NEJM200007133430201 PMID:10891514

Lindström S, Vachon CM, Li J, Varghese J, Thompson D, Warren R et al. (2011). Common variants in *ZNF365* are associated with both mammographic density and breast cancer risk. *Nat Genet*, 43(3):185–7. doi:10.1038/ng.760 PMID:21278746

Liu C, Wang QS, Wang YJ (2012a). The *CHEK2* I157T variant and colorectal cancer susceptibility: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*, 13(5):2051–5. doi:10.7314/APJCP.2012.13.5.2051 PMID:22901170

Liu C, Wang Y, Wang QS, Wang YJ (2012b). The *CHEK2* I157T variant and breast cancer susceptibility: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*, 13(4):1355–60. doi:10.7314/APJCP.2012.13.4.1355 PMID:22799331

Liu JJ, Freedman DM, Little MP, Doody MM, Alexander BH, Kitahara CM et al. (2014). Work history and mortality risks in 90,268 US radiological technologists. *Occup Environ Med*, 71(12):819–35. doi:10.1136/oemed-2013-101859 PMID:24852760

London SJ, Connolly JL, Schnitt SJ, Colditz GA (1992). A prospective study of benign breast disease and the risk of breast cancer. *JAMA*, 267(7):941–4. doi:10.1001/jama.1992.03480070057030 PMID:1734106

Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, Marchió C, Reis-Filho JS (2010). Breast cancer precursors revisited: molecular features and progression pathways. *Histopathology*, 57(2):171–92. doi:10.1111/j.1365-2559.2010.03568.x PMID:20500230

Lu YJ, Osin P, Lakhani SR, Di Palma S, Gusterson BA, Shipley JM (1998). Comparative genomic hybridization analysis of lobular carcinoma in situ and atypical lobular hyperplasia and potential roles for gains and losses of genetic material in breast neoplasia. *Cancer Res*, 58(20):4721–7. PMID:9788628

Lundell M, Mattsson A, Karlsson P, Holmberg E, Gustafsson A, Holm LE (1999). Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants. *Radiat Res*, 151(5):626–32. doi:10.2307/3580039 PMID:10319736

Ly D, Forman D, Ferlay J, Brinton LA, Cook MB (2013). An international comparison of male and female breast cancer incidence rates. *Int J Cancer*, 132(8):1918–26. doi:10.1002/ijc.27841 PMID:22987302

Lynge E, Törnberg S, von Karsa L, Segnan N, van Delden JJ (2012). Determinants of successful implementation of population-based cancer screening programmes. *Eur J Cancer*, 48(5):743–8. doi:10.1016/j.ejca.2011.06.051 PMID:21788130

Lythgoe JP, Leck I, Swindell R (1978). Manchester regional breast study. Preliminary results. *Lancet*, 1(8067):744–7. doi:10.1016/S0140-6736(78)90859-0 PMID:76750

Mac Bride MB, Pruthi S, Bevers T (2012). The evolution of breast self-examination to breast awareness. *Breast J*, 18(6):641–3. doi:10.1111/tbj.12023 PMID:23009674

MacMahon B, Cole P, Brown J (1973). Etiology of human breast cancer: a review. *J Natl Cancer Inst*, 50(1):21–42. PMID:4571238

Maddox WA, Carpenter JT Jr, Laws HL, Soong SJ, Cloud G, Urist MM et al. (1983). A randomized prospective trial of radical (Halsted) mastectomy versus modified radical mastectomy in 311 breast cancer patients. *Ann Surg*, 198(2):207–12. doi:10.1097/00000658-198308000-00016 PMID:6870379

Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN (1995). Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst*, 87(22):1681–5. doi:10.1093/jnci/87.22.1681 PMID:7473816

Mahoney L, Csima A (1982). Efficiency of palpation in clinical detection of breast cancer. *Can Med Assoc J*, 127(8):729–30. PMID:7139488

Mahoney MC, Bevers T, Linos E, Willett WC (2008). Opportunities and strategies for breast cancer prevention through risk reduction. *CA Cancer J Clin*, 58(6):347–71. doi:10.3322/CA.2008.0016 PMID:18981297

Malmgren JA, Parikh J, Atwood MK, Kaplan HG (2014). Improved prognosis of women aged 75 and older with mammography-detected breast cancer. *Radiology*, 273(3):686–94. doi:10.1148/radiol.14140209 PMID:25093690

Mark K, Temkin SM, Terplan M (2014). Breast self-awareness: the evidence behind the euphemism. *Obstet Gynecol*, 123(4):734–6. doi:10.1097/AOG.0000000000000139 PMID:24785598

Masannat YA, Bains SK, Pinder SE, Purushotham AD (2013). Challenges in the management of pleomorphic lobular carcinoma in situ of the breast. *Breast*, 22(2):194–6. doi:10.1016/j.breast.2013.01.003 PMID:23357705

Masciari S, Dillon DA, Rath M, Robson M, Weitzel JN, Balmana J et al. (2012). Breast cancer phenotype in women with *TP53* germline mutations: a Li-Fraumeni syndrome consortium effort. *Breast Cancer Res Treat*, 133(3):1125–30. doi:10.1007/s10549-012-1993-9 PMID:22392042

Mattsson A, Rudén BI, Hall P, Wilking N, Rutqvist LE (1993). Radiation-induced breast cancer: long-term follow-up of radiation therapy for benign breast disease. *J Natl Cancer Inst*, 85(20):1679–85. doi:10.1093/jnci/85.20.1679 PMID:8411245

Mattsson A, Rudén BI, Palmgren J, Rutqvist LE (1995). Dose- and time-response for breast cancer risk after radiation therapy for benign breast disease. *Br J Cancer*, 72(4):1054–61. doi:10.1038/bjc.1995.461 PMID:7547222

Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H et al.; HEBON; EMBRACE; GEMO Study Collaborators; kConFab Investigators; SWE-BRCA Collaborators; Consortium of Investigators of Modifiers of BRCA1/2 (2012). Pathology of breast and ovarian cancers among *BRCA1* and *BRCA2* mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev*, 21(1):134–47. doi:10.1158/1055-9965.EPI-11-0775 PMID:22144499

McCormack VA, dos Santos Silva I (2006). Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15(6):1159–69. doi:10.1158/1055-9965.EPI-06-0034 PMID:16775176

McCormack VA, Joffe M, van den Berg E, Broeze N, Silva IS, Romieu I et al. (2013). Breast cancer receptor status and stage at diagnosis in over 1,200 consecutive public hospital patients in Soweto, South Africa: a case series. *Breast Cancer Res*, 15(5):R84. doi:10.1186/bcr3478 PMID:24041225

McCready T, Littlewood D, Jenkinson J (2005). Breast self-examination and breast awareness: a literature review. *J Clin Nurs*, 14(5):570–8. doi:10.1111/j.1365-2702.2004.01108.x PMID:15840071

McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2014). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*, 383(9935):2127–35. doi:10.1016/S0140-6736(14)60488-8 PMID:24656685

McWhirter R (1948). The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast. *Br J Radiol*, 21(252):599–610. doi:10.1259/0007-1285-21-252-599 PMID:18099752

Meijers-Heijboer H, van den Ouweland A, Klijn J, Wasielewski M, de Snoo A, Oldenburg R et al.; CHEK2-Breast Cancer Consortium (2002). Low-penetrance susceptibility to breast cancer due to *CHEK2*(*)1100delC in noncarriers of *BRCA1* or *BRCA2* mutations. *Nat Genet*, 31(1):55–9. doi:10.1038/ng879 PMID:11967536

Mendonça GA, Silva AM, Caula WM (2004). Tumor characteristics and five-year survival in breast cancer patients at the National Cancer Institute, Rio de Janeiro, Brazil [in Portuguese]. *Cad Saude Publica*, 20(5):1232–9. PMID:15486666

Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL et al.; Breast and Ovarian Cancer Susceptibility Collaboration; Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON); kConFab Investigators; Australian Ovarian Cancer Study Group; GENICA (Gene Environment Interaction and Breast Cancer in Germany) Network (2013). Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet*, 45(4):353–61, e1–2. doi:10.1038/ng.2563 PMID:23535729

Mikeljevic JS, Haward R, Johnston C, Crellin A, Dodwell D, Jones A et al. (2004). Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer*, 90(7):1343–8. doi:10.1038/sj.bjc.6601693 PMID:15054452

Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE (2004). Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. *J Natl Cancer Inst*, 96(24):1856–65. doi:10.1093/jnci/djh336 PMID:15601642

Mittra I, Mishra GA, Singh S, Aranke S, Notani P, Badwe R et al. (2010). A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *Int J Cancer*, 126(4):976–84. PMID:19697326

Moelans CB, de Wegers RA, Monsuurs HN, Maess AH, van Diest PJ (2011). Molecular differences between ductal carcinoma in situ and adjacent invasive breast carcinoma: a multiplex ligation-dependent probe amplification study. *Cell Oncol (Dordr)*, 34(5):475–82. doi:10.1007/s13402-011-0043-7 PMID:21547576

Mohan AK, Hauptmann M, Linet MS, Ron E, Lubin JH, Freedman DM et al. (2002). Breast cancer mortality among female radiologic technologists in the United States. *J Natl Cancer Inst*, 94(12):943–8. doi:10.1093/jnci/94.12.943 PMID:12072548

Moinfar F, Man YG, Bratthauer GL, Ratschek M, Tavassoli FA (2000). Genetic abnormalities in mammary ductal intraepithelial neoplasia-flat type ("clinging ductal carcinoma in situ"): a simulator of normal mammary epithelium. *Cancer*, 88(9):2072–81. doi:10.1002/(SICI)1097-0142(20000501)88:9<2072::AID-CNCR13>3.0.CO;2-H PMID:10813719

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V et al. (2012). Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*, 4:CD006243. doi:10.1002/14651858.CD006243.pub2 PMID:22513938

Moolgavkar SH, Stevens RG, Lee JA (1979). Effect of age on incidence of breast cancer in females. *J Natl Cancer Inst*, 62(3):493–501. PMID:283278

Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Novetsky Friedman D et al. (2014). Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*, 32(21):2217–23. doi:10.1200/JCO.2013.54.4601 PMID:24752044

Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL et al. (2009). Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*, 100(1):206–12. doi:10.1038/sj.bjc.6604825 PMID:19127272

Munzone E, Curigliano G, Burstein HJ, Winer EP, Goldhirsch A (2012). CMF revisited in the 21st century. *Ann Oncol*, 23(2):305–11. doi:10.1093/annonc/mdr309 PMID:21715566

Murthy V, Chamberlain RS (2011). Recommendation to revise the AJCC/UICC breast cancer staging system for inclusion of proven prognostic factors: ER/PR receptor status and HER2 neu. *Clin Breast Cancer*, 11(5):346–7. doi:10.1016/j.clbc.2011.05.003 PMID:21820971

Nagata C, Hu YH, Shimizu H (1995). Effects of menstrual and reproductive factors on the risk of breast cancer: meta-analysis of the case-control studies in Japan. *Jpn J Cancer Res*, 86(10):910–5. doi:10.1111/j.1349-7006.1995.tb03000.x PMID:7493908

Nagel JH, Peeters JK, Smid M, Sieuwerts AM, Wasielewski M, de Weerd V et al. (2012). Gene expression profiling assigns *CHEK2* 1100delC breast cancers to the luminal intrinsic subtypes. *Breast Cancer Res Treat*, 132(2):439–48. doi:10.1007/s10549-011-1588-x PMID:21614566

Narod SA (2010). Testing for *CHEK2* in the cancer genetics clinic: ready for prime time? *Clin Genet*, 78(1):1–7. doi:10.1111/j.1399-0004.2010.01402.x PMID:20597917

National Research Council (2006). Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington (DC), USA: National Academies Press.

Navarrete Montalvo D, González M N, Montalvo V MT, Jiménez A A, Echiburú-Chau C, Calaf GM (2008). Patterns of recurrence and survival in breast cancer. *Oncol Rep*, 20(3):531–5. PMID:18695902

Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA (2006). Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol*, 24(9):1342–9. doi:10.1200/JCO.2005.03.3472 PMID:16549828

NHSBSP (2005). Pathology reporting of breast disease: a joint document incorporating the third edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the second edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology. NHSBSP Publication No. 58. Sheffield, UK: NHS Cancer Screening Programmes and The Royal College of Pathologists.

NHSBSP (2006). Be breast aware. NHS Cancer Screening Programmes information leaflet. London, UK: Department of Health. Available from: https://www.gov.uk/government/publications/nhs-breast-screening-awareness-leaflet.

NICE (2013). Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. NICE diagnostics guidance [DG10]. London, UK: National Institute for Health and Care Excellence. Available from: http://www.nice.org.uk/guidance/dg10/.

Nieuwenhuis B, Van Assen-Bolt AJ, Van Waarde-Verhagen MA, Sijmons RH, Van der Hout AH, Bauch T et al. (2002). *BRCA1* and *BRCA2* heterozygosity and repair of X-ray-induced DNA damage. *Int J Radiat Biol*, 78(4):285–95. doi:10.1080/09553000110097974 PMID:12020440

Nieuwenhuis MH, Kets CM, Murphy-Ryan M, Yntema HG, Evans DG, Colas C et al. (2014). Cancer risk and genotype-phenotype correlations in *PTEN* hamartoma tumor syndrome. *Fam Cancer*, 13(1):57–63. doi:10.1007/s10689-013-9674-3 PMID:23934601

Norman SA, Localio AR, Zhou L, Weber AL, Coates RJ, Malone KE et al. (2006). Benefit of screening mammography in reducing the rate of late-stage breast cancer diagnoses (United States). *Cancer Causes Control*, 17(7):921–9. doi:10.1007/s10552-006-0029-3 PMID:16841259

Norsa'adah B, Rampal KG, Rahmah MA, Naing NN, Biswal BM (2011). Diagnosis delay of breast cancer and its associated factors in Malaysian women. *BMC Cancer*, 11(1):141. doi:10.1186/1471-2407-11-141 PMID:21496310

Norum JH, Andersen K, Sørlie T (2014). Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy. *Br J Surg*, 101(8):925–38. doi:10.1002/bjs.9562 PMID:24849143

Offit K (2006). BRCA mutation frequency and penetrance: new data, old debate. *J Natl Cancer Inst*, 98(23):1675–7. doi:10.1093/jnci/djj500 PMID:17148764

Ohene-Yeboah M, Amaning E (2008). Spectrum of complaints presented at a specialist breast clinic in Kumasi, Ghana. *Ghana Med J*, 42(3):110–3. PMID:19274109

Okonkwo QL, Draisma G, der Kinderen A, Brown ML, de Koning HJ (2008). Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. *J Natl Cancer Inst*, 100(18):1290–300. doi:10.1093/jnci/djn292 PMID:18780864

OMIM (2015). Online Mendelian Inheritance in Man database. Baltimore (MD), USA: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University. Available from: www.omim.org.

Osborne CK (1998). Tamoxifen in the treatment of breast cancer. *N Engl J Med*, 339(22):1609–18. doi:10.1056/NEJM199811263392207 PMID:9828250

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ et al. (2012). Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer

and noncancer diseases. *Radiat Res*, 177(3):229–43. doi:10.1667/RR2629.1 PMID:22171960

Paci E, Del Turco MR, Palli D, Buiatti E, Bruzzi P, Piffanelli A (1988). Selection of high-risk groups for breast cancer screening. Evidence from an Italian multicentric case control study. *Tumori*, 74(6):675–9. PMID:3068864

Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA (1995). Continued local recurrence of carcinoma 15–25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. *Cancer*, 76(7):1197–200. doi:10.1002/1097-0142(19951001)76:7<1197::AID-CNCR2820760715>3.0.CO;2-0 PMID:8630897

Palacios J, Robles-Frías MJ, Castilla MA, López-García MA, Benítez J (2008). The molecular pathology of hereditary breast cancer. *Pathobiology*, 75(2):85–94. doi:10.1159/000123846 PMID:18544963

Park S, Kim Y, Shin HR, Lee B, Shin A, Jung KW et al. (2014). Population-attributable causes of cancer in Korea: obesity and physical inactivity. *PLoS ONE*, 9(4):e90871. doi:10.1371/journal.pone.0090871 PMID:24722008

Patey DH, Scarff RW (1928). The position of histology in the prognosis of carcinoma of the breast. *Lancet*, 211(5460):801–4. doi:10.1016/S0140-6736(00)76762-6

Peng S, Lü B, Ruan W, Zhu Y, Sheng H, Lai M (2011). Genetic polymorphisms and breast cancer risk: evidence from meta-analyses, pooled analyses, and genome-wide association studies. *Breast Cancer Res Treat*, 127(2):309–24. doi:10.1007/s10549-011-1459-5 PMID:21445572

Pereira H, Pinder SE, Sibbering DM, Galea MH, Elston CW, Blamey RW et al. (1995). Pathological prognostic factors in breast cancer. IV: Should you be a typer or a grader? A comparative study of two histological prognostic features in operable breast carcinoma. *Histopathology*, 27(3):219–26. doi:10.1111/j.1365-2559.1995.tb00213.x PMID:8522285

Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr et al. (2011). Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*, 29(25):3366–73. doi:10.1200/JCO.2011.35.0868 PMID:21768458

Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al. (2000). Molecular portraits of human breast tumours. *Nature*, 406(6797):747–52. doi:10.1038/35021093 PMID:10963602

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L et al., editors (2006). European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition. Luxembourg: European Commission, Office for Official Publications of the European Communities; pp. 15–56. Available from: http://ec.europa.eu/health/ph_projects/2002/cancer/cancer_2002_01_en.htm.

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L (2008). European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition–summary document. *Ann Oncol*, 19(4):614–22. doi:10.1093/annonc/mdm481 PMID:18024988

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L (2013a). European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition, Supplements. Luxembourg: European Commission, Office for Official Publications of the European Union.

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L (2013b). Executive summary. In: Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, editors. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition, Supplements. Luxembourg: European Commission, Office for Official Publications of the European Union; pp. XIV–XX.

Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2012). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*, 379(9814):432–44. doi:10.1016/S0140-6736(11)61625-5 PMID:22152853

Pettersson A, Graff RE, Ursin G, Santos Silva ID, McCormack V, Baglietto L et al. (2014). Mammographic density phenotypes and risk of breast cancer: a meta-analysis. *J Natl Cancer Inst*, 106(5):dju078. doi:10.1093/jnci/dju078 PMID:24816206

Pieri A, Harvey J, Bundred N (2014). Pleomorphic lobular carcinoma in situ of the breast: can the evidence guide practice? *World J Clin Oncol*, 5(3):546–53. doi:10.5306/wjco.v5.i3.546 PMID:25114868

Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Noguès C et al.; GENEPSO; EMBRACE; HEBON (2012). Exposure to diagnostic radiation and risk of breast cancer among carriers of *BRCA1/2* mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ*, 345:e5660. doi:10.1136/bmj.e5660 PMID:22956590

Pike MC, Pearce CL (2013). Mammographic density, MRI background parenchymal enhancement and breast cancer risk. *Ann Oncol*, 24(Suppl 8):viii37–41. doi:10.1093/annonc/mdt310 PMID:24131968

Pike MC, Wu AH, Spicer DV, Lee S, Pearce CL (2007). Estrogens, progestins, and risk of breast cancer. *Ernst Schering Found Symp Proc*, 2007(1):127–50. PMID:18540571

Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E (2013). Cowden syndrome and the *PTEN* hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst*, 105(21):1607–16. doi:10.1093/jnci/djt277 PMID:24136893

Pinto AC, Ades F, de Azambuja E, Piccart-Gebhart M (2013). Trastuzumab for patients with HER2 positive breast cancer: delivery, duration and combination therapies. *Breast*, 22(Suppl 2):S152–5. doi:10.1016/j.breast.2013.07.029 PMID:24074778

Polyak K (2007). Breast cancer: origins and evolution. *J Clin Invest*, 117(11):3155–63. doi:10.1172/JCI33295 PMID:17975657

Porta M (2008). A dictionary of epidemiology, 5th edition. Oxford, UK: Oxford University Press.

Porter PL, El-Bastawissi AY, Mandelson MT, Lin MG, Khalid N, Watney EA et al. (1999). Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst*, 91(23):2020–8. doi:10.1093/jnci/91.23.2020 PMID:10580027

Poum A, Promthet S, Duffy SW, Parkin DM (2014). Factors associated with delayed diagnosis of breast cancer in northeast Thailand. *J Epidemiol*, 24(2):102–8. doi:10.2188/jea.JE20130090 PMID:24335087

Powell SN, Kachnic LA (2003). Roles of *BRCA1* and *BRCA2* in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. *Oncogene*, 22(37):5784–91. doi:10.1038/sj.onc.1206678 PMID:12947386

Pradhan M, Dhakal HP (2008). Study of breast lump of 2246 cases by fine needle aspiration. *JNMA J Nepal Med Assoc*, 47(172):205–9. PMID:19079396

Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr (2002). Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res*, 158(2):220–35. doi:10.1667/0033-7587(2002)158[0220:REOBCR]2.0.CO;2 PMID:12105993

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M et al. (2007). Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res*, 168(1):1–64. doi:10.1667/RR0763.1 PMID:17722996

Prokopcova J, Kleibl Z, Banwell CM, Pohlreich P (2007). The role of *ATM* in breast cancer development. *Breast Cancer Res Treat*, 104(2):121–8. doi:10.1007/s10549-006-9406-6 PMID:17061036

Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M et al.; EUROSCREEN Working Group (2012). Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J Med Screen*, 19(Suppl 1):42–56. doi:10.1258/jms.2012.012082 PMID:22972810

Rahman N (2014a). Realizing the promise of cancer predisposition genes. *Nature*, 505(7483):302–8. doi:10.1038/nature12981 PMID:24429628

Rahman N (2014b). Mainstreaming genetic testing of cancer predisposition genes. *Clin Med*, 14(4):436–9. doi:10.7861/clinmedicine.14-4-436 PMID:25099850

Rakha EA, Lee AH, Evans AJ, Menon S, Assad NY, Hodi Z et al. (2010b). Tubular carcinoma of the breast: further evidence to support its excellent prognosis. *J Clin Oncol*, 28(1):99–104. doi:10.1200/JCO.2009.23.5051 PMID:19917872

Renwick A, Thompson D, Seal S, Kelly P, Chagtai T, Ahmed M et al.; Breast Cancer Susceptibility Collaboration (UK) (2006). *ATM* mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. *Nat Genet*, 38(8):873–5. doi:10.1038/ng1837 PMID:16832357

Retsky MW, Demicheli R, Hrushesky WJ, Baum M, Gukas ID (2008). Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer. *APMIS*, 116(7–8):730–41. doi:10.1111/j.1600-0463.2008.00990.x PMID:18834415

Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA et al.; British Childhood Cancer Survivor Study Steering Group (2011). Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA*, 305(22):2311–9. doi:10.1001/jama.2011.747 PMID:21642683

Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ (1999). Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet*, 353(9159):1119–26. doi:10.1016/S0140-6736(99)02143-1 PMID:10209974

Robb K, Wardle J, Stubbings S, Ramirez A, Austoker J, Macleod U et al. (2010). Ethnic disparities in knowledge of cancer screening programmes in the UK. *J Med Screen*, 17(3):125–31. doi:10.1258/jms.2010.009112 PMID:20956722

Robbins P, Pinder S, de Klerk N, Dawkins H, Harvey J, Sterrett G et al. (1995). Histological grading of breast carcinomas: a study of interobserver agreement. *Hum Pathol*, 26(8):873–9. doi:10.1016/0046-8177(95)90010-1 PMID:7635449

Ronckers CM, Doody MM, Lonstein JE, Stovall M, Land CE (2008). Multiple diagnostic X-rays for spine deformities and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 17(3):605–13. doi:10.1158/1055-9965.EPI-07-2628 PMID:18349278

Ronckers CM, Erdmann CA, Land CE (2005). Radiation and breast cancer: a review of current evidence. *Breast Cancer Res*, 7(1):21–32. doi:10.1186/bcr970 PMID:15642178

Ronckers CM, Land CE, Miller JS, Stovall M, Lonstein JE, Doody MM (2010). Cancer mortality among women frequently exposed to radiographic examinations for spinal disorders. *Radiat Res*, 174(1):83–90. doi:10.1667/RR2022.1 PMID:20681802

Sanders ME, Schuyler PA, Dupont WD, Page DL (2005). The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. *Cancer*, 103(12):2481–4. doi:10.1002/cncr.21069 PMID:15884091

Sankaranarayanan R (2000). Integration of cost-effective early detection programs into the health

services of developing countries. *Cancer*, 89(3):475–81. doi:10.1002/1097-0142(20000801)89:3<475::AID-CNCR1>3.0.CO;2-8 PMID:10931445

Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Prabhakar J, Augustine P et al. (2011). Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst*, 103(19):1476–80. doi:10.1093/jnci/djr304 PMID:21862730

Sankaranarayanan R, Swaminathan R (2011). Cancer survival in Africa, Asia, the Caribbean and Central America. Introduction. *IARC Sci Publ*, 162(162):1–5. PMID:21675400

Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG et al. (2010). Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol*, 11(2):165–73. doi:10.1016/S1470-2045(09)70335-3 PMID:20005175

Sant M, Allemani C, Capocaccia R, Hakulinen T, Aareleid T, Coebergh JW et al.; EUROCARE Working Group (2003). Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer*, 106(3):416–22. doi:10.1002/ijc.11226 PMID:12845683

Saphner T, Tormey DC, Gray R (1996). Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol*, 14(10):2738–46. PMID:8874335

Savage KI, Gorski JJ, Barros EM, Irwin GW, Manti L, Powell AJ et al. (2014). Identification of a BRCA1-mRNA splicing complex required for efficient DNA repair and maintenance of genomic stability. *Mol Cell*, 54(3):445–59. doi:10.1016/j.molcel.2014.03.021 PMID:24746700

Schmidt-Kittler O, Ragg T, Daskalakis A, Granzow M, Ahr A, Blankenstein TJ et al. (2003). From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. *Proc Natl Acad Sci USA*, 100(13):7737–42. doi:10.1073/pnas.1331931100 PMID:12808139

Schrader KA, Masciari S, Boyd N, Salamanca C, Senz J, Saunders DN et al.; kConFab (2011). Germline mutations in *CDH1* are infrequent in women with early-onset or familial lobular breast cancers. *J Med Genet*, 48(1):64–8. doi:10.1136/jmg.2010.079814 PMID:20921021

Scoccianti C, Lauby-Secretan B, Bello PY, Chajes V, Romieu I (2014). Female breast cancer and alcohol consumption: a review of the literature. *Am J Prev Med*, 46(3 Suppl 1):S16–25. doi:10.1016/j.amepre.2013.10.031 PMID:24512927

Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens – Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*, 10(11):1033–4. doi:10.1016/S1470-2045(09)70326-2 PMID:19891056

SEER (2014a). Cancer statistics fact sheets: female breast cancer. Bethesda (MD), USA: Surveillance, Epidemiology, and End Results Program, US National Cancer Institute. Available from: http://seer.cancer.gov/statfacts/html/breast.html.

SEER (2014b). Staging a cancer case. Bethesda (MD), USA: Surveillance, Epidemiology, and End Results Program, US National Cancer Institute. Available from: http://training.seer.cancer.gov/staging/, accessed 24 September 2014.

Seitz HK, Pelucchi C, Bagnardi V, La Vecchia C (2012). Epidemiology and pathophysiology of alcohol and breast cancer: update 2012. *Alcohol Alcohol*, 47(3):204–12. doi:10.1093/alcalc/ags011 PMID:22459019

Shah NR, Borenstein J, Dubois RW (2005). Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. *Menopause*, 12(6):668–78. doi:10.1097/01.gme.0000184221.63459.e1 PMID:16278609

Shah SP, Roth A, Goya R, Oloumi A, Ha G, Zhao Y et al. (2012). The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature*, 486(7403):395–9. PMID:22495314

Shore RE, Hildreth N, Woodard E, Dvoretsky P, Hempelmann L, Pasternack B (1986). Breast cancer among women given X-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst*, 77(3):689–96. PMID:3462410

Shulman LN, Willett W, Sievers A, Knaul FM (2010). Breast cancer in developing countries: opportunities for improved survival. *J Oncol*, 2010:1. doi:10.1155/2010/595167 PMID:21253541

Sibbering M, Watkins R, Winstanley J, Patnick J, editors (2009). Quality assurance guidelines for surgeons in breast cancer screening, 4th edition. NHSBSP Publication No. 20. Sheffield, UK: NHS Cancer Screening Programmes.

Siegel R, Ma J, Zou Z, Jemal A (2014). Cancer statistics, 2014. *CA Cancer J Clin*, 64(1):9–29. doi:10.3322/caac.21208 PMID:24399786

Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M et al. (2003). Cancer incidence in the US radiologic technologists health study, 1983–1998. *Cancer*, 97(12):3080–9. doi:10.1002/cncr.11444 PMID:12784345

Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ et al. (1996). A prognostic index for ductal carcinoma in situ of the breast. *Cancer*, 77(11):2267–74. doi:10.1002/(SICI)1097-0142(19960601)77:11<2267::AID-CNCR13>3.0.CO;2-V PMID:8635094

Silverstein MJ, Poller DN, Waisman JR, Colburn WJ, Barth A, Gierson ED et al. (1995). Prognostic classification of breast ductal carcinoma-in-situ. *Lancet*,

345(8958):1154–7. doi:10.1016/S0140-6736(95)90982-6 PMID:7723550

Simpson PT, Gale T, Fulford LG, Reis-Filho JS, Lakhani SR (2003). The diagnosis and management of pre-invasive breast disease: pathology of atypical lobular hyperplasia and lobular carcinoma in situ. *Breast Cancer Res*, 5(5):258–62. doi:10.1186/bcr624 PMID:12927036

Simpson PT, Gale T, Reis-Filho JS, Jones C, Parry S, Sloane JP et al. (2005). Columnar cell lesions of the breast: the missing link in breast cancer progression? A morphological and molecular analysis. *Am J Surg Pathol*, 29(6):734–46. doi:10.1097/01.pas.0000157295.93914.3b PMID:15897740

Singh D, Malila N, Pokhrel A, Anttila A (2015). Association of symptoms and breast cancer in population-based mammography screening in Finland. *Int J Cancer*, 136(6):E630–7. doi:10.1002/ijc.29170 PMID:25160029

Singletary SE, Greene FL; Breast Task Force (2003). Revision of breast cancer staging: the 6th edition of the TNM classification. *Semin Surg Oncol*, 21(1):53–9. doi:10.1002/ssu.10021 PMID:12923916

Sinn P, Aulmann S, Wirtz R, Schott S, Marmé F, Varga Z et al. (2013). Multigene assays for classification, prognosis, and prediction in breast cancer: a critical review on the background and clinical utility. *Geburtshilfe Frauenheilkd*, 73(9):932–40. doi:10.1055/s-0033-1350831 PMID:24771945

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*, 235(4785):177–82. doi:10.1126/science.3798106 PMID:3798106

Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A et al. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*, 344(11):783–92. doi:10.1056/NEJM200103153441101 PMID:11248153

Sledge GW, Mamounas EP, Hortobagyi GN, Burstein HJ, Goodwin PJ, Wolff AC (2014). Past, present, and future challenges in breast cancer treatment. *J Clin Oncol*, 32(19):1979–86. doi:10.1200/JCO.2014.55.4139 PMID:24888802

Sloan FA, Gelband H, editors (2007). Cancer control opportunities in low- and middle-income countries. Washington (DC), USA: Institute of Medicine of the National Academies.

Smith E, Heaney E, Dooher P (2012). Interim quality assurance guidelines for clinical nurse specialists in breast cancer screening, 5th edition. NHSBSP Publication No. 29. Sheffield, UK: NHS Cancer Screening Programmes.

Solin L, Schwartz G, Feig S, Shaber G, Patchefsky A (1984). Risk factors as criteria for inclusion in breast cancer screening programs. In: Ames F, Blumenschein G, Montague E, editors. Current controversies in breast cancer. Austin (TX), USA: University of Texas Press; pp. 565–73.

Solin LJ, Yeh IT, Kurtz J, Fourquet A, Recht A, Kuske R et al. (1993). Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation. Correlation of pathologic parameters with outcome of treatment. *Cancer*, 71(8):2532–42. doi:10.1002/1097-0142(19930415)71:8<2532::AID-CNCR2820710817>3.0.CO;2-0 PMID:8384070

Sopik V, Phelan C, Cybulski C, Narod S (2014). *BRCA1* and *BRCA2* mutations and the risk for colorectal cancer. *Clin Genet*, 87(5):411–8. doi:10.1111/cge.12497 PMID:25195694

Sørlie T (2004). Molecular portraits of breast cancer: tumour subtypes as distinct disease entities. *Eur J Cancer*, 40(18):2667–75. doi:10.1016/j.ejca.2004.08.021 PMID:15571950

Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H et al. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA*, 98(19):10869–74. doi:10.1073/pnas.191367098 PMID:11553815

Sotiriou C, Pusztai L (2009). Gene-expression signatures in breast cancer. *N Engl J Med*, 360(8):790–800. doi:10.1056/NEJMra0801289 PMID:19228622

Soumian S, Verghese ET, Booth M, Sharma N, Chaudhri S, Bradley S et al. (2013). Concordance between vacuum assisted biopsy and postoperative histology: implications for the proposed Low Risk DCIS Trial (LORIS). *Eur J Surg Oncol*, 39(12):1337–40. doi:10.1016/j.ejso.2013.09.028 PMID:24209431

Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED et al.; WHI Investigators (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*, 295(14):1647–57. doi:10.1001/jama.295.14.1647 PMID:16609086

Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, Wedge DC et al.; Oslo Breast Cancer Consortium (OSBREAC) (2012). The landscape of cancer genes and mutational processes in breast cancer. *Nature*, 486(7403):400–4. PMID:22722201

Storm HH, Andersson M, Boice JD Jr, Blettner M, Stovall M, Mouridsen HT et al. (1992). Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst*, 84(16):1245–50. doi:10.1093/jnci/84.16.1245 PMID:1640483

Stratton MR, Campbell PJ, Futreal PA (2009). The cancer genome. *Nature*, 458(7239):719–24. doi:10.1038/nature07943 PMID:19360079

Stratton MR, Collins N, Lakhani SR, Sloane JP (1995). Loss of heterozygosity in ductal carcinoma in situ of the breast. *J Pathol*, 175(2):195–201. doi:10.1002/path.1711750207 PMID:7738715

Stuart-Harris R, Caldas C, Pinder SE, Pharoah P (2008). Proliferation markers and survival in early breast

cancer: a systematic review and meta-analysis of 85 studies in 32,825 patients. *Breast*, 17(4):323–34. doi:10.1016/j.breast.2008.02.002 PMID:18455396

Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E et al. (2011). Delivering affordable cancer care in high-income countries. *Lancet Oncol*, 12(10):933–80. doi:10.1016/S1470-2045(11)70141-3 PMID:21958503

Tabár L, Dean PB, Chen SL, Chen HH, Yen AM, Fann JC et al. (2014). Invasive lobular carcinoma of the breast: the use of radiological appearance to classify tumor subtypes for better prediction of long-term outcome. *J Clin Exp Pathol*, 4(4).

Tabár L, Dean PB, Péntek Z (1983). Galactography: the diagnostic procedure of choice for nipple discharge. *Radiology*, 149(1):31–8. doi:10.1148/radiology.149.1.6611939 PMID:6611939

Tabár L, Fagerberg G, Day NE, Duffy SW, Kitchin RM (1992). Breast cancer treatment and natural history: new insights from results of screening. *Lancet*, 339(8790):412–4. doi:10.1016/0140-6736(92)90090-P PMID:1346670

Tamakoshi K, Yatsuya H, Wakai K, Suzuki S, Nishio K, Lin Y et al.; JACC Study Group (2005). Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. *Cancer Sci*, 96(1):57–62. doi:10.1111/j.1349-7006.2005.00010.x PMID:15649257

Taplin SH, Ichikawa L, Buist DS, Seger D, White E (2004). Evaluating organized breast cancer screening implementation: the prevention of late-stage disease? *Cancer Epidemiol Biomarkers Prev*, 13(2):225–34. doi:10.1158/1055-9965.EPI-03-0206 PMID:14973097

Taylor R, Davis P, Boyages J (2003). Long-term survival of women with breast cancer in New South Wales. *Eur J Cancer*, 39(2):215–22. doi:10.1016/S0959-8049(02)00486-0 PMID:12509954

Telle-Lamberton M (2008). Epidemiologic data on radiation-induced breast cancer [in French]. *Rev Epidemiol Sante Publique*, 56(4):235–43. doi:10.1016/j.respe.2008.05.024 PMID:18672338

Thierry-Chef I, Simon SL, Weinstock RM, Kwon D, Linet MS (2012). Reconstruction of absorbed doses to fibroglandular tissue of the breast of women undergoing mammography (1960 to the present). *Radiat Res*, 177(1):92–108. doi:10.1667/RR2241.1 PMID:21988547

Thornton H, Pillarisetti RR (2008). 'Breast awareness' and 'breast self-examination' are not the same. What do these terms mean? Why are they confused? What can we do? *Eur J Cancer*, 44(15):2118–21. doi:10.1016/j.ejca.2008.08.015 PMID:18805689

Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K (2008). Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med*, 148(5):337–47. doi:10.7326/0003-4819-148-5-200803040-00004 PMID:18316752

Tikk K, Sookthai D, Johnson T, Rinaldi S, Romieu I, Tjønneland A et al. (2014). Circulating prolactin and breast cancer risk among pre- and postmenopausal women in the EPIC cohort. *Ann Oncol*, 25(7):1422–8. doi:10.1093/annonc/mdu150 PMID:24718887

Tonelli M, Connor Gorber S, Joffres M, Dickinson J, Singh H, Lewin G et al.; Canadian Task Force on Preventive Health Care (2011). Recommendations on screening for breast cancer in average-risk women aged 40–74 years. *CMAJ*, 183(17):1991–2001. doi:10.1503/cmaj.110334 PMID:22106103

Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E et al. (2003). Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*, 290(4):465–75. doi:10.1001/jama.290.4.465 PMID:12876089

Trichopoulos D, Hsieh CC, MacMahon B, Lin TM, Lowe CR, Mirra AP et al. (1983). Age at any birth and breast cancer risk. *Int J Cancer*, 31(6):701–4. doi:10.1002/ijc.2910310604 PMID:6862681

Tryggvadóttir L, Gislum M, Bray F, Klint A, Hakulinen T, Storm HH et al. (2010). Trends in the survival of patients diagnosed with breast cancer in the Nordic countries 1964–2003 followed up to the end of 2006. *Acta Oncol*, 49(5):624–31. doi:10.3109/02841860903575323 PMID:20429724

Tubiana M, Koscielny S (1991). Natural history of human breast cancer: recent data and clinical implications. *Breast Cancer Res Treat*, 18(3):125–40. doi:10.1007/BF01990028 PMID:1756255

Tung N, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K et al. (2014). Frequency of mutations in individuals with breast cancer referred for *BRCA1* and *BRCA2* testing using next-generation sequencing with a 25-gene panel. *Cancer*, 121(1):25–33. doi:10.1002/cncr.29010 PMID:25186627

Tworoger SS, Eliassen AH, Zhang X, Qian J, Sluss PM, Rosner BA et al. (2013). A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. *Cancer Res*, 73(15):4810–9. doi:10.1158/0008-5472.CAN-13-0665 PMID:23783576

UICC (2010). TNM classification of breast cancer [in French]. UICC stage, 7th edition. Geneva, Switzerland: Union for International Cancer Control. Available from: http://www.canceraquitaine.org/sites/default/files/documents/INFOS-PRO/surveillance-sein/kit/base-documentaire/TNM.pdf.

UNDP (2012). Human development reports. United Nations Development Programme. Available from: http://hdr.undp.org/en/content/table-1-human-development-index-and-its-components.

Unger-Saldaña K (2014). Challenges to the early diagnosis and treatment of breast cancer in developing countries. *World J Clin Oncol*, 5(3):465–77. doi:10.5306/wjco.v5.i3.465 PMID:25114860

United Nations (2012). World population prospects (demographic data). Available from: http://www.un.org/esa/population/unpop.htm.

UNSCEAR (2010). Sources and effects of ionizing radiation, UNSCEAR 2008 Report, Volume I: Sources - Report to the General Assembly Scientific Annexes A and B. New York (NY), USA: United Nations Scientific Committee on the Effects of Atomic Radiation. Available from: http://www.unscear.org/unscear/en/publications/2008_1.html.

UNSCEAR (2013). Sources, effects and risks of ionizing radiation, UNSCEAR 2013 Report, Volume II: Scientific Annex B: Effects of radiation exposure of children. New York (NY), USA: United Nations Scientific Committee on the Effects of Atomic Radiation. Available from: www.unscear.org/docs/reports/2013/UNSCEAR2013Report_AnnexB_Children_13-87320_Ebook_web.pdf.

van der Groep P, van der Wall E, van Diest PJ (2011). Pathology of hereditary breast cancer. *Cell Oncol (Dordr)*, 34(2):71–88. doi:10.1007/s13402-011-0010-3 PMID:21336636

van Dongen JA, Fentiman IS, Harris JR, Holland R, Peterse JL, Salvadori B et al. (1989). In-situ breast cancer: the EORTC consensus meeting. *Lancet*, 2(8653):25–7. doi:10.1016/S0140-6736(89)90263-8 PMID:2567800

van Leeuwaarde RS, Vrede MA, Henar F, Does R, Issa P, Burke E et al. (2011). A nationwide analysis of incidence and outcome of breast cancer in the country of Surinam, during 1994–2003. *Breast Cancer Res Treat*, 128(3):873–81. doi:10.1007/s10549-011-1404-7 PMID:21340478

van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM et al. (2003). Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst*, 95(13):971–80. doi:10.1093/jnci/95.13.971 PMID:12837833

van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol AD, Vetter UA et al. (2000). Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol*, 18(3):487–97. PMID:10653864

Vargas AC, Reis-Filho JS, Lakhani SR (2011). Phenotype-genotype correlation in familial breast cancer. *J Mammary Gland Biol Neoplasia*, 16(1):27–40. doi:10.1007/s10911-011-9204-6 PMID:21400086

Venkitaraman AR (2002). Cancer susceptibility and the functions of *BRCA1* and *BRCA2*. *Cell*, 108(2):171–82. doi:10.1016/S0092-8674(02)00615-3 PMID:11832208

Vincent-Salomon A, Lucchesi C, Gruel N, Raynal V, Pierron G, Goudefroye R et al.; Breast cancer study group of the Institut Curie (2008). Integrated genomic and transcriptomic analysis of ductal carcinoma in situ of the breast. *Clin Cancer Res*, 14(7):1956–65. doi:10.1158/1078-0432.CCR-07-1465 PMID:18381933

von Karsa L (1995). Mammography screening – comprehensive, population-based quality assurance is required! [in German]. *Z Allgemeinmed*, 71:1863–7.

von Karsa L, Anttila A, Primic Žakelj M, de Wolf C, Bielska-Lasota M, Törnberg S et al. (2013). Stockholm statement on successful implementation of population-based cancer screening programmes. Annex 1a. In: Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, editors. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition, Supplements. Luxembourg: European Commission, Office for Official Publications of the European Union; pp. 123–8.

von Karsa L, Arrossi S (2013). Development and implementation of guidelines for quality assurance in breast cancer screening: the European experience. *Salud Publica Mex*, 55(3):318–28. PMID:23912545

von Karsa L, Dean PB, Arrossi S, Sankaranarayanan R (2014a). Screening – principles. In: Stewart BW, Wild CP, editors. World cancer report 2014. Lyon, France: International Agency for Research on Cancer; pp. 322–9.

von Karsa L, Qiao Y-L, Ramadas K, Keita N, Arrossi S, Dean PB et al. (2014b). Screening – implementation. In: Stewart BW, Wild CP, editors. World cancer report 2014. Lyon, France: International Agency for Research on Cancer; pp. 330–6.

Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J et al. (2006). Spectrum of mutations in *BRCA1*, *BRCA2*, *CHEK2*, and *TP53* in families at high risk of breast cancer. *JAMA*, 295(12):1379–88. doi:10.1001/jama.295.12.1379 PMID:16551709

Walters S, Maringe C, Butler J, Brierley JD, Rachet B, Coleman MP (2013b). Comparability of stage data in cancer registries in six countries: lessons from the International Cancer Benchmarking Partnership. *Int J Cancer*, 132(3):676–85. doi:10.1002/ijc.27651 PMID:22623157

Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J et al.; ICBP Module 1 Working Group (2013a). Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000–2007: a population-based study. *Br J Cancer*, 108(5):1195–208. doi:10.1038/bjc.2013.6 PMID:23449362

Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C et al. (1999). Prevalence and penetrance of *BRCA1* and *BRCA2* gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst*, 91(14):1241–7. doi:10.1093/jnci/91.14.1241 PMID:10413426

Warren GW, Alberg AJ, Kraft AS, Cummings KM (2014). The 2014 Surgeon General's report: "The health consequences of smoking – 50 years of progress": a paradigm shift in cancer care. *Cancer*, 120(13):1914–6. doi:10.1002/cncr.28695 PMID:24687615

Washbrook E (2006). Risk factors and epidemiology of breast cancer. *Women's Health Med*, 3(1):8–14. doi:10.1383/wohm.2006.3.1.8

WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: World Cancer Research Fund and American Institute for Cancer Research.

WCRF/AICR (2009). Ministério da Saúde, Instituto Nacional de Câncer, Políticas e ações para prevenção do câncer no Brasil: alimentação, nutrição e atividade física. Rio de Janeiro, Brazil: World Cancer Research Fund and American Institute for Cancer Research.

WCRF/AICR (2010). Continuous Update Project Report. Food, nutrition, physical activity, and the prevention of breast cancer. World Cancer Research Fund and American Institute for Cancer Research. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/Breast-Cancer-2010-Report.pdf.

Webster P, Austoker J (2006). Women's knowledge about breast cancer risk and their views of the purpose and implications of breast screening–a questionnaire survey. *J Public Health (Oxf)*, 28(3):197–202. doi:10.1093/pubmed/fdl030 PMID:16902075

Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG (2008). *CHEK2**1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. *J Clin Oncol*, 26(4):542–8. doi:10.1200/JCO.2007.12.5922 PMID:18172190

Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ et al. (2012). *CHEK2**1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J Clin Oncol*, 30(35):4308–16. doi:10.1200/JCO.2012.42.7336 PMID:23109706

Welch HG, Black WC (1997). Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? *Ann Intern Med*, 127(11):1023–8. doi:10.7326/0003-4819-127-11-199712010-00014 PMID:9412284

WHO (2007). Cancer control: Knowledge into action. WHO guide for effective programmes. Module 3: Early detection. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/cancer/publications/cancer_control_detection/en/index.html.

WHO (2013a). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

WHO (2013b). Implementation tools: Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/133525/1/9789241506557_eng.pdf?ua=1&ua=1.

WHO (2014). World Health Organization Cancer Mortality Database. Available from: http://www-dep.iarc.fr/WHOdb/WHOdb.htm.

Wilson JMG, Jungner G (1968). Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization. Public Health Papers No. 34. Available from: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf.

Wohlfahrt J, Melbye M (2001). Age at any birth is associated with breast cancer risk. *Epidemiology*, 12(1):68–73. doi:10.1097/00001648-200101000-00012 PMID:11138822

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH et al.; American Society of Clinical Oncology; College of American Pathologists (2013). Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*, 31(31):3997–4013. doi:10.1200/JCO.2013.50.9984 PMID:24101045

Wu Y, Zhang D, Kang S (2013). Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat*, 137(3):869–82. doi:10.1007/s10549-012-2396-7 PMID:23274845

Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA (2010). Ki67 in breast cancer: prognostic and predictive potential. *Lancet Oncol*, 11(2):174–83. doi:10.1016/S1470-2045(09)70262-1 PMID:20152769

Yip CH, Smith RA, Anderson BO, Miller AB, Thomas DB Ang ES et al.; Breast Health Global Initiative Early Detection Panel (2008). Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer*, 113(8 Suppl):2244–56. doi:10.1002/cncr.23842 PMID:18837017

Yoshida K, Miki Y (2004). Role of *BRCA1* and *BRCA2* as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer Sci*, 95(11):866–71. doi:10.1111/j.1349-7006.2004.tb02195.x PMID:15546503

Zahl PH, Maehlen J, Welch HG (2008). The natural history of invasive breast cancers detected by screening mammography. *Arch Intern Med*, 168(21):2311–6. doi:10.1001/archinte.168.21.2311 PMID:19029493