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CANCER CENTRE

Breast cancer risk factors

a review of the evidence

July 2009

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Funded by the Australian Government Department of Health and Ageing

Breast cancer risk factors: a review of the evidence
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ISBN Online: 978-1-74127-141-6

Copies of this booklet can be downloaded or ordered from National Breast and Ovarian Cancer Centre's website: www.nbocc.org.au.

Recommended citation

National Breast and Ovarian Cancer Centre. Breast cancer risk factors: a review of the evidence. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2009.

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National Breast and Ovarian Cancer Centre is funded by the Australian Government Department of Health and Ageing.

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Acknowledgments

This report was prepared on behalf of National Breast and Ovarian Cancer Centre (NBOCC) by Dr Gianluca Severi and Dr Laura Baglietto. It is an update of the *Summary of Risk Factors for Breast Cancer* report prepared in 2005 by Professor Beth Newman, Ms Tracey Round and Dr Beverly Rockhill on behalf of National Breast Cancer Centre*.

NBOCC gratefully acknowledges the contribution of Professor Graham Giles and Professor David Roder who provided expert comment on the report.

Funding

Funding for the development of this report was provided by the Australian Government Department of Health and Ageing.

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* *In February 2008, National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC).*

Executive summary

Breast cancer is the most common cancer in women in Australia (excluding basal and squamous cell carcinomas of the skin). Despite more than 100 years of epidemiological research (mostly over the past 50 years), and the identification of numerous factors that influence risk of breast cancer, we have so far been unable to reduce its occurrence. Although we continue to seek effective ways to prevent breast cancer, there have been improvements in treatment and early detection, which together have decreased mortality from this disease.

Research into the causes of breast cancer has progressed to the point that we can describe with some certainty the profile of women at high risk of the disease. We are also gaining understanding of the underlying biology, including hormonal influences and molecular changes that contribute to its development. These various lines of scientific inquiry are converging, and suggest that breast cancer occurs as a consequence of combinations of individual factors and events, such as inherited genetic susceptibility, exposure to carcinogens, levels of various hormones within the body, function of the body's immune system and changes in the molecular structure of DNA in breast cells that might occur just by chance. Most of the recognised breast cancer risk factors relate to one or more of these individual factors and events.

The incidence of breast cancer has also increased worldwide. Because the incidence of breast cancer for migrants and their offspring approaches that of their adopted homeland rather than remaining that of their country of origin, we know that environmental and lifestyle factors must contribute to breast cancer risk. However, most of the personal, environmental and lifestyle exposures and events associated with breast cancer risk are not necessarily established "causes" of disease; rather, they serve as markers of risk or surrogates for causes of disease that help differentiate between women at different levels of risk. We therefore call them "risk factors".

Absolute risk (in this summary referred to as "risk") is a person's chance of developing a specific disease over a specified period. A person's risk of disease is estimated by examining a large number of people who are similar in some respect (eg in terms of age or gender), and counting the number of people in this group who develop the disease within a defined period.

Relative risk is the ratio of two absolute risks. It is calculated by dividing the absolute risk for those who have the factor by the absolute risk for those without the factor. Thus, the following statements all say the same thing: "the relative risk is 1.25", "there is a 25% increase in risk" and "risk is increased by 1.25 times".

Table 1 provides a brief overview of the key risk factors for breast cancer for women. Relative risks (RRs), which provide estimates of the risk of breast cancer for those exposed compared with those not exposed, we categorise here as modest (RR 1.25–1.99), moderate (RR 2.00–3.99), strong (RR 4+), or potentially protective (RR <0.8). To avoid over-interpretation of weak effects, we have placed emphasis on those factors that either increase relative risk by at least 25% or decrease relative risk by at least 20%.

Factors known to be associated with a moderately to strongly increased risk of breast cancer

A number of factors are associated with an increased risk of breast cancer; that is, they are more common for women with breast cancer than for those without the disease. These factors are not necessarily "causes" of breast cancer. Some are markers for other as yet unknown or suspected factors that influence risk.

Sex

Being a woman is the strongest risk factor for breast cancer. Women are 100 times more likely to develop breast cancer than men. Not all women get breast cancer, nor do all men avoid breast cancer. Sex is therefore a marker for events and exposures that happen more often or more strongly to women than to men.

Age

Increasing age is one of the strongest risk factors for breast cancer. Although breast cancer can occur early in life, in general it is a disease of ageing. For a woman in her 30s the risk is approximately 1 in 250, whereas for a woman in her 70s, it is approximately 1 in 30. Most breast cancers are diagnosed after the menopause; about 75% of breast cancer cases occur after 50 years of age. Age is considered to be a likely surrogate for DNA damage accumulated during life.

Affluence

Breast cancer occurs more frequently in affluent and western populations, such as that of Australia, and in subpopulations of higher socioeconomic status within countries. This suggests that lifestyle factors related to westernisation and affluence are associated with increased risk of breast cancer.

Family history

Family history is an important and well-established breast cancer risk factor. Women with a mother, sister or daughter with breast cancer are, on average, at twice the risk of those with no affected first-degree relative (ie RR 2). The risk increases with the number of first-degree relatives affected and, when three or more first-degree relatives are affected, the risk becomes more than three times that for women with no affected first-degree relatives (ie RR >3). The risk associated with family history increases also when relatives with breast cancer are diagnosed at a young age and when the family is of Jewish descent. The association between family history and breast cancer might indicate that women share environmental or lifestyle factors, or that they share genetic factors that increase the risk of breast cancer. There are some rare deleterious mutations in genes such as BRCA1 and BRCA2 that are associated with a high risk of the disease. A family history of ovarian cancer increases the risk of breast cancer because the risk of ovarian cancer is also associated with these genes. In addition, common variants in other genes are each associated with only a small increase in risk.

Breast conditions

Women diagnosed with invasive breast cancer are at two to six times the population risk of developing cancer in the contralateral breast (other breast). There are also a number of pre-invasive breast conditions that are associated with an increased risk of breast cancer. These include lobular carcinoma in situ, ductal carcinoma in situ and atypical ductal hyperplasia. Mammographic breast density is emerging as a strong risk factor for breast cancer. Women having the highest degree of breast density are at four to six times greater risk than women with little or no breast density.

Endogenous oestrogens

Postmenopausal women with high levels of circulating oestrogens (women with levels in the top 20%) have a two-fold increased risk of breast cancer compared with women with low levels of circulating oestrogens (women with levels in the bottom 20%).

Other factors known to be associated with a modestly increased or decreased risk of breast cancer

Hormonal factors

Factors such as reproductive history, menstrual history, menopausal status and exogenous hormone use are associated with breast cancer risk, although these have a more modest influence on risk than the factors discussed above. This suggests that hormones, both exogenous (taken in some form) and endogenous (produced by one's body), are involved in determining breast cancer risk.

Factors associated with a modestly increased risk (RR 1.25–1.99) include:

- older age at menopause (over 55 years vs 55 years or less)
- use of combined hormone replacement therapy (current users vs never)
- use of oral contraceptive pill (vs never, risk decreases to normal 10 years after ceasing use)
- younger age at menarche (commencement of menstruation younger than 12 years vs 12 years or more)
- high circulating levels of androgens (women with levels in the top 20% vs women with levels in the bottom 20% for postmenopausal women and possibly for premenopausal women)
- high circulating levels of insulin-like growth factors (IGF-1 and IGFBP-3, women with levels in the top 25% vs women with levels in the bottom 25%, possibly only for postmenopausal women)
- use of diethylstilbestrol during pregnancy
- exposure to diethylstilbestrol in utero

Factors associated with a decreased risk (RR <0.8) include:

- parity (giving birth to at least one child vs never having carried a pregnancy; ie nulliparity)
- earlier age at first birth (<25 years vs >29 years)
- breastfeeding (at least 12 months' total duration vs no breastfeeding)
- number of births (≥4 vs 1).

Personal and lifestyle factors

A number of personal and lifestyle factors are associated with risk of breast cancer, some of which are modifiable.

Factors associated with a modestly increased risk (RR 1.25–1.99) include:

- taller height (≥175 cm vs <160 cm)
- overweight and obesity for postmenopausal women (body mass index >25 kg/m^2 vs <21 kg/m^2)
- alcohol consumption (three or more standard drinks per day compared with none)
- a previous personal history of some types of cancer other than breast cancer including melanoma, colorectal, ovarian, endometrial and thyroid cancer
- high-dose ionising irradiation, especially before age 20.

Factors associated with a decreased risk (RR <0.8) include:

- physical activity (two or more hours of brisk walking or equivalent per week vs no activity).

Factors that have not been shown to impact on risk for breast cancer

For a number of factors, there is no evidence to support an association with risk. This might be due to there being no risk, to poor quality studies, or to conflicting study findings. These factors include:

- pregnancy termination or abortion
- tobacco smoking (study findings are inconsistent)
- exposure to environmental tobacco smoke (study findings are inconsistent)
- environmental pollutants
- wearing a bra or different types of bra
- silicone implants
- use of underarm deodorant or antiperspirant
- stress.

Table 1 Summary of risk factors for invasive breast cancer

	RR >4 +++	RR 2–3.99 ++	RR 1.25–1.99 +	RR <0.8 –
Sex, age and residence	Female, increasing age (50+ years vs <50 years) Affluent country of residence (NAm/Aus/ NZ/Eur vs Africa/Asia)			
Family history and genetics	BRCA1, BRCA2, ATM or TP53 gene (p53) mutation carrier	Two or more first-degree relatives with breast cancer CHEK2 mutation carriers	One first-degree relative or multiple second-degree relatives with breast cancer	
Breast conditions	DCIS in same breast LCIS High breast density	Atypical ductal hyperplasia	DCIS in opposite breast Proliferate BBD without atypia	
Reproductive and menstrual history			Age at first period younger than 12 years (vs >12 years) Age at menopause older than 55 years (vs < 55 years)	Parity (vs nulliparity) Four births or more (compared with one) Age at first birth younger than 25 years (vs older than 29 years) Breastfeeding at least 12 months total duration (vs no breastfeeding)
Endogenous and exogenous hormones		High circulating levels of oestrogen (top 20% vs bottom 20%, in postmenopausal women only)	Use of oral contraceptives within past 10 years (vs never) Use of combined hormone replacement therapy (current users vs never) High circulating levels of androgens (top 20% of levels vs bottom 20%) high circulating levels of IGF-1 and IGFBP-3 (top 25% of levels vs bottom 25%, possibly only for postmenopausal women)	Use of tamoxifen for more than 5 years Use of raloxifene
Body size and lifestyle behaviours			Height >175 cm (vs < 160 cm) BMI >25 kg/m^2 (vs <21 kg/m^2), for postmenopausal breast cancer Daily intake of three or more standard alcoholic drinks (vs none)	Obesity for premenopausal breast cancer (BMI ≥31 kg/m^2 vs BMI <21 kg/m^2) Physical activity - two or more hours of brisk walking or equivalent per week (vs no activity)
Medical history	Radiation treatment for Hodgkin's disease before age 30 years History of breast cancer in opposite breast		History of cancer in other organs (including ovary, thyroid, endometrium, colon, melanoma) Treatment with high-dose ionising radiation, especially before age 20 In utero exposure to diethylstilbestrol	
Environmental exposures			High-dose ionising radiation, especially before age 20	

1 Background

The purpose of this summary is to give an overview of publicly available information from epidemiological studies about factors associated with risk of breast cancer. By presenting simple information with some indication of the sources of that information, we intend this document to be useful for health professionals, cancer organisations and others who prepare resources for the public. The document is not designed to be a comprehensive scientific account of biological mechanisms of risk factors, but rather an overview of the state of current epidemiological knowledge. In our overview we did not consider studies with limited sample size or inadequate study design. The best evidence for associations with breast cancer is provided by randomised studies, pooled analyses of prospective cohort studies, large prospective cohort studies and meta-analyses. We have considered the evidence for an association between a particular factor and breast cancer risk to be strong only when observed in these types of studies.

Breast cancer is the most common cause of death from cancer for Australian women. Despite more than 100 years of epidemiological research (mostly during the past 50 years) and the successful identification of numerous factors that influence risk of breast cancer, we have so far been unable to reduce the incidence of the disease. Although we continue to seek effective ways to prevent breast cancer, there have been significant improvements in treatment and early detection, which together have decreased mortality from this disease.

Below we expand on what is known about the various factors that influence the occurrence of breast cancer and the implications for breast cancer prevention. However, we first present some useful background information to help readers to understand the terminology we use and some of the limits to our understanding.

1.1 Absolute risk

Absolute risk (referred to here as “risk”) is a person’s chance of developing a specific disease over a specified period. A person’s risk of disease is estimated by examining a large number of people similar in some respect (eg in terms of age or gender) and counting the number of individuals in this group who develop the disease within a defined period, usually one year. For instance, if we were to observe 100,000 Australian women between the ages of 20 and 29 for one year, approximately four would develop breast cancer during this period. The annual risk of breast cancer for a 20 to 29-year-old woman is thus 4 per 100,000 women, or 1 per 25,000 women. If we observed 100,000 Australian women aged 70–74 for one year, approximately 330 of them would develop breast cancer. The annual risk of breast cancer for this age group is thus 330 per 100,000, or 1 per 300 women.

Lifetime risk is very different from the one-year risk of breast cancer. It is a measure of the risk of contracting breast cancer by the age of 85 years, and is estimated by cumulating all the annual risks over a woman’s life span up to age 85. The lifetime risk of breast cancer for an Australian woman is now approximately 1 in 9, if she lives to be 85 years old. This means that for every 9 women who live to age 85, one of them will have been diagnosed with breast cancer during her lifetime. This assumes, of course, that the annual age-specific risks will remain constant. The use of 75 years to estimate lifetime risk was adopted as a standard to enable international comparisons of populations having quite different life expectancies. However, because of increasing life expectancies, we now calculate lifetime risks to older ages (eg 80 and 85 years).

This does not take into account that the life expectancy increase is estimated for a person born in the current year and that, for much of the older population, the life expectancy is lower than this estimate.

1.2 Relative risk

Often, when new research findings on breast cancer are reported by the media, information is provided in terms of the increase in risk due to a particular factor rather than the absolute risk. For example, a report might state that women with a particular risk factor have a 25% increased risk of breast cancer compared with women who do not have the risk factor. This notion of increase in risk is based on the concept of relative risk (RR). A relative risk is the ratio of two absolute risks: the numerator is the absolute risk for those with the factor, while the denominator is the absolute risk for those without the factor. The following statements are thus equivalent: "there is a 25% increase in risk", "the relative risk is 1.25" and "risk is increased by 1.25 times". When a relative risk associated with a risk factor is two or more, this is often communicated by stating how many times the risk for a woman with the factor is increased compared with a woman without the factor. For example, a factor with a relative risk of three means that those with the factor have three times the risk of those without it, although it is often referred to as causing "a three-fold increase in risk" or that "risk is increased three times."

The importance of a relative risk associated with a risk factor can be measured in terms of the number of cases in the population that could be explained by that factor, or the excess number of cases attributable to the factor. This number increases with the proportion of persons in the population exposed to the factor and with the incidence rate of the disease in the population (ie absolute risk). The probability of being diagnosed with breast cancer increases sharply with age. Before the age of 40, it is approximately 500 per 100,000 women, and after the age of 40 it is 10,000 per 100,000 women. A strong risk factor (ie high relative risk) might only be responsible for a few extra cases of disease when the disease probability is rare, such as it is for young women. By contrast, when a disease is more common, as breast cancer is for older women, even weak risk factors (ie small relative risks) can be responsible for many cases of disease. A strong risk factor for breast cancer associated, for example, with a relative risk of 5 and with a proportion of women exposed of 1 in 100 would explain 4% of the cases occurring in the population; that is, only 20 of the 500 cases occurring before age 40, but 400 of the 10,000 cases occurring after age 40. A factor associated with a relative risk of 2 and affecting one in 10 women would explain 9% of the cases in the population, that is 45 of the 500 cases occurring before age 40 and 900 of the 10,000 cases occurring after age 40.

When relative risks are reported in scientific journals, they are nearly always accompanied by confidence intervals. For example, a researcher might report a relative risk of 2.1 for the association between postmenopausal obesity and breast cancer, with a 95% confidence interval (95% CI) of 1.5 to 2.9. A confidence interval has a technical and somewhat abstract definition in statistics. But with little disservice to its actual definition, one can think of a confidence interval as reflecting the degree of uncertainty as to whether the relative risk observed in the study (ie here 2.1) is a good and accurate estimate of the *true* relative risk. The construction of the confidence interval around a particular study's estimate reflects the reality that the researchers can never be positive that their study has produced the exact, correct relative risk; the confidence interval gives information on the *range* of estimates (in this case, from 1.5 to 2.9) in which the true relative risk probably lies; the wider the confidence interval, the higher the degree of uncertainty.

1.3 Risk factors

A “risk factor” can be anything from a lifestyle choice (eg diet) to a personal characteristic (eg menarche [age when menstruation started]) to an environmental exposure (eg radiation) that can influence a person’s risk of developing a certain disease. Sometimes, people who have a risk factor are referred to as “exposed,” even when the risk factor isn’t an “exposure” in the typical sense. For example, researchers refer to people as “exposed” to alcohol drinking, to an early menarche, to obesity or to chemicals in the environment. The concept of exposure is important to determining whether observed associations might be causal. A dose-response relationship — where the risk increases with increasing levels of the exposure — is an important aspect of the strength of an association.

Although we tend to think of risk factors as only being associated with increased risk, the absence of a risk factor can often be associated with a decreased risk, and high levels of certain risk factors can also be associated with decreased risk. Risk factors that are associated with a decreased risk of disease are sometimes called “protective factors”. For example, women who have breastfed for some time have a lower risk of breast cancer than women who have not. Thus, breastfeeding is a protective factor against breast cancer. A major goal in epidemiology is to identify risk or protective factors that can be modified. Although modification of environmental exposures or individual behaviours can be difficult to achieve, there are many examples of successful public health campaigns where such changes have reduced the occurrence of disease. For example, improvements in diet have made diseases such as rickets and scurvy almost unheard of and improved sanitation engineering has greatly reduced diarrheal diseases. When risk factors are not easily modified, cancer-control activities designed to prevent disease are much more difficult. This has mostly been the case for breast cancer, as we show in this report.

1.4 Study types for identifying risk factors

Epidemiologists use research designs other than descriptive studies to identify factors that are common to the personal histories of those with cancer. They also seek to understand their findings in relation to current biological knowledge. Case–control and cohort studies, both of which rely on observation of people, are the main types of epidemiological studies that have identified risk factors for breast cancer; experimental studies referred to as “trials” are sometimes used to confirm these associations.

Case–control studies examine two groups of people — for example, those diagnosed with breast cancer (cases) and those free of the disease (controls) — and ask them, usually by questionnaire, about key factors that have been suspected, through descriptive studies or biological research, of an association with breast cancer. Case–control studies are called retrospective because they ask questions about events that happened in the past, before the diagnosis of breast cancer, such as reproductive history or diet. For example, age at first full-term pregnancy was first established as a risk factor for breast cancer in 1970, following a large, international case–control study of women with breast cancer and controls free from breast cancer. Case–control studies are one of the most basic study designs for this kind of research. As a consequence of their design, case–control studies produce a statistic known as an “odds ratio” (OR) to estimate relative risk. A major limitation of case–control studies is their proneness to various forms of bias (mostly related to their retrospective design), which can lead to spurious findings.

Cohort studies, in comparison, assemble a large group of unaffected people for whom the disease of interest (eg breast cancer) could be expected to occur as time passes; gather both past and current information on "exposures" or the factors of interest; follow the subjects forward in time, continuing to measure exposures of interest; and identify the women who develop the disease of interest. Because these studies measure the exposures before the diagnosis of disease they are termed prospective. The US Nurses' Health Study (NHS) is a major cohort study that has investigated many potential risk and protective factors for breast cancer. Cohort studies permit direct calculation of the relative risk to estimate the risk of breast cancer for those exposed to the factor of interest, compared with those not exposed. Cohort studies are considered superior to case–control studies for research about risk factors because they are less prone to bias; however, because of their expense and long duration, they are not always feasible.

Randomised trials involve groups of people who are randomly allocated to the exposures of interest. For ethical reasons, they are not feasible for examining hazardous factors, but they can be used to evaluate protective factors or the removal of potential risk factors. For example, they are used extensively for the evaluation of pharmaceutical agents, such as tamoxifen and new chemopreventive treatments. The US Women's Health Initiative Dietary Modification Trial is a groundbreaking trial that includes breast cancer as one of three leading health issues for women. It is designed to show whether a sustained (nine-year) low fat, high-fruit and high-vegetable eating pattern will lower the incidence of breast cancer for women who will be aged between 59 and 88 when the trial ends. Randomised trials are considered the most rigorous study design, but usually do not take place until the later stages of the research process, after evidence has already accrued from case–control and cohort studies. Relative risks can be calculated directly from randomised, controlled trials.

Meta-analyses and pooled analyses summarise findings across a variety of studies. The findings of a particular study depend on the quality of its design and conduct. Because research about human populations can be challenging, we rarely accept as definitive a risk factor that has been reported by only one or two studies. Rather, the scientific community demands replication of risk estimates across studies, and is most satisfied when these are consistent across various study designs or, at least, are supported consistently by research using the most rigorous designs. To get a picture of the burden of evidence for a particular risk factor, researchers now conduct systematic reviews to identify relevant research and then attempt to quantitatively summarise the findings across all studies. This requires standardisation across studies conducted at different times by different researchers in different locations. The risk estimates are then aggregated in one of two ways: meta-analyses retain the separate studies and combine the risk estimates using statistical models, while pooled analyses actually combine the individual data from each study and conduct new statistical analyses on the much larger, combined data set. During the past five years, a number of meta-analyses and pooled analyses have been published for risk factors in relation to breast cancer. Chief among these are a series of papers published by the Collaborative Group on Hormonal Factors in Breast Cancer, which has pooled data from over 50 different studies of breast cancer.

1.5 Breast cancer heterogeneity

Breast cancer is a condition in which normal cellular regulation ceases to function, and cells in the breast are allowed to multiply unchecked and to invade adjacent tissues. For this reason, it is called invasive breast cancer. Eventually, these cells gain the ability to leave their original location (ie the breast) and spread to other parts of the body (eg the lungs, liver, bones and

brain), where they continue to grow and disrupt normal function. This latter development is known as metastasis and is essentially the reason that breast cancer causes death.

There is more than one kind of invasive breast cancer. Most cancer in the breast arises from cells that make up the internal structures of the breast involved in secreting milk. These structures are known as ducts (tubes that drain the milk from the lobules to the nipple) and lobules (where milk is produced). About 75–80% of invasive breast cancers involves the ducts and is known as infiltrating ductal carcinoma. Another 5–10% involves the lobules and is known as infiltrating lobular carcinoma. There are a variety of other cancer types arising from other structures in the breast, but each of these is relatively rare.

Breast cancers might also present with different characteristics (eg the expression of specific biological markers that make them different from one another), even when they originate from the same cell type. For example, some infiltrating ductal carcinomas have hormone receptors — proteins on the surface of a cell that allow specific hormones to bind to the cell. The hormone can then influence the way in which the cell functions. Some of these carcinomas have oestrogen receptors (ER) and progesterone receptors (PR), and these are known as ER or PR-positive tumours. Such tumours are amenable to treatment with hormonal (or anti-oestrogen) therapies, and often have a better outcome than infiltrating ductal carcinomas that lack these hormone receptors (ie ER or PR-negative tumours).

The use of new technologies to detect patterns of gene expression has recently led to a new classification of breast carcinomas The four groups in this new classification appear to be associated with prognosis and response to treatment.[1]

1.5.1 Luminal A and Luminal B breast cancer

Luminal A and Luminal B breast cancers are characterised by high expression of ER and patterns of gene expression similar to normal cells lining the breast ducts and glands (the lining of a duct or gland is called the lumen). The important therapeutic target HER2 is expressed by Luminal B but not by Luminal A cancers.[2] Luminal breast cancers are generally low grade and tend to grow slowly. Luminal A cancers are associated with a better prognosis than Luminal B cancers.

1.5.2 HER2 breast cancer

HER2 breast cancers are characterised by over-expression of HER2, and are generally high-grade tumours. They tend to grow rapidly and are associated with a relatively poor prognosis, although they often respond to treatment with trastuzumab (Herceptin). HER2 breast cancers are often classified further according to their expression or lack of expression of ER.

1.5.3 Basal-like breast cancer

Basal-like breast cancers are characterised by lack of ER or PR expression, and a pattern of expression of genes characteristic of breast basal epithelial cells such as cytokeratin 5/6 (CK5/6). These are generally high-grade tumours that grow rapidly and are associated with a poor prognosis.

When we study risk factors for breast cancer, we usually fail to take into account that there are many different kinds of breast cancer, and we combine all women with breast cancer into one group. By doing this we assume that all breast cancers occur for basically the same reasons and

proceed to analyse the data to identify those factors that contribute to or increase the risk of all breast cancer.

But what if different factors give rise to one form of breast cancer but not another; or what if there are multiple ways in which the same kind of breast cancer can develop? Studies of all breast cancers taken together would only be able to identify risk factors for the more common types of breast cancer that affect the largest numbers of women and, even then, only the strongest risk factors would be uncovered. Many risk factors that might be associated strongly with only one type of breast cancer would be impossible to detect. This underlying heterogeneity of breast cancer types might explain why findings have varied from study to study and, until this issue is addressed, it will continue to be difficult to identify risk factors and determine just how they might interact to cause breast cancer.

1.6 Current status

We still know little about the causes of breast cancer and thus we cannot tell anyone exactly how to prevent this disease or how it developed. Nevertheless, we have gained some important clues and insights. During recent years, it has become increasingly clear that at least some factors that influence development of breast cancer might differ for younger, premenopausal women and older, postmenopausal women. This recognition has helped advance our understanding of some apparent paradoxes and has shaped how we think breast cancer might arise. The discovery of distinct breast cancer subtypes might be important not only for treatment but also to understand why breast cancer develops and to identify targets for prevention. Epidemiologists are now investigating whether potential risk factors are associated with particular breast cancer subtypes.

The sections that follow attempt to summarise our current understanding, as of early 2008, of the causes of breast cancer and the factors that influence risk of this disease. We conducted a systematic Pubmed search for articles on breast cancer risk factors. We focused in particular on meta-analyses and pooled analyses, which are considered the best sources of estimates for the strength of associations with breast cancer risk. When these were not available, other review articles and recent publications were used. A list of references is provided at the end of this summary.

2 Sex, age and residence

More than 12,000 Australian women were diagnosed with breast cancer in 2004. At the same time, around 2660 women died of breast cancer, and the disease accounted for almost 29,000 person years of life lost before age 75.[3] Breast cancer incidence rates have been increasing during the past two decades, whereas mortality rates have been decreasing in the most recent decade (Figure 1). About half of breast cancers affect women in their 50s or 60s (Figure 2). Since the introduction of the national mammographic screening program, incidence rates have increased most steeply for women aged 50–69, the target age group of mammographic screening. It is highly likely that the increased incidence of breast cancer in Australia since 1992–1993 is largely due to increased detection through the widespread use of mammographic screening.

Figure 1 Annual female breast cancer incidence and mortality in Australia

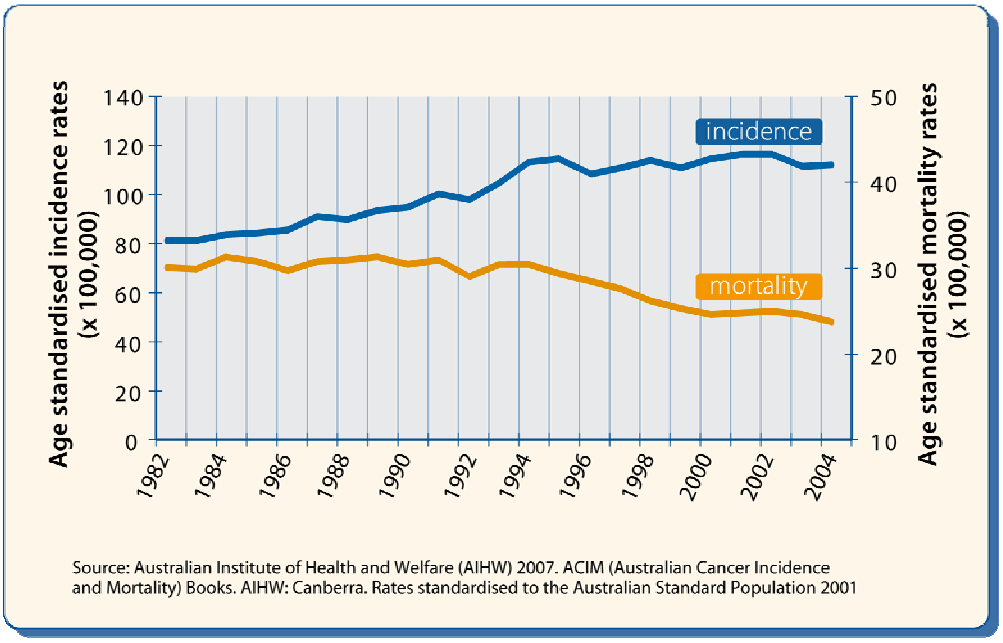
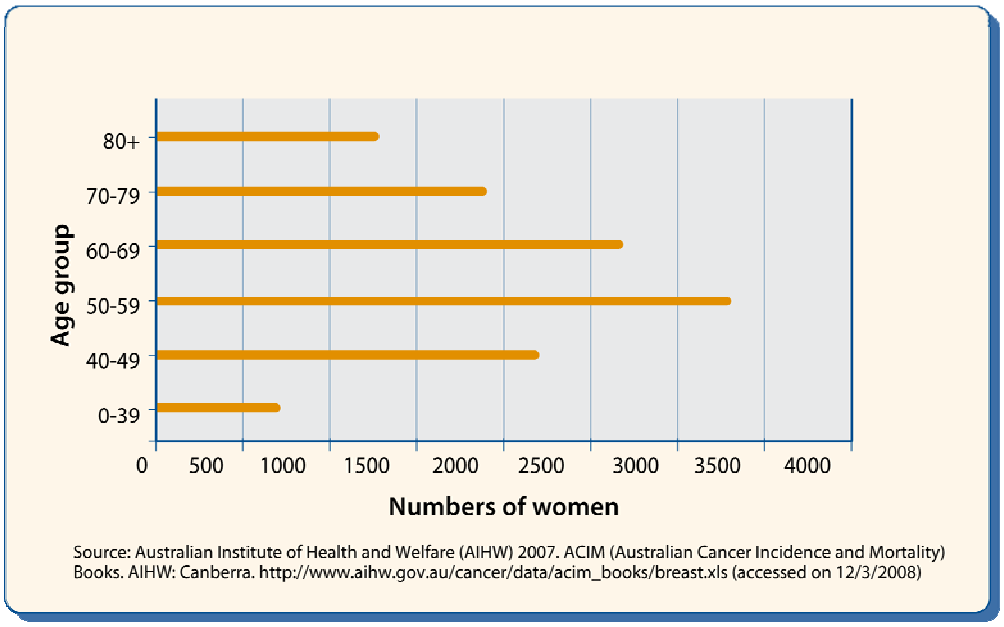


Figure 2 Numbers of women diagnosed with breast cancer in Australia in 2004



Source: Australian Institute of Health and Welfare (AIHW) 2007. ACIM (Australian Cancer Incidence and Mortality) Books. AIHW: Canberra. http://www.aihw.gov.au/cancer/data/acim_books/breast.xls (accessed on 12/3/2008)

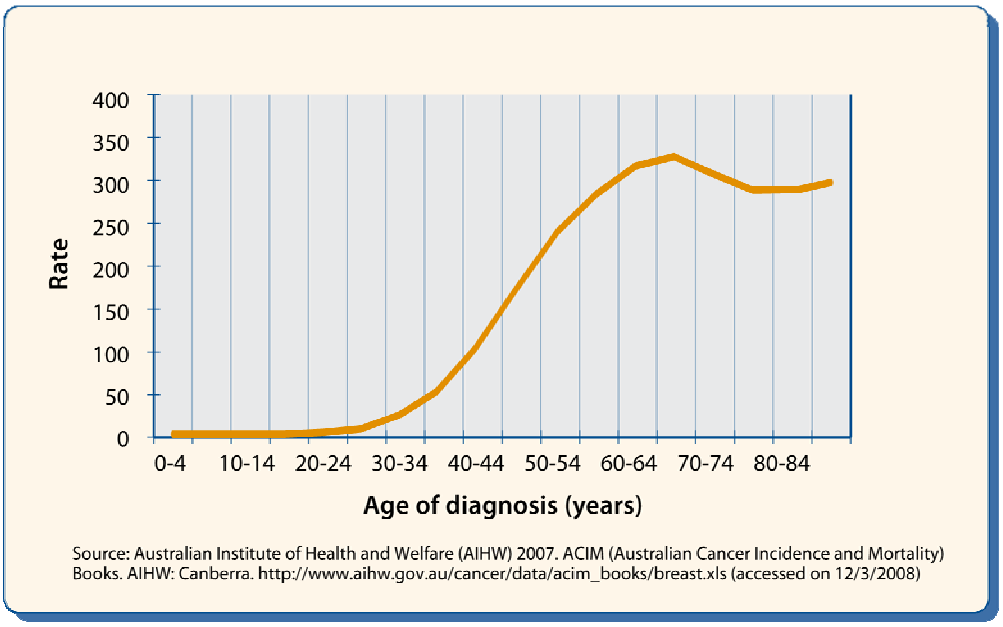
2.1 Sex

Breast cancer affects both men and women; however, the incidence is much higher for women. Overall, women are at 100-fold higher risk of breast cancer than men.[4] In 2004, in Australia, the age-standardised incidence rate of breast cancer was 113 per 100,000 for women and 1 per 100,000 for men.[3] Female sex, therefore, can be considered a major risk factor for breast cancer. Although there are many potential differences between men and women, this is one of the strongest and earliest clues that ovarian and other female hormones play an important role in the development of breast cancer. The remainder of this summary pertains solely to female breast cancer.

2.2 Age

Breast cancer incidence increases with age. It is rare before the age of 25, then incidence rises, increasing steeply with age 30–49. After age 50, breast cancer incidence continues to increase, although more slowly, to the oldest ages. For example, in Australia during 2004, breast cancer incidence rates were 5 per 100,000 women aged 20–29, increasing to 42 per 100,000 women in their 30s, 149 per 100,000 women in their 40s, 265 per 100,000 women in their 50s, 327 per 100,000 women in their 60s and 301 per 100,000 women aged 70 or older (see Figure 3) The reduction around menopause in the rate at which breast cancer incidence increases again suggests that ovarian and other female hormones are involved in the development of breast cancer. In contrast, the incidence of other adult cancers that are not hormone-dependent rises continuously with age, and does not show the same dampening of increase in mid life.

Figure 3 Age-specific incidence rates of breast cancer in Australian women in 2004



Source: Australian Institute of Health and Welfare (AIHW) 2007. ACIM (Australian Cancer Incidence and Mortality) Books. AIHW: Canberra. http://www.aihw.gov.au/cancer/data/acim_books/breast.xls (accessed on 12/3/2008)

In addition to showing increasing risk by age, Table 2 also shows that the incidence of breast cancer increased in Australia across the three time periods for which information is available: 1987–1991 and 1992–1996 and 2003–2004.[3] This increase was most evident for women aged 40 and older, resulting in an overall increase in the risk of breast cancer to age 74 years from 1 in 14 women during the period 1987–1991, to 1 in 11 women during the period 2003–2004.

Table 2 Risk for a woman of age=Startage of being diagnosed with breast cancer up to age=Endage by calendar years

		Years		
Startage	Endage	1987–1991	1992–1996	2003–2004
0	29	1 in 2399	1 in 2247	1 in 2307
30	39	1 in 241	1 in 241	1 in 232
40	49	1 in 73	1 in 66	1 in 67
50	59	1 in 54	1 in 41	1 in 38
60	69	1 in 42	1 in 35	1 in 31
70	79	1 in 37	1 in 33	1 in 34
0	74	1 in 14	1 in 12	1 in 11

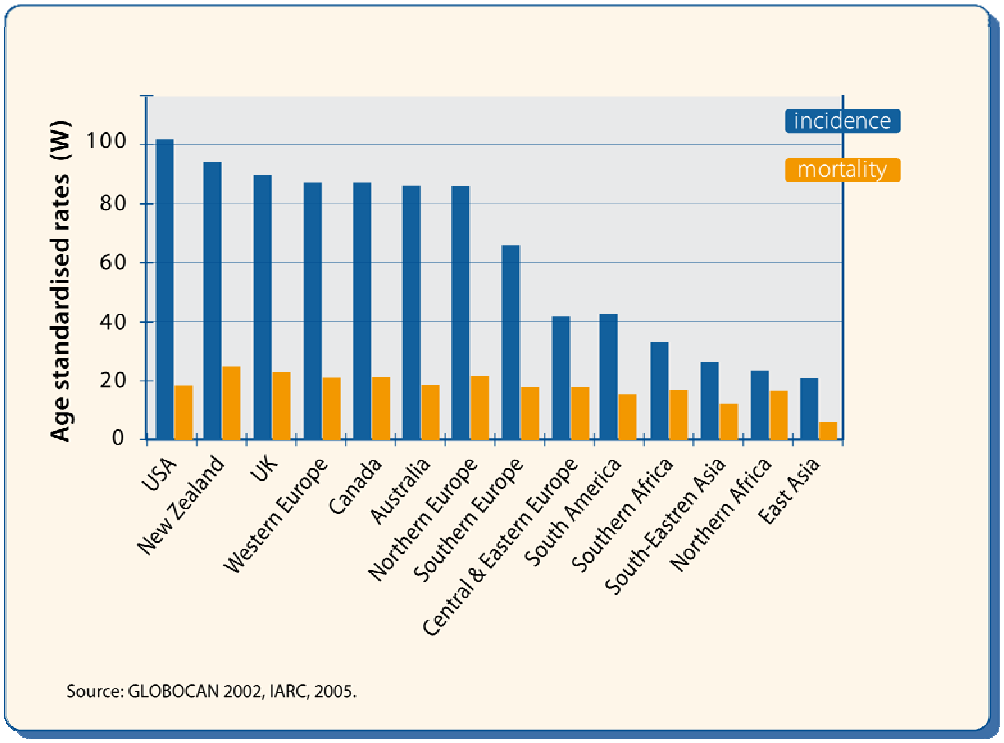
Source: Australian Institute of Health and Welfare (AIHW) 2007. ACIM (Australian Cancer Incidence and Mortality) Books. AIHW: Canberra. Rates standardised to the Australian Standard Population 2001. http://www.aihw.gov.au/cancer/data/acim_books/breast.xls (accessed on 12/3/2008)

2.3 Residence

Breast cancer incidence and mortality varies among populations around the world (see Figure 4). Age-standardised incidence rates vary by around five-fold, and are highest in the more affluent, so-called "developed" countries (ie those in North America and western Europe) and lowest in the less-developed countries (ie Africa and parts of Asia). Regionally, breast cancer incidence in Australia/New Zealand is second only to North America[5] although several European countries individually have higher incidence of breast cancer than Australia. Over time, migrants tend to experience the breast cancer incidence rates of their adoptive countries, although it might take

two to three generations before this occurs.[6] Also, many countries from both lower and higher incidence groups are now experiencing increases in breast cancer.[6] Although this is attributed, in part, to greater use of mammography and therefore increased detection of cancers, increases are also occurring in countries that make little use of mammographic screening. These observations support the notion that breast cancer is influenced, at least in part, by environmental or lifestyle exposures that are changing over time. In contrast to incidence, age-standardised mortality due to breast cancer differs by only two to three-fold among these countries, in large part due to the aggressive and successful management of the disease pursued in the high-incidence locations.

Figure 4 Estimated annual female breast cancer incidence and mortality rates by world region or country in 2002



Notes: Cancer rates are estimates for the middle of 2002, from the most recent data available, generally 3–5 months earlier.

Rates are expressed per 100,000 populations and age-standardised using the year 2002 population of the corresponding country and the World Standard Population (ASR (W)).

Table 3 Average annual numbers and rates of female breast cancer by Australian state and territory (2000–2004)

	Incidence		Mortality	
	Number of cases	Age-standardised rates	Number of cases	Age-standardised rates
NSW	4027	114.8	893	24.2
VIC	2940	113.5	705	25.8
QLD	2177	115.7	450	23.5
WA	1112	115.8	227	23.4
SA	1010	116.9	243	26.3
TAS	300	113.2	70	25.1
ACT	200	132.5	33	23.3
NT	60	93	11	20.6

Notes: Age-standardised rates were calculated using the direct method, per 100,000 population, using the Australian standard population 2001

Source: Australian Institute of Health and Welfare (AIHW) 2005. State & Territories GRIM (General Record of Incidence of Mortality) Books. AIHW: Canberra; and the National Cancer Statistics Clearing House, AIHW - http://www.aihw.gov.au/cancer/data/excel_tables/state_and_territory_averages.xls (accessed on 13 March 2008)

2.4 Summary

Female sex and increasing age are the two strongest risk factors for breast cancer. The rate of increase in incidence declines following menopause, suggesting a role for ovarian and other female hormones in the development of breast cancer. Breast cancer incidence rates also vary by country of residence, with the more affluent, developed countries having rates that are up to five times those experienced by less-developed countries. The rates in these countries have increased rapidly during the past century, and breast cancer incidence for migrants and their offspring approaches the rates of their adopted homeland rather than their country of origin. This suggests that environmental and lifestyle factors contribute to breast cancer risk. Based on rates from 2004, it is estimated that 1 in 11 Australian women will develop breast cancer by age 75 and approximately 1 in 9 women by age 85.

3 Family history and genetics

In the past two decades, much attention has been devoted to the role that genes play in the development of breast cancer. This has led to some important insights into breast cancer biology. It has also contributed to our recognition that some women might be at increased risk of the disease due to inherited susceptibility. Because the testing of individual genes remains a specialised and often expensive and time-consuming activity, a family history of breast cancer, especially when multiple family members are affected, is often used as a marker of the possibility of inherited susceptibility. However, it should be remembered that families share not only genes but also environmental exposures and a cultural background, which also potentially contribute to risk of breast cancer. Two publications that provide more specific advice and clinical guidelines on assessing family history, managing women with family history of breast cancer and making referrals for genetic testing are *Advice about familial aspects of breast cancer and ovarian cancer: A guide for health professionals*, developed by the National Breast Cancer Centre (NBCC)*[7] and the *Clinical practice guidelines for the familial aspects of cancer: A guide to clinical practice*, issued by NBCC* and the National Health and Medical Research Council.[8]

3.1 Family history

A woman's risk of breast cancer is increased if she has a family history of breast cancer. Although this risk is influenced by the number of women (and men) with breast cancer in her extended family of blood relatives, the most useful indicator is whether one or more first-degree relatives (mother, sister, daughter) are affected. A collaborative reanalysis of data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without breast cancer has estimated the risks associated with varying degrees of breast cancer history among first-degree relatives.[6] Compared with women reporting no such family history of breast cancer, women with one, two, and three or more affected first-degree relatives had relative risks of 1.80 (99% CI: 1.69-1.91), 2.93 (99% CI: 2.36-3.64) and 3.90 (99% CI: 2.03-7.49), respectively. The findings were similar for women reporting mothers or sisters with breast cancer. According to a meta-analysis, the relative risk of breast cancer for one or more second-degree relatives (grandmother, aunt, niece) diagnosed with the disease was lower, at 1.5 (95% CI: 1.4-1.6).[9] Relative risks associated with family history were greater for younger women, and breast cancer risk for women of a given age was greater, the younger the relative was when diagnosed.[9] The numbers in Table 4 provide estimates of the probability that women free from breast cancer at certain ages will develop breast cancer during the next 10 years, according to the number of affected relatives. These findings are relevant for women from more developed countries, such as Australia. More detailed figures referring to lifetime risks of breast cancer by age of the woman and her family history status are available from an Australian study.[10]

Table 4 Probability (%) that women in more developed countries who are free from breast cancer at certain ages would develop breast cancer during the next 10 years (ie absolute risk), according to the number of first-degree relatives affected

Risk ages (years)	Number of first-degree relatives affected		
	Two	One	None
20	0.2	0.1	0.04
40	5.2	2.5	1.4
50	5.3	3.2	1.9
60	5.6	3.5	2.3
70	5.7	4.2	2.5

Source: Collaborative Group on Hormonal Factors in Breast Cancer (2001). Familial breast cancer: reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 358:1389–1399.

While there is a demonstrated link between family history and breast cancer, it has been observed that the implications of this finding for the individual woman may not be as severe as it would seem. In discussing the findings of the comprehensive reanalysis,[6] the authors observed the following:

- eight out of nine women who develop breast cancer do not have an affected mother, sister, or daughter
- although women who have first-degree relatives with a history of breast cancer are at increased risk of the disease, most will never develop breast cancer
- although relative risks of breast cancer associated with a family history of breast cancer are greater at younger age, absolute risk of breast cancer is higher at middle or old age than at young age.

3.2 High-risk genes

An exciting chapter in breast cancer research has been the identification of specific genes that potentially confer a high risk of developing breast cancer. We all inherit two copies of each gene; these are necessary for normal physiological function. However, the exact form of the gene can vary between individuals. Some forms (also-called variants, mutations or specific alleles) have been shown to increase risk of breast cancer for those women (and sometimes men) who inherit them rather than other forms of the genes.

3.2.1 BRCA1 and BRCA2

BRCA1 and BRCA2 are two genes that have been identified as having the strongest association with breast cancer risk. Both appear to have similar biological functions, including repair of DNA damage and, in their variant form, they increase the risk of breast cancer and other cancers (in particular, ovarian cancer). The best information available to date is based on a combined analysis of 22 studies,[11] which found that the cumulative risk of breast cancer by age 70 is 65% (95% CI: 44-78%) for those who inherited a BRCA1 variant and 45% (95% CI: 31-56%) for carriers of BRCA2 variants. For both genes, the risk of breast cancer for carriers of specific variants is substantially higher (10–30 times) than for women not inheriting those genetic variants. Relative risks of breast cancer declined significantly with age for BRCA1 mutation carriers but not for BRCA2 mutation carriers. Despite the large increase in breast cancer risk associated with BRCA1 and BRCA2 variants, they account for only about 5% of all breast

cancers, because only 1 in 1000 women has inherited one of them. There are some ethnic subgroups in which BRCA1 and BRCA2 variants are more likely to be inherited (eg around 1% of women of Ashkenazi Jewish descent have inherited a high-risk BRCA1 or BRCA2 variant; similar variants are also more common in those from Iceland and various Scandinavian countries).

Individual risk prediction as a consequence of genetic testing for BRCA1 and BRCA2 remains a challenging exercise. Nearly 2000 variants have been described in the two genes and, for many, it is still not known whether or not they increase risk of breast cancer. One potential clue is the location of the variant in the gene; it appears that variants in some portions of the genes might confer greater risk of breast cancer than others.[11,12] Although all women who inherit a BRCA1 or BRCA2 variant do not necessarily develop breast cancer, it is unclear what other factors (environmental or genetic) influence the risk of disease. There is also evidence emerging that risk factors for breast cancer might act differently for carriers of BRCA1 or BRCA2 variants than for women without genetic susceptibility due to these genes.[13] Statistical analyses also suggest that high-risk genes other than BRCA1 and BRCA2 probably contribute to risk of breast cancer, particularly for younger women.[14] Research is underway to identify those additional genes, but some that have already been identified are described below.

3.2.2 Other high-risk genes

Women suffering from a number of rare genetic disorders have also experienced an increased risk of breast cancer. As the genes underlying these conditions have been identified, their relationships with breast cancer in the general population have been investigated.

Li-Fraumeni syndrome is characterised by increased risk of breast cancer and a range of other cancers within families. Tumours in these families tend to occur in childhood and early adulthood, and often present as multiple primaries in the same individual. Inherited variants in the TP53 tumour suppressor gene have been implicated in at least 50% of these families. The function of the TP53 gene is to limit the proliferation of cells when DNA damage occurs, thereby preventing growth of tumours. A large number of variants have been described for the TP53 gene, although their specific relationships with breast cancer risk are still being clarified.[15,16] It is estimated that less than 1% of breast cancers can be attributed to inherited variants in TP53.

Other syndromes characterised by a large increase in breast cancer risk include Cowden syndrome and Peutz-Jeghers syndrome. Cowden syndrome is characterised by multiple malformations called hamartomas and an excess of breast cancer and other cancer types. The syndrome is caused by deleterious mutations in PTEN, a tumour suppressor gene. Lifetime risks of developing breast cancer for women with Cowden syndrome range from 25% to 50%.

Peutz-Jeghers syndrome is characterised by pigmented lesions in lips, mouth, hands and feet, and gastrointestinal polyps. Mutations in the STK11 gene, also known as LKB1, were found to be associated with the syndrome. Risk of breast cancer by age 60 for women with the syndrome was found to be around 30%.[17]

A number of studies have shown that a rare mutation (1000delC) in the CHEK2 gene, which is involved in DNA damage repair, is associated with increased risk of breast cancer. This mutation is carried by about 1% of people in the general population and in 4–11% cases of familial breast cancer.[18-20] Recent meta-analyses and collaborative re-analyses estimated that the 1000delC mutation increases breast cancer risk by two-fold and familial breast cancer risk by three to five-fold.[19,21]

3.3 Low-risk genetic variant

In addition to so-called high-risk genes, in recent years research has focused on genetic variants associated with a minimal to moderate increase in breast cancer risk. The definition of a minimal to moderate risk is arbitrary but it is often considered to be in the range of relative risks between 1.5 and 2.0.

Ataxia Telangiectasia (AT) is an example of syndrome characterised by a small increase in breast cancer risk. AT is a disorder involving neurological deterioration, immunodeficiency and unusual sensitivity to ionising radiation. It is an autosomal recessive condition associated with mutations in the ATM gene, which means that only people carrying two mutated alleles will have the AT condition. The ATM gene is involved in repair of DNA damage and more than 300 mutations have been identified.[22] Past studies that evaluated the risk of breast cancer associated with variants in ATM have provided conflicting findings but two recent large epidemiological studies have shown that carriers of one or two mutated alleles in ATM have a two-fold increased risk of breast cancer.[23,24] It is estimated that approximately 1% of people in the general population have inherited a variant in the ATM gene.

Research into low-risk genes has gone beyond syndromes such as AT and has broadened its perspective to the entire genome. Intensive research in happening in this field for three reasons:

- the identification of low-risk genes promises may provide additional insights into the underlying biology of breast cancer
- low-risk genes might modify the influence of other risk factors through gene–environment interaction, thereby explaining why many of the known risk factors appear to be such weak causes of breast cancer
- some variants of these genes might be relatively common in the population, and may therefore account for a substantial proportion of breast cancers.

Two strategies have been followed to identify genetic variants associated with moderate increases or reductions in breast cancer risk: the candidate gene approach and genome-wide searches.

In the candidate gene approach, a number of genes and variants are selected because of their known or presumed biological function and relevance to carcinogenesis. These variants are then tested for association with breast cancer risk, usually in case–control studies, so far with relatively disappointing results. The few confirmed associations include CASP8 and TGFB1.[25] About 24% and 62% of women carry at least one copy of the rare allele for CASP8 and TGFB1. respectively. Relative risks were consistent with a small decrease in risk (up to 26%) associated with the variant in CASP8 and a small increase in risk (up to 16%) associated with the variant in TGFB1.

With the development of new technologies based on microarrays, or gene chips, capable of assessing more than 200,000 variants in a single sample, genome-wide scans became feasible, and have led to the identification of associations between variants in at least six genes or regions and breast cancer risk. The strongest association has been found with a variant in the FGFR2 gene, a member of the fibroblast growth factor family. About 14% of women carry two copies of the variant and their breast cancer risk is 63% higher than that of women not carrying the variant.[26]

We do not know the biological function of most low-risk variants. It is possible that these variants do not modify breast cancer risk per se, but are merely markers correlated with other variants that are causally related to breast cancer and not yet identified.

3.4 Summary

Women with a family history of breast cancer are 1.5–3.9 times more likely to develop breast cancer than are women without a family history, depending on the number and degree of relatedness of the family members affected. Although this association might arise because of shared environment and lifestyle, it might also be due to inherited genetic susceptibility. A number of genes have been identified that substantially influence risk of breast cancer (so-called high-risk genes), including BRCA1, BRCA2, TP53, PTEN and CHEK2. Risk of breast cancer for women carrying mutations in one of these genes is more than two-fold greater than for women who do not carry any variant, and for some mutations the increase is more than 10-fold. However, mutations in high-risk genes are rare and altogether they only account for 5–10% of breast cancers. Recently, a number of genes have been identified that are associated with small changes in breast cancer risk, and it is likely that others of these so-called “low-risk genes” will be identified in the near future. Despite the small effect of these variants on breast cancer risk, they might account for a large number of breast cancer cases because some of them are very common. We do not know whether these low-risk variants have any biological function, and more work needs to be done to determine whether they are causally associated with breast cancer risk.

4 Breast conditions

A number of breast characteristics or changes that occur in breasts may have some association with the development of invasive cancers, and are discussed in this section. Some of these changes might represent earlier stages, or precursors, of invasive disease. Others represent conditions that might increase risk of invasive breast cancer, while still others may not influence cancer risk at all.

4.1 Carcinoma in situ

Breast carcinoma in situ (CIS) occurs when cells have the appearance of invasive cancer but do not invade adjacent tissue (ie they are non-invasive). Ductal carcinoma in situ (DCIS) remains confined to the milk ducts and accounts for approximately 85% of breast CIS. Lobular carcinoma in situ (LCIS) remains confined to the lobules and accounts for approximately 10% of breast CIS. These two conditions are most often diagnosed during mammography and hence their incidence has increased with increased detection due to more widespread mammographic screening.

4.1.1 Ductal carcinoma in situ

The age-standardised incidence rates for DCIS in Australia increased from 11 cases per 100,000 women (total number of cases = 5489) in 1993–1998 to 13 cases per 100,000 women in 1997–2002 (total number of cases = 7434).[27] The increase is more pronounced for the screening target age group of 50–69 years. The risk of being diagnosed with DCIS increases with age and then falls, with a mean age of diagnosis of about 59, which is younger than for invasive breast cancer. At present, for women over 50, approximately 15–25% of all breast tumours diagnosed within mammographic screening programs are DCIS.[28]

Unlike invasive breast cancer, DCIS does not spread outside the ducts but still requires medical treatment because it raises the risk of a subsequent invasive breast cancer. The most common treatment is surgical removal, often followed by radiation therapy. Estimates of risk of subsequent invasive breast cancer in women with DCIS come from published reports of the follow-up of cases of DCIS that were initially misdiagnosed as benign lesions and were not treated. In these studies, the proportion of women who developed invasive breast cancer ranged from 14% to 53%.[28] These studies support the idea that DCIS is a precursor lesion for invasive breast cancer but also a marker of risk.

A meta-analysis of series of DCIS cases treated with conservative surgery alone showed that 23% will develop recurrent disease and half of the recurrences will be invasive cancers. This proportion drops to 9% for women with DCIS treated with conservative surgery and radiotherapy, while treatment with mastectomy virtually removes the risk of recurrence.[29] Women who have been diagnosed with DCIS are estimated to have a two to six-fold increased risk of a subsequent invasive breast cancer in the same breast, and up to a two-fold increase in risk of invasive cancer in the opposite breast, compared with women who have never had DCIS diagnosed.[30]

Current research is trying to identify which DCIS are likely to recur, to ensure more effective management. [31] Information on the risk factors for DCIS are only now becoming available and, to a large extent, these are similar to risk factors for invasive breast cancer.[28,32] Family history of breast cancer has been associated with an increased risk of DCIS in all studies. Nulliparity

(never having carried a pregnancy), older age at first full-term pregnancy and biopsy for benign breast disease were also associated with DCIS across multiple studies. Current use of oral contraceptives was modestly associated with DCIS, although the risk estimate was not considered significant.[33] Further research is necessary to establish a more complete risk factor profile for DCIS and to identify risk factors that distinguish invasive and in situ disease.

4.1.2 Lobular carcinoma in situ

Estimating the incidence of lobular carcinoma in situ (LCIS) of the breast is challenging because it is not associated with clinical symptoms, cannot be detected at mammography and is usually an incidental finding in breast biopsies performed for other reasons. The average age at diagnosis for LCIS, at around 54, is slightly younger than for DCIS; in contrast to DCIS, LCIS tends to be spread more diffusely throughout the breast. Women with LCIS are seven to nine times more likely to develop invasive breast cancer within 15 years than women with no LCIS.[34,35] Few studies have evaluated risk factors for LCIS separately from DCIS, largely because the rarity of LCIS makes such studies difficult. To date, most risk factors for LCIS and DCIS appear similar.[32,36] Where differences are reported, these are considered inconclusive and interpreted cautiously because of small numbers.

4.2 Benign breast disease

Benign breast disease (BBD) or "fibrocystic disease" are general terms applied to a range of changes in breast tissue. These changes can be difficult to distinguish clinically from invasive cancer until a biopsy is conducted for definitive diagnosis. Estimates of occurrence differ according to the classifications used. Nevertheless, BBD is a fairly common diagnosis. Many forms of BBD have no clinical symptoms, so the extent of mammographic screening in the population also influences the frequency of diagnosis. BBD is detected mainly before the menopause,[37,38] whereas about 75% of cases of breast cancer occur after the menopause. Three basic classifications of BBD have been agreed:[4,35] non-proliferative BBD, including ductal ectasia, fibroadenoma, adenosis, fibrosis, cysts, mild hyperplasia, mastitis or fat necrosis,[39] proliferative BBD without atypia, including ductal hyperplasia, lobular hyperplasia or papilloma with fibrovascular core; and atypical hyperplasia, including atypical ductal hyperplasia or atypical lobular hyperplasia.[40]

Women with biopsy-confirmed BBD have been shown to have overall modest increases in risk of subsequent breast cancer, similar for the opposite breast and the breast in which the benign condition was diagnosed. However, this obscures heterogeneity across the specific diagnoses of BBD.[37]

A recent study followed 9087 women who received a diagnosis of BBD at the Mayo Clinic in the US from 1967 to 1991.[41] Sixty-seven per cent of women had non-proliferative BBD, 30% had proliferative BBD without atypia and 4% had proliferative BBD with atypia. Over a median follow-up length of 15 years, women with non-proliferative BBD, proliferative without atypia BBD and proliferative with atypia BBD, small, moderate and large increases in breast cancer risk were observed respectively. The corresponding relative risks for each of these conditions are presented in Table 5. Despite the large increase in risk associated with proliferative with atypia BBD, only 19% of these women developed breast cancer during follow-up. The proportion was lower for the other two types of BBD.

Table 5 Risk of female breast cancer after a diagnosis of benign breast disease

Diagnosis	Relative risk
No diagnosis of benign breast disease	1.0*
Non-proliferative disease	1.2–1.4
Proliferative disease without atypia	1.7–2.1
Proliferative disease with atypia (atypical hyperplasia)	3.3–5.4

* Comparison group

Source: Hartmann LC, Sellers TA, Frost MH et al. Benign breast disease and the risk of breast cancer. New Engl J Med 2005;353:229–37.

In summary:

- atypical hyperplasia is a risk factor for breast cancer, however, most women with these lesions will not develop breast cancer
- the relative risk of breast cancer, compared with the general population, is 3–5 for women with atypical hyperplasia and much lower for other types of BBD
- the excess risk of breast cancer applies to both breasts, although the risk is greater on the affected side at least for the first 10–15 years after the diagnosis of BBD
- there is no means of identifying which women with these lesions will develop breast cancer
- the effectiveness of different management and screening strategies is unknown for atypical hyperplasia.

The current consensus is that even atypical hyperplasia is merely a marker of increased breast cancer risk, because only around 19% of women with this diagnosis develop breast cancer in the subsequent 10–15 years and risk of breast cancer is reduced further after that.[42] More recent research about atypical lobular hyperplasia, in particular, suggests that it might function as a precursor lesion as well as a risk indicator. Two studies have shown that breast cancer is three times more likely to occur in the same breast as the atypical lobular hyperplasia than in the opposite breast.[43,44]

4.3 Mammographic breast density

Mammography has commonly been used to investigate breast disease for the past 30 years, and to screen for breast cancer for the past 15 years. The mammographic appearance of breast tissue varies between women, due to the different proportions of fat and epithelial or connective (the latter also known as stromal) tissue. The fat tissue appears dark on mammogram, whereas the epithelial or connective tissue appears light.

A measure of mammographic breast density is the percentage of dense (ie epithelial or connective) tissue in the breast. Several classification systems of mammographic breast density distinguish breast tissue comprised mainly of fat, degrees of density referring to increasing ductal prominence and a pattern that is comprised mostly of dense tissue (previously called “dysplasia”).[45]

Mammographic breast density is emerging as one of the strongest risk factors for breast cancer. Women with the highest degree of breast density are at a four to six-fold increased risk of breast cancer compared with women with little or no breast density, after controlling for other known breast cancer risk factors. This has resulted in a whole new area of research — seeking risk factors for breast density.

Both family and twin studies suggest that the degree of mammographic breast density might be under genetic control, explaining somewhere between 30 and 70% of the variation in density.[46-48]

Hence, work has commenced to identify the genes that influence breast composition. Another strong factor influencing breast density is age: mammographic breast density is inversely correlated with age, because younger women have denser breasts, on average, than older women after menopause.

Other breast cancer risk factors are also associated with increased breast density.[49, 50] These include nulliparity, later age at first full-term pregnancy, lower parity and alcohol consumption. Associations between denser breasts and lower body mass index (BMI) for premenopausal women and current use of hormone replacement therapy (HRT) by postmenopausal women, are also consistent with relationships observed for breast cancer. An early report showed that women who reported higher levels of physical activity had lower mammographic breast density.[51]

The mechanism underlying the association between breast density and breast cancer is not yet understood. One explanation suggesting that breast density is a marker for cellular proliferation in breast tissue has received recent support, with reports that breast density is associated with increased serum levels of insulin-like growth factor (IGF-I) in premenopausal women and serum prolactin levels in postmenopausal women.[47] These hormones are known to promote cell growth.

The relationships observed between breast density and many established breast cancer risk factors are also being interpreted as evidence that these influence breast cancer risk through their effect on breast density. If true and breast density is an intermediate along the causal pathway, a reduction in breast density should prevent breast cancer. To date, use of medications designed to block or reduce oestrogen[52,53] and a low-fat, high-carbohydrate diet[54] have been shown to reduce mammographic breast density.

4.4 Summary

A variety of breast conditions have been described, resulting in a quasi continuum from normal, low-risk breast density to normal, high-risk breast density, benign breast disease without or with atypia and CIS. Whereas high breast density, benign breast disease and LCIS are considered potential risk factors for breast cancer, DCIS is viewed as both a risk factor and a precursor lesion for invasive disease. There is some discrepancy, depending on the source of data, but overall, the reported relative risks are highest for LCIS (RR 7–9), DCIS (RR up to 6 for breast cancer in same breast) and high breast density (RR 4–6); intermediate for atypical hyperplasia (RR 3–5); and modest for DCIS (for breast cancer in opposite breast) and proliferative disease without atypia (RR 1.5–2).

5 Reproductive and menstrual history

Many of the most established breast cancer risk factors relate to menstrual and reproductive events, with research findings dating back to the early 1900s.[55] These are addressed below in the context of a model of breast cancer risk originally described by Malcolm Pike and colleagues, and refined by others.[50,56]

5.1 Age at menarche and menstrual cycle length

Menarche, the time of commencement of menstrual cycles, is characterised by monthly fluctuations in hormone levels, ovulation and cellular proliferation in the breast. The breast actually begins to develop 1–2 years before menarche and, during the time of early adolescence, breast tissue grows rapidly. In this relatively immature state, the breast epithelial cells are considered vulnerable to carcinogens and random errors in the genetic material that can be passed on to additional breast cells as they divide. Age at menarche and age at telarche (breast development) have progressively decreased in different parts of the world for the past century, but the degree of change and the reasons for it remain subject to controversy. Factors that contribute to the decrease in age at menarche include improved nutrition, increased body size and earlier average attainment of sufficient body fat to commence reproductive life. Increased height and body mass index (BMI) accelerate the onset of menarche, perhaps because menarche depends on the attainment of a critical body mass.[57,58] In the century before 1950, age at menarche fell by two to three months per calendar decade in the UK and USA.[57,59] This decline has been associated with an increasing breast cancer incidence.[56,60] The trends in Australia were probably similar.[61] Epidemiological studies of breast cancer have shown that women who had their first menstrual period at an age less than 12 years have a slightly higher risk of breast cancer (10% to 25%) than women who had their first menstrual period later (ie ≥12 years).[50,62-64] It is difficult to be certain of the size of the risk, because of errors in recalling age at menarche. Early menarche prolongs a woman's exposure to oestrogens and other female hormones.[64,65] Studies also have shown that women with an early age at menarche might have higher levels of oestrogens for several years after menarche and possibly throughout their reproductive lives, than women with later menarche. Early menarche also might be associated with more regular ovulatory cycles, contributing to greater lifetime exposure of breast tissue to endogenous hormones. Similarly, shorter cycle length has been shown to increase breast cancer risk. This has been attributed to more frequent cycles and more time spent in the luteal phase, when oestrogen and progesterone levels are high and cell proliferation in the breast appears to be higher.[63,64]

Age at menarche may be a potentially modifiable breast cancer risk factor. A school-based intervention study in the US designed to decrease television viewing and the consumption of high-fat foods while at the same time increasing exercise and the consumption of fruit and vegetables has shown that menarche might be delayed through reduction of BMI and increasing physical activity.[66] This finding is promising but needs to be confirmed by further studies.

5.2 Parity and age at first full-term pregnancy

On average, women who have had children (ie parous women) have up to about a 30% lower risk of breast cancer than women who have had no children (ie nulliparous women).[50,62,63,67] For parous women, breast cancer risk decreases with the number of children and increases with the age at first full-term pregnancy, and both associations appear to be independent of the effect of breastfeeding.[63,67,68] In a collaborative reanalysis of 47 studies from 30 countries including 50,302 women with and 96,973 women without breast cancer, researchers showed that each birth following the first (ie all women were parous) reduced the risk of breast cancer by approximately 7% (95% CI: 5-9%).[68] This means that parous women who have given birth to at least four children have a breast cancer risk 20–30% lower than that of parous women who have given birth to only one child.

The protective effect of parity is thought to be due to permanent changes that occur in the breast epithelial cells during the third trimester. in preparation for lactation. These more mature (ie differentiated) cells are thought to be less vulnerable to DNA damage that might lead to cancer; hence, breast cancer risk during the years following a full-term pregnancy is reduced.[69]

For parous women, a younger age at first childbirth is associated with a lower lifetime risk of breast cancer.[67,68] The collaborative reanalysis mentioned above, restricted to women who had never breastfed, showed that the relative risk of breast cancer decreased by 3% for each year younger the age at which the first child was born.[68] For women who have their first child at younger ages (ie before 25 years) their breast cancer risk is about 43% lower than for women who have their first child late (ie after 29 years), irrespective of the number of children and the duration of breastfeeding. For some women who have their first child at older ages (ie after 29 years), in particular those who had only one child and who did not breastfeed, breast cancer risk is higher than for nulliparous women. There is some evidence that the increased risk associated with late age at first birth is stronger for premenopausal breast cancer than for postmenopausal breast cancer.[50,62,63,67]

Finally, some but not all studies find a transient increased risk of breast cancer in the years immediately following pregnancies.[63] This increased risk observed early after pregnancies would be probably due to the short-term effect of the hormones produced during pregnancy that would promote cell division and accelerate the growth of existing tumours.[69] Pregnancy marks a time when rapid proliferation of immature epithelial cells takes place. If DNA damage has already occurred in the breast cells, it can become established as cancer during this growth period and be diagnosed sometime during or following the pregnancy. The longer the time between menarche and a first full-term pregnancy, the greater the likelihood that mutations might have occurred in the DNA of the breast epithelial cells, which might be passed on as the cells proliferate.

In Australia, the median age of all mothers who gave birth in 2005 was 30.7 years, 3.7 years older than in 1985 (27.3 years). Australia's total fertility rate in 2005 was 1.81 babies per woman, higher than in 2004 (1.77) and the highest since 1995 (1.82).[70]

5.3 Breastfeeding

Breastfeeding reduces risk of breast cancer, probably through several mechanisms, including differentiation of the epithelial cells, reduction in the cumulative number of ovulatory cycles due to delay in re-establishing ovulation after a completed pregnancy and the reduction of epithelial

cells following completion of breastfeeding.[71] Studies in Chinese populations show a progressive reduction in risk with increasing length of nursing years, but in western populations it is rare for many mothers to have attained sufficiently long periods of nursing to estimate the effects of lactation on breast cancer risk.[72] Only 5% of women in the US have breastfed for 25 months or more in total, compared with Chinese studies in which 50% of women have breastfed for at least three years.[63,73]

Although not all studies are consistent, breastfeeding is now generally regarded as being associated with a modest decrease in risk of breast cancer. Breastfeeding is strongly correlated with parity and possibly with age at first birth. The effect of breastfeeding adjusted for the effect of parity and age at first birth was estimated in a collaborative re-analysis of 47 epidemiological studies including 50,302 women with breast cancer and 96,973 women without breast cancer from 30 countries.[68] The relative risk of breast cancer for parous women decreased by 4% (95% CI: 3-6%) for every 12 months of breastfeeding.[68] This means that, in addition to the protective effect of number of children, women who breastfed in total for at least three years have about an extra 10–20% reduction in risk compared with women who did not breastfeed. For a total duration of breastfeeding of more than four years the reduction in risk is about 30%.

In Australia, 88% of children aged up to three years in 2004–2005, had, at some stage, obtained nutrition from breast milk, with similar figures in 2001 (87%) and 1995 (86%).[74,75] There has been a general increase in the proportion of women initiating breastfeeding after discharge from hospital (40–45% in 1970, 82% in the early nineties and 83% in 2001). However, findings from the National Health Surveys indicate that the proportion of children receiving any breast milk declines steadily with age. In 2001, by age six months around half (48%) of all children were being breastfed, this had declined to 23% of children who were being breastfed by age one and 1% of children being breastfed by age two. The 2003 NHMRC dietary guidelines recommend an initiation rate of 90% and 80% of infants being breastfed at the age of six months, as important objectives for Australia.[76]

5.4 Pregnancy termination

The interruption of breast cell maturation that takes place when a pregnancy is ended before term has been hypothesised to increase breast cancer risk. While a meta-analysis that summarised 23 earlier studies reported a weak increase in breast cancer risk associated with an induced abortion,[77] more recent studies indicate that this is not the case. The meta-analysis was based largely on case–control studies and these types of studies are likely to suffer from the problem that the women in the control group may be less willing than breast cancer cases to reveal that they had experienced a pregnancy termination.[50,78] More recent studies provide little support for the hypothesis that termination increases breast cancer risk, with most suggesting that induced abortions have no effect on overall risk of breast cancer. The strongest evidence comes from a reanalysis of 53 epidemiological studies including 83,000 women with breast cancer from 16 countries.[79] When studies were analysed according to whether the information on pregnancy termination was available before or after diagnosis of breast cancer, the more reliable cohort and record-linkage studies showed no evidence of an association between premature pregnancy termination and risk of breast cancer. The relative risk for spontaneous miscarriage was 0.98 (95% CI: 0.92-1.04) and for induced abortion was 0.93 (95% CI: 0.89-0.96). The relative risk estimates were similar regardless of the number or timing for either type of pregnancy termination. More recent data from the Nurses Study II[80] and the prospective

European Prospective Investigation into Cancer and Nutrition (EPIC) study[81] provide further evidence of the lack of an association between pregnancy termination and breast cancer risk.

5.5 Age at menopause

During menopause, in addition to the gradual cessation of ovarian hormone production, a process called involution occurs in the breast; this process is characterised by decreased cell proliferation and an eventual reduction in the proportion of epithelial cells. Postmenopausal women have a 15– to 50% lower risk of breast cancer than premenopausal women of the same age and childbearing.[62,82] For postmenopausal women, breast cancer risk is lower than for premenopausal women, but it increases with age at menopause. Breast cancer risk is lowest for women who experience menopause at age less than 40 (~50% of the risk for premenopausal women), while for women who experience a late menopause (ie age at menopause ≥55 years), the risk of breast cancer is close to that for premenopausal women of the same age. For women not using HRT, the relative risk of breast cancer increases, on average, by about 3% per year of delay in age at menopause (RR 1.03, 95% CI: 1.02-1.03), regardless of whether menopause is natural or medically induced by surgical removal of both ovaries. [62,82] Women aged 55 or older at menopause have about twice the risk of breast cancer than women who experienced natural menopause at ages under 45.[72]

5.6 Summary

Reproductive history and menstrual cycle characteristics represent some of the most strongly established risk factors for breast cancer. Women who had their first menstrual period at age 12 or later have a slightly lower risk of breast cancer (10–25%) than women who had their first menstrual period earlier. On average, breast cancer risk for postmenopausal women is lower than for premenopausal women of the same age. For postmenopausal women the relative risk increases with age at menopause. Breast cancer risk is lowest for women who experience menopause at age less than 40 (~50% of the risk for premenopausal women) while for women who experience menopause at 55 or over the risk of breast cancer is close to that for premenopausal women. On average, women who have had children (ie parous women) have about a 10–30% lower risk of breast cancer than women who have had no children (ie nulliparous women). For parous women, breast cancer risk decreases with the number of children and increases with the age at first full-term pregnancy. Women who give birth to at least four children have a breast cancer risk 20–30% lower than that of parous women who give birth to one child. For women who have their first child at older ages (ie after 29 years) breast cancer risk is about 40% higher than for women who have their first child early (ie before 25 years) irrespective of their number of children and duration of breastfeeding. This means that for some who have their first child at older ages (ie after 29 years) women, in particular women with only one child and who did not breastfeed, breast cancer risk is higher than for nulliparous women. Breastfeeding is associated with a decreased risk of breast cancer. In addition to the protective effect of number of children, women who breastfed in total for at least three years have about an extra 10–20% reduction in risk compared with women who did not breastfeed. There is no established evidence of an association between pregnancy termination and breast cancer risk.

These factors related to reproductive and menstrual history are important because, although the associations are small to modest, they are all potentially modifiable, at least at the population level. A large part of the difference in breast cancer incidence rates between developing and developed countries is thought to be due to differences in reproductive factors and breastfeeding.[68] This suggests that, in developed countries, interventions directed towards increasing fertility rates and duration of breastfeeding and decreasing age at first birth might reduce breast cancer incidence significantly.

6 Endogenous and exogenous hormones

Ovarian and other steroid hormones are clearly related to risk of breast cancer. However, only in the past decade or so have researchers begun to move beyond studies of reproductive and menstrual characteristics to investigating more directly the roles played by endogenous (produced by a person's own body) and exogenous (introduced from outside) hormones. Associations between breast cancer and exogenous sources of female hormones, most particularly in the form of oral contraceptives and hormone replacement therapy (HRT), have been clarified in recent years, because these preparations have been used for a sufficiently long period to study comprehensively.

6.1 Endogenous hormones

In the past, it has been very difficult to study the role of the body's own hormones in relation to breast cancer risk. This is because blood concentrations of hormones vary considerably, and the laboratory analysis of hormones has been prone to error. Of particular concern for measuring hormone levels in premenopausal women has been the variation during the menstrual cycle, but some hormones also vary with a circadian cycle, and others vary as a consequence of stress or other physiological states. In addition, measurement of hormone levels has not been standardised, resulting in poor reproducibility across laboratories, and even across time within any given laboratory. Further, it has been unclear whether a single measure of hormone levels would be adequate to represent long-term exposure, and whether samples taken after diagnosis of breast cancer, which might be affected by the disease process or its treatment, could be used. In recent years, research has begun to clarify how endogenous hormone levels may influence risk of breast cancer; these findings are summarised below.

6.1.1 Oestrogen

There are several steroid hormones collectively known as oestrogens (female hormones) that have varying levels of oestrogenic activity in the body. In animals, oestrogens have been shown to promote development of mammary tumours. Oestrogens contribute to tumour growth by promoting proliferation of cells with existing mutations and increasing the probability of new mutations.[83] For premenopausal women, the main oestrogen is oestradiol produced by the ovaries; for postmenopausal women, when the ovaries stop working, the main oestrogen is oestrone, which is formed from androgens produced in adipose (fat) tissue. Obese postmenopausal women have both higher levels of oestrogens and a higher risk of breast cancer.[83] A pooled analysis of nine prospective studies on the association between circulating levels of oestrogens and other sex hormones and breast cancer risk for postmenopausal women was published in 2002.[84] The analysis included 663 incident breast cancer cases and 1765 controls; women were postmenopausal and not using HRT at blood collection. The risk of breast cancer was significantly associated with increasing concentration for each of the five oestrogens tested, showing a relative risk of 2.0–2.6 for the highest category (top 20%) of each oestrogen when compared with the lowest category. Similar findings have been reported by more recent studies.[85-88] Only a few studies investigated the association between circulating oestrogens and breast cancer risk by oestrogen receptors (ER) and progesterone receptors (PR) status of the tumours and the findings are still inconclusive.[88-91]

A number of prospective studies have reported on premenopausal breast cancer.[83,92,93] Some of these studies reported an association between circulating hormone levels and premenopausal breast cancer risk. It is possible that high levels of sex hormones are associated with increased risk of premenopausal breast cancer, but the evidence remains inconclusive. Studies of circulating levels of sex hormones and premenopausal breast cancer risk are difficult because of the large variation in hormone levels, particularly oestrogen levels, during the menstrual cycle.

6.1.2 Androgens

Although androgens, such as testosterone, are more typically considered "male hormones" they are also present in women, secreted by the ovaries and adrenal glands. They might increase breast cancer risk either directly, by increasing cell proliferation, or indirectly, by conversion to oestrogens.[83] The pooled analysis of prospective studies mentioned above also evaluated the association between androgens and breast cancer risk for postmenopausal women.[84] Again, each of the four androgens tested was significantly associated with a 1.8–2.2 increase in risk of breast cancer when comparing the top quintile with the lowest quintile. Similar findings have been reported by subsequent studies.[85-88] The association between androgens and breast cancer risk appeared to be independent of oestradiol levels.[84,85]

Only a few studies have investigated the associations between androgen levels and breast cancer risk for premenopausal women.[83] The two larger studies published to date are the European Prospective Investigation into Cancer and Nutrition (EPIC) study and the NHSII.[92, 93] The first reported an increased risk of breast cancer associated with high levels of androgens similar to those reported for postmenopausal women,[92] the second reported a modest association with androgens, which was stronger for tumours expressing ER and PR.[93]

6.1.3 Other hormones

Two other "female hormones" have been studied in relation to breast cancer risk: progesterone (which prepares the uterus for implantation of the fertilized ovum, maintains pregnancy and promotes development of the mammary glands) and prolactin (which stimulates and maintains the secretion of milk).[50] Before menopause, progesterone is produced by the corpus luteum in the ovaries; after menopause, levels are extremely low. Prolactin is secreted by the pituitary gland, and prolactin levels are much lower after menopause. As with oestrogens, both progesterone and prolactin promote mammary tumour development in animals. In addition, breast cell proliferation is highest during the luteal phase of the menstrual cycle, when progesterone levels also peak. Although several studies have sought to assess the association between these hormones and breast cancer risk, all have been small and their findings are considered too inconsistent to draw even preliminary conclusions.

In contrast, a growing body of research is accumulating on the role of insulin-like growth factor 1 (IGF-1) and breast cancer.[94-100] IGF-1 is a hormone, similar to insulin, which stimulates proliferation, differentiation and death of normal breast epithelial cells. Its activity in the breast is influenced by its own levels as well as by local concentrations of IGF-binding proteins, including one known as IGFBP-3. In addition, IGF-1 is positively associated with mammographic breast density, birth weight and height. The past literature on the relationship between breast cancer risk and circulating concentrations of IGF-1 and IGFBP-3 had indicated an increased risk for premenopausal women with increasing levels of IGF-1 and IGFBP-3, but no association with risk for postmenopausal women.[94-97] Recently, data from three large prospective studies that

included more incident cases than all previous studies contradicted the previous findings and showed that IGF-I and IGFBP-3 levels were not associated with premenopausal breast cancer risk,[98-100] but were positively associated with postmenopausal breast cancer risk.[98,100] Findings from the Melbourne Collaborative Cohort Study showed that, for women aged 60 or more, the risk of breast cancer for those with high levels of IGF-1 (fourth quartile) was about 60% higher than for those with low levels of IGF-1 (first quartile; hazard ratio = 1.61, 95% CI: 1.04-2.51).[100]

6.1.4 Prenatal exposure to hormones

There is increasing evidence that hormonal exposures in utero might influence subsequent risk of breast cancer, possibly through their influence on the number or state of cells in the undeveloped breast of the foetus.[62] A large cohort study of around 117,000 Danish women that was followed up for an average of 28 years, during which 3340 breast cancer cases were diagnosed, showed that a high birth weight and other factors that are potential indicators of exposure in utero to higher levels of oestrogens are associated with a modest increase in breast cancer risk.[101] A recent meta-analysis of 57 studies that looked at intrauterine factors and breast cancer risk confirmed these findings, and showed that higher maternal age and higher paternal age, both implicated in altered hormonal environment for the developing foetus, were associated with a small increase in breast cancer risk in adulthood.[102] Conversely, the same meta-analysis showed that maternal eclampsia or pre-eclampsia during pregnancy, which are indicators of lower oestrogen levels for the foetus, are associated with a 50% reduction in breast cancer risk later in life.

6.2 Exogenous hormones

Circulating hormonal levels are associated with breast cancer risk. It is therefore not surprising that exogenous sources of hormones, usually taken in the form of medications, also may influence breast cancer risk. However, the increase in breast cancer risk associated with exogenous hormones seems to disappear quite rapidly after a woman ceases to take the medication, and probably not all forms of exogenous hormones are associated with breast cancer risk.

6.2.1 Oral contraceptives

Australian women's use of the oral contraceptive pill (the Pill) increased rapidly from its introduction in January 1961[103] to the point where, by the late 1980s, about 80% of Australian women reported using the Pill at some time.[104] More recently, a 10% reduction has been reported in the proportion of women who have ever used the Pill.[105] The most current information from a survey conducted in 2001–2002 indicates that 32% of women aged 16–59 use the Pill, including over 50% of women younger than 30 years, 32% of women in their 30s, 12% of women in their 40s and 3% of women in their 50s.[106]

An analysis of worldwide epidemiological data on the relationship between breast cancer risk and use of the Pill published in 1996 by the Collaborative Group on Hormonal Factors in Breast Cancer concluded that there was a small increase in risk while women were using combined oral contraceptives and in the 10 years after stopping.[107] This analysis included 53,297 women with breast cancer and 100,239 women without breast cancer from 54 studies conducted in

25 countries. It found that, while women were taking the Pill, their risk was increased by an average of 24% compared with women who never used the Pill (RR 1.24, 95% CI: 1.15-1.33). The effect of the Pill on breast cancer risk was gradually reduced after cessation and, by 10 years after cessation, was no different than risk for women who had never used the Pill. There was some variability in risk depending on the age of the woman. However, the effect of the Pill on lifetime risk of breast cancer was small because the underlying risk of breast cancer was low at ages when women commonly use the Pill. There was also a clear finding that the cancers detected in Pill users were less advanced clinically and thus were potentially more curable than the cancers in women who had never used the Pill. The authors speculated that the less-advanced cancers might have been due to earlier diagnosis for users, possibly because these women had closer surveillance since they were under medical care to receive the Pill. It is also possible that the Pill might reduce the growth rate of cancers or the tendency of tumours to metastasise (spread).

A cohort study of more than 100,000 women conducted in Norway and Sweden reported an elevated risk of breast cancer for current or recent oral contraceptive users at start of follow-up (RR 1.6, 95% CI: 1.2-2.1), with similar findings for the combination Pill and the progestin-only Pill.[108] The findings from the Women's Contraceptive and Reproductive Experience Study were in contrast to those described above.[109] The study, involving approximately 4500 breast cancer cases and more than 4500 controls, suggested that oral contraceptives do not increase the risk of breast cancer. Similarly, the Royal College of General Practitioners' oral contraceptive study, which included about 339,000 woman years of observation for never users of oral contraceptives and 744,000 woman years for ever users, showed that incidence rates of cancer for women who had ever used the Pill were similar to rates for women who had never used the Pill.[110] These inconsistent findings show that the association between oral contraceptive use and breast cancer risk, if any, is likely to be modest.

6.2.2 Hormone replacement therapy (HRT)

Until the 1980s, oestrogen was mainly prescribed for postmenopausal women with symptoms such as hot flushes and genitourinary atrophy. Its use was relatively short tem. In the past two decades, many observational studies have suggested that oestrogen reduces the incidence of coronary heart disease and osteoporotic fractures; therefore, HRT has been commonly prescribed for longer periods to asymptomatic women to prevent disease and prolong life. Long-term use of oestrogen-alone was found to increase the risk of endometrial cancer. To reduce that risk, progestins were added to hormonal preparations.

In 1997, the Collaborative Group on Hormonal Factors in Breast Cancer reported a pooled analysis of 51 studies in 21 countries, involving data on 52,705 women with and 108,411 women without breast cancer.[82] The study concluded that HRT users had a 14% higher risk of breast cancer compared with never users. Risk increased by 2.3% for each year of use for current or recent (within the past 1–4 years) users. For women who had used HRT for five or more years (average 11 years), breast cancer risk was 35% higher than for never users. The increase in risk was limited to current users and was not significant for past users.

In the pooled analysis of the Collaborative Group on Hormonal Factors in Breast Cancer, the composition of the hormonal preparations used by the women, where known, was predominantly oestrogen alone; only 12% of the women reported use of oestrogen progestin combination regimens.

In 2004, the Women's Health Initiative (WHI) Estrogen Alone trial comparing oestrogen only treatment with placebo in 10,739 women with prior hysterectomy was halted, after almost seven years of follow-up, because of a failure to detect a benefit related to heart disease.[111] A later report from this trial concluded that HRT based on oestrogens does not increase breast cancer risk, although the study had limited statistical power to address this question.[112]

More recent observational studies of postmenopausal women have suggested that the breast cancer risk associated with oestrogen plus progestin might be greater than the risk associated with oestrogen only preparations.[50,62,113] The Million Women Study conducted in the United Kingdom in a cohort of more than one million women aged 50–64 showed that for current users of HRT breast cancer risk was higher than for non-users and that relative risk varied by type of hormonal regimen; the relative risk was higher for combined oestrogen and progestin (RR 2.00, 95%CI: 1.88-2.12) than for oestrogen only regimens (RR 1.30, 95% CI: 1.21-1.40).[114] These findings were confirmed by a recent re-analysis and update of the Million Women Study, which also showed that use of HRT was associated with an increased risk of all histological types of breast cancer.[115]

In May 2002, another trial from the WHI designed to compare the health effects of combined HRT (oestrogen plus progestin) with placebo in 16,608 women, was abruptly discontinued after slightly more than five years of follow-up. This was based on evidence that risk of breast cancer was increased and no benefit was seen for cardiovascular disease.[116] This trial, like the WHI trial on oestrogen-only HRT, had limited statistical power to test the association with breast cancer risk that, however, appeared slightly increased for women taking oestrogen plus progestin compared with women in the placebo control group (RR 1.26, 95% CI: 1.00-1.59). Recent re-analyses of the trial reported a similar but non-statistically significant relative risk for breast cancer[117] and showed that the risk was increased for women who had had exposure to HRT before the commencement of the trial (RR 1.96, 95% CI: 1.17-3.27) but not for women without previous exposure to HRT (RR 1.02, 95% CI: 0.77-1.36).[118]

The observational studies give some indications about how long it would take for breast cancer risk for HRT users who stopped treatment to return to the levels of non-users. Both the pooled analysis of the Collaborative Group on Hormonal Factors in Breast Cancer and the Million Women Study show that the increased risk is restricted to current users. The WHI trials do not have enough statistical power to answer this question.

A report from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registries published in 2007 showed a sharp decline in breast cancer incidence rates in 2003.[119] The decline was evident only for women who were 50 or older, and was more evident for cancers that were ER positive than for those that were ER negative. The authors related this decrease in breast cancer incidence to the drop in the use of HRT by postmenopausal women in the US that followed the first report of the Women's Health Initiative. The authors did not exclude the contribution of other causes to the observed decline in breast cancer incidence, although they note that it seemed less likely to have played a major role. Similar findings were recently reported in Australia.[120] The findings of these studies are based on observational data and do not prove that ceasing to use HRT leads to a reduction in breast cancer. In 2001, responses to the National Health Survey revealed that 19% of Australian women aged 40 or older were using HRT, with over half of these (56%) reporting use for five years or longer, and 34% reporting use for 10 years or more.[121] Figures from the 2004–2005 survey show a decline in HRT use, with 11% of the women aged 45 or older using HRT (68% of these reporting use for 5 years or longer).[122] Combination HRT preparations are the most widely used in Australia.

6.2.3 Phytoestrogens

Phytoestrogens are chemicals produced by plants that act like oestrogens in animal and human cells. For a summary of the literature about their association with breast cancer risk see Chapter 7.

6.3 Drugs interfering with oestrogen synthesis

6.3.1 Tamoxifen and raloxifene

Tamoxifen and raloxifene are selective ER modulators (SERMs), a class of medication that selectively inhibits or stimulates oestrogen-like action in various tissues, acting on oestrogen receptors. Tamoxifen exerts its oestrogen antagonist activity in many tissues including breast, bone, liver and uterus. After more than 20 years of use as adjuvant therapy for patients with ER-positive breast cancer,[123] tamoxifen was approved by the US Food and Drug Administration (FDA) in 1998 for the prevention of breast cancer for women at high risk. This decision was based on the results of a trial conducted by the US National Cancer Institute that was halted early because an interim analysis showed that tamoxifen reduced breast cancer incidence by almost one half.[124] Four large prospective trials have assessed the effect of tamoxifen versus placebo for breast cancer risk reduction for women at high risk of breast cancer.[125] An overview of these trials showed a 38% overall reduction in breast cancer incidence for women at high risk of breast cancer who took tamoxifen for five years and also showed that tamoxifen prevents only ER-positive breast cancers (RR ~50%) without effect on ER-negative breast cancer.[126] A range of side effects have been noted for women taking tamoxifen, including hot flushes, menstrual problems, endometrial cancer, cataracts and venous thrombosis. An updated analysis of the International Breast Cancer Intervention Study I (IBIS-I) showed that the risk reducing effect of tamoxifen extends beyond the active treatment period of five years, and persists for at least 10 years, while most side effects do not continue after the five year treatment period.[127]

Raloxifene, a second generation SERM, has also been shown to reduce risk of breast cancer, but seems to induce fewer side effects.[128] During the past decade, clinical trials conducted to evaluate the benefit of raloxifen on osteoporosis and fracture, reported a 44%–76% risk reduction of breast cancer incidence in the raloxifen arm compared with the placebo arm.[129] The Study of Tamoxifen and Raloxifen (STAR) was a prospective, randomised clinical trial designed for comparing the effects of tamoxifen and raloxifen on postmenopausal women with an increased five-year risk of breast cancer as estimated by the Gail model.[125,130] The trial found that raloxifen was as effective as tamoxifen in reducing the risk of invasive breast cancer and was associated with a lower risk of thromboembolic events and cataracts than tamoxifen. In 2007, almost 10 years after the approval of tamoxifen, the FDA approved raloxifen for the prevention of breast cancer for postmenopausal women with osteoporosis and for postmenopausal women at high risk for breast cancer. In Australia, tamoxifen is used to treat osteoporosis and established breast cancer. Another drug, raloxifene, is also used to treat osteoporosis, but neither drug is currently used to prevent breast cancer for women at a high risk of the disease.

6.3.2 Aromatase Inhibitors

Aromatase inhibitors are compounds developed for reducing oestrogen synthesis by targeting aromatase, the enzyme complex responsible for the final step in oestrogen biosynthesis: the conversion of androgens to oestrogens. The third-generation aromatase inhibitors anastrozole, exemastane and letrozole are in current use. Adjuvant breast cancer trials have shown that these agents have an excellent efficacy in treating women with advanced disease.[131] Their use as chemopreventive agents is under investigation, after adjuvant clinical trials showed that women treated with aromatase inhibitors had a higher contralateral breast cancer risk reduction than women treated with tamoxifen.[132]

6.4 Summary

Studies on premenopausal women of the relationship between endogenous sex hormones and breast cancer risk are often difficult because circulating levels of these hormones vary during the menstrual cycle. An association between high levels of endogenous sex hormones and increased premenopausal breast cancer risk is possible, but the evidence is still limited. In contrast, levels of endogenous sex hormones are strongly associated with postmenopausal breast cancer risk. For postmenopausal women with high levels of oestrogens (top quintile), breast cancer risk is double that for women with low levels (bottom quintile). The effect of androgen levels appears to be similar and independent of oestrogen levels. Similarly, postmenopausal breast cancer risk for women with high circulating levels of IGF-1 (top 25%) is 60% higher than for women with low levels of IGF-1 (bottom 25%). Recent studies suggest that factors potentially associated with exposure to high levels of oestrogens in utero (including high birth weight) would be associated with a small increase in breast cancer risk.

In regard to exogenous sources of hormones, current users of HRT may have a breast cancer risk higher than never users, particularly for prolonged use and for combined oestrogen and progestin HRT. The estimates of the increase in risk associated with HRT vary across studies and could range from less than 20% to two-fold. Evidence from large observational studies suggests that this increase in risk decreases rapidly after a woman stops taking HRT or is limited to current users. Findings for oral contraceptives are more inconsistent and the increased risk, if any, is likely to be small and to decrease gradually after cessation. Since oral contraceptives are generally not used after age 50 or so, when breast cancer becomes more common, they will contribute little to increased risk of breast cancer for older women. Tamoxifen and, more recently, raloxifene, are compounds with anti-oestrogenic activity. They have been used to treat breast cancer that is positive for hormone receptors and have been shown to reduce the risk of incidence of breast cancer in high-risk women, but they are associated with side effects. Aromatase Inhibitors are another class of drugs interfering with oestrogen synthesis; their role in the prevention of breast cancer risk is still under investigation.

7 Body size and lifestyle

A number of personal behaviours and exposures have been implicated as risk factors for breast cancer. They include habitual activities, such as diet, drinking alcoholic beverages, smoking and physical activity, as well as personal characteristics, such as body size, which are also influenced by lifestyle.

7.1 Body size and shape

In epidemiological research about breast cancer, the most commonly used measures of body size and shape are adult or attained height and weight (including measures of weight change and of obesity). Body mass index (BMI) has been a preferred measure because it represents weight adjusted for height. BMI is a person's weight in kilograms divided by their height in metres squared (kg/m^2). According to the World Health Organization classification, individuals with BMI over 25 kg/m^2 are considered overweight, while those with BMI over 30 kg/m^2 are considered obese. The distribution of fat mass in the body is another consideration; some women tend to deposit fat in the abdomen (known as central fat distribution), whereas others tend to deposit fat in the hips and thighs (known as peripheral fat distribution). Breast size also is a consideration. All these characteristics are known to depend on an individual's genetic background and on environmental exposures such as diet and physical activity. Hence, any mechanisms underlying observed associations with breast cancer are assumed to be potentially complex, including the influence of nutrition and energy balance on circulating levels of growth factors and hormones.

7.1.1 Height

Consistent findings have been reported of an association between increased height and increased risk of breast cancer.[50,133] The most comprehensive assessment to date involves a pooled analysis of data from seven prospective cohort studies including 337,819 women, of whom 4385 were diagnosed with incident, invasive breast cancer.[134] After adjustment for reproductive, dietary and other breast cancer risk factors, a 7% increase in breast cancer risk was reported for every 5 cm increase in adult height (relative risk [RR] 1.07, 95% confidence interval [CI]: 1.02–1.11). The positive association was observed for both premenopausal and postmenopausal women; however, there was a suggestion that the magnitude of risk differed. Compared with women shorter than 160 cm, women who were 175 cm or taller were at 42% increased risk of breast cancer if they were premenopausal (RR 1.42, 95% CI: 0.95-2.12) and were at 28% increased risk if they were postmenopausal (RR 1.28, 95% CI: 0.94-1.76). These findings are comparable to other more recent research investigating the relationship between height and breast cancer.[135-137]

Height might increase risk of breast cancer by a number of mechanisms.[133] Because famine is known to cause stunting of growth, and secular trends demonstrate increasing height in affluent countries, height is generally considered a marker of childhood or adolescent nutrition and energy balance. In addition, height might serve as a marker of hormonal activity during puberty, since a number of growth factors and sex steroids involved in development are also known to influence breast cancer risk, including insulin-like growth factors and sex hormones. Height also

might be related to the number of breast epithelial cells that develop in utero; hence, more cells are at risk of becoming cancerous later in life.

7.1.2 Weight and BMI

The relationship between weight and BMI and breast cancer risk differs by menopausal status. In western countries such as Australia, there is an inverse association between weight and breast cancer risk for premenopausal women, and a positive association between weight and breast cancer risk for postmenopausal women, after adjustment for a range of other risk factors.[138] Findings from the pooled analysis described above[134] indicate that premenopausal women weighing 80 kg or more are at 42% less risk of breast cancer than those weighing less than 60 kg (RR 0.58, 95% CI: 0.40-0.83). BMI shows a significant inverse association with breast cancer risk for premenopausal women, but the inverse association was limited to women in the highest BMI categories, with obese women being at about half the risk of the leanest women (RR 0.54, 95% CI:0.34-0.85 for BMI≥31 kg/m^2 compared with BMI <21 kg/m^2). The mechanisms underlying this association have not been explained. It has been suggested that heavier women are more likely to experience lower levels of oestrogens and progesterone, and consequently a reduction of breast cancer risk, in part due to more frequent menstrual cycles where ovulation does not occur.[133] In the Nurses' Health Study II, the inverse association between obesity and breast cancer risk for premenopausal women was not explained by menstrual cycle characteristics or infertility due to an ovulation disorder.[139] This suggests that factors other than ovulation might contribute to the inverse association between BMI and breast cancer risk before menopause.

For postmenopausal women, the pooled analysis found breast cancer risk increased with increasing weight.[134] Breast cancer risk for women weighing 80 kg or more was 25% higher than for women weighing less than 60 kg (RR 1.25, 95% CI: 1.02-1.52). Similarly, breast cancer risk increased with increasing BMI. For example, the relative risk of breast cancer for women with BMI higher than 25 kg/m^2 compared with the leanest women (BMI <21 kg/m^2) varied between 1.21 and 1.43.

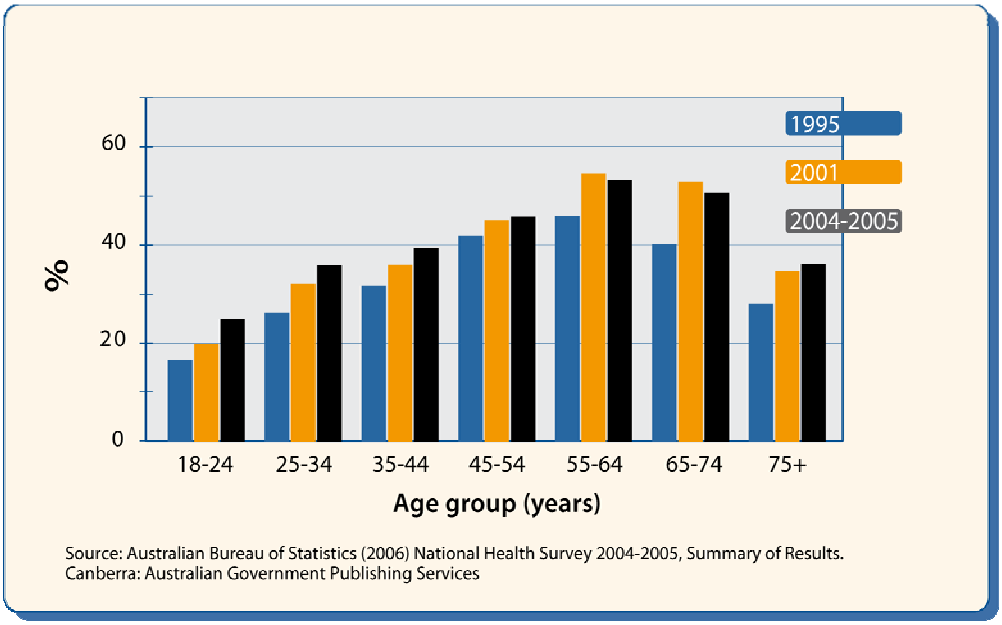
These initial reports suggesting that weight gain during adulthood is associated with increased risk of postmenopausal breast cancer, whereas weight loss, particularly later in life, reduces postmenopausal breast cancer risk[133] were confirmed by recent reports from large cohort studies including the Nurses' Health Study, the National Institutes of Health AARP Diet and Health Study and the Iowa women's health study.[93,140,141]

The most likely explanation for the positive association between postmenopausal breast cancer risk and weight or BMI relates to circulating hormone levels.[133,138] In particular, because ovarian production of oestrogens decreases dramatically following menopause, most oestrogens are produced from the conversion of adrenal androgens in fat cells, which themselves increase in number and size as a consequence of weight gain. For postmenopausal women, levels of endogenous sex hormones have been found to be positively associated with body size.[142] Recent reports have shown that the increased relative risk of postmenopausal breast cancer associated with increasing BMI can be at least partly attributed to increases in endogenous levels of sex hormones, especially oestrogens.[142, 143] Some studies suggest that obesity would increase the risk of postmenopausal tumours expressing both oestrogen receptors (ER) and progesterone receptors (PR), but not the risk of other tumours.[144] Another possible explanation for the association between BMI and postmenopausal breast cancer risk is that fat tissue can

accumulate fat-soluble potential carcinogens increasing their concentrations adjacent to epithelial tissue and making them more available within the body.[133]

Although greater weight is associated with lower breast cancer risk for younger women, it must be remembered that premenopausal breast cancer is relatively rare, and the number of premenopausal breast cancers that might be avoided by weight gain for younger women are few, while the same weight gain would increase the risk of much more common postmenopausal breast cancer later in life. The increased risk of postmenopausal breast cancer associated with increasing BMI is of concern because of the high and increasing prevalence of overweight and obesity in Australia (Figure 5). In the period 2004–2005, the prevalence of overweight and obesity was 40% for women aged 18 and older,[122] however, for women aged 45–74, the prevalence approached or exceeded 50%. For Europe it has been estimated that excess body weight accounts for 8.5% of breast cancer diagnosed after the age of 50.[145]

Figure 5 Percentage of Australian women with an overweight and obese body mass index (BMI) based on self-reported height and weight



Source: Australian Bureau of Statistics (2006) National Health Survey 2004-2005, Summary of Results. Canberra: Australian Government Publishing Services

7.1.3 Fat distribution

Findings from studies of the distribution of body fat have been somewhat less consistent. Independent of BMI, central body fat distribution has been associated with an increased risk of breast cancer compared with a more peripheral distribution of body fat.[133,137,138] This association tends to be stronger for postmenopausal women than for premenopausal women. Weight gain that is deposited in the abdomen or upper body is known as central adiposity, which is considered a better marker for the metabolic consequences of obesity. Centrally located fat has been linked to higher levels of a range of hormones, including insulin and sex hormones. In contrast, fat deposited in the buttocks, hips and thighs is considered to be comparatively inert, metabolically.

7.1.4 Breast size

The theory that breast size is associated with the risk of breast cancer[146] is supported by some indirect evidence: breast cancer occurs more frequently in the left breast, which is typically slightly larger than the right; women who undergo surgical reduction of their breast experience a lower than expected incidence of breast cancer and, in Asia, where breast cancer incidence is lower than in western countries, women have smaller breasts. Few studies have directly investigated the effect of breast size as a risk factor for breast cancer, those studies used a variety of designs and techniques, and the evidence is inconclusive.[133,146]

Breast tumours are thought to arise from the epithelial tissue within the mammary glands. The proportion of dense breast tissue, measured using mammograms, is strongly related to breast cancer risk (see Chapter 4). Breast size might be associated with breast cancer risk, because large breasts have more epithelial tissue than small breasts. It is also possible that total breast tissue has some predictive value, in that the fat tissue contained in large breasts would contribute to increased breast cancer risk by increasing local concentrations of oestrogens and possibly also those of lipid soluble carcinogens.

7.2 Physical activity

Several but not all studies report an inverse association between physical activity and breast cancer risk. There is some evidence to support the hypothesis that physical activity is protective against premenopausal breast cancer, and consensus is emerging about a protective effect of physical activity against postmenopausal breast cancer. Although findings across studies vary, most report a reduced risk of postmenopausal breast cancer for physically active women compared with those with a sedentary lifestyle. Most meta-analyses and reviews place this reduction in risk somewhere between 20% and 40%, comparing the most active with the least active women, and confirm the presence of a dose–response relationship that shows greater reductions in risk with increasing levels of activity.[133,138,147,148] This association seems to hold for either activity undertaken at work or during leisure time. The strongest associations are observed for activity sustained throughout life, but there is also evidence that activity performed earlier in life (including during puberty or adolescence) as well as after menopause reduces breast cancer risk. [138] A number of mechanisms might underlie this inverse association with physical activity. [51] Increased levels of activity are known to decrease weight gain and obesity, thereby reducing risk of postmenopausal breast cancer. It is also clear that physical activity is associated with a reduced risk independent of body mass[138] and is effective even for lean, postmenopausal women.[149] Physical activity can influence the production, metabolism and excretion of endogenous hormones, resulting in lower levels of bioactive oestrogen, insulin, IGF-1 and other growth factors. There are studies showing that higher levels of physical activity are associated with lower circulating oestrogen levels and that this association is independent of the level of adiposity.[150]

The “dose” of physical activity necessary to achieve this apparent beneficial effect is not clear, but a number of studies indicate that four or more hours per week of moderate to vigorous activity is necessary.[138,147,148,150] A recent report from the Women’s Health Initiative Cohort Study, which followed 74,171 women aged 50–79 for an average of 4.7 years, indicates that 1.25–2.5 hours per week of brisk walking or the equivalent is associated with an 18% reduced risk of postmenopausal breast cancer (RR 0.82, 95% CI: 0.68-0.97).[149] The report concludes that longer durations of physical activity provide the most benefit, and that moderate intensity activity is sufficient. This is consistent with the National Physical Activity Guidelines for Australians, which

recommend undertaking 30 minutes of moderate physical activity on most days of the week.[151] There is obvious room for modifying population behaviour in this regard because the Australian National Health Survey indicates that, in 2004–2005, 34% of women reported being sedentary and 39% reported low levels of activity during the previous two weeks, while 22% reported moderate activity and only 4% reported high levels of activity.[122]

7.3 Diet and nutrition

Differences in diet have attracted much attention as a possible explanation for the international differences in breast cancer risk. The accumulating findings from extensive research now show that, for breast cancer, the role of diet is probably less important than for other types of cancer.

7.3.1 Fat, including meat and dairy sources

Consumption of animal (saturated) fat in general and red meat in particular is associated with several cancers. Whereas higher breast cancer rates are observed in countries with higher levels of fat consumption, epidemiological studies of fat consumption reported by individuals during adulthood (usually within a single country) have found no clear or consistent relationships with breast cancer risk.[50] A pooled analysis was conducted using data from eight prospective cohort studies of 351,041 women from North America and western Europe, including 7379 women with breast cancer diagnosed during up to 15 years of follow-up.[152] No significant associations were found between breast cancer risk and the consumption of either total meat, red meat, white meat, total dairy fluids or total dairy solids. Similar conclusions were drawn by a recent comprehensive review of dairy products[153] but a more recent meta-analysis has reported small increases in breast cancer risk associated with high intake of total fat (highest versus lowest level of intake, RR 1.13, 95% CI: 1.03-1.25) and saturated fat (RR 1.19, 95% CI: 1.06-1.35) but not of monounsaturated or polyunsaturated fat.[154] This was confirmed in 2007 by the National Institutes of Health AARP Diet and Health Study, a US cohort comprising 188,736 postmenopausal women who completed a 124-item food-frequency questionnaire in 1995–1996.[155] In this cohort, breast cancer risk for women in the highest quintile of consumption of total fat (median intake = 40% energy from total fat) was 11% higher than for women in the lowest quintile (median intake = 20% energy from fat, RR 1.11, 95% CI: 1.00-1.24, *P* trend = 0.02). The meta-analysis also found a small increase in breast cancer risk associated with high intake of meat (highest versus lowest level of intake RR 1.17, 95% CI: 1.06-1.29). A study investigated the association of red meat intake and breast cancer risk by ER and PR status for 90,659 premenopausal women participating in the Nurses' Health Study II.[156] Risk of ER or PR-positive breast cancer for women with the highest intake of red meat (more than 1.5 servings per day) was twice the risk for women with the lowest intake (three or fewer servings per week, RR 1.97, 95% CI: 1.35-2.88). No increased risk was observed for ER and PR-negative breast cancer.

It has been suggested that meat consumption might increase the risk of breast cancer because some components of red meat — including heterocyclic amines in cooked meat, iron and exogenous hormone residuals — are oestrogenic.[154] Some studies suggest that consumption of meat cooked by methods that promote formation of carcinogens (eg meat cooked at high temperature) might increase postmenopausal breast cancer risk,[157] but others fail to confirm this hypothesis.[158] An alternative explanation for the association between high intake of red meat and breast cancer risk is that red meat contains high levels of fat.

Dietary fat and energy content of foods are strongly correlated, and it is possible that total caloric intake leading to obesity might be the real problem. In addition, differences in other breast cancer

risk factors between western countries with high rates of breast cancer and Asian and other countries with low rates of the disease have not been adequately taken into account in international studies of diet. Animal studies have suggested that fish or plant sources of fat might actually reduce breast cancer risk. Some support for this theory comes from a few European studies related to consumption of olive oil or monounsaturated fat.[50, 157] Studies of omega 3 fatty acids, or their major source fish, have so far failed to show a reduced risk of breast cancer.[50,157]

7.3.2 Fruits and vegetables

Although there is convincing evidence that diets high in fruits and vegetables reduce the risk of some cancers, the evidence for breast cancer is not clear. Three different pooled analyses have been performed on varying subsets of available studies, each including observations on thousands of women.[159-161] Overall, the three re-analyses all showed small-to-moderate reductions in risk of breast cancer with increasing consumption of vegetables and fruits. One pooled analysis and one meta-analysis showed that associations were not statistically significant when only cohort studies were included,[160,161] suggesting that recall and selection bias might account for some of the findings. The meta-analysis that included both case–control and cohort studies reported reduced relative risks for breast cancer and daily consumption (at least 250 g) compared with less frequent intake of vegetables based on 17 studies (RR 0.75, 95% CI: 0.66-0.85) and found no association with fruits, based on 12 studies (RR 0.94, 95% CI: 0.79-1.11).[159]

More recently, data from a prospective study of 285,526 women between the ages of 25 and 70, participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, did not show any significant association between fruit and vegetable consumption and breast cancer risk.[162]

7.3.3 Phytoestrogens

Phytoestrogens are chemicals contained in plants, which act as oestrogens on animal cells. Phytoestrogens can bind to ERs but are much less potent than some endogenous oestrogens. Thus, they have the potential (similar to tamoxifen) to block oestrogen action; this might reduce risk. However, for postmenopausal women who have low levels of endogenous oestrogens, phytoestrogens could conceivably increase oestrogen action.[50,157] Isoflavones are a class of phytoestrogen contained in soybeans and derived foods such as tofu and miso, and in some legumes. Because these foods are consumed in Asian countries, which have lower rates of breast cancer, the hypothesis that they reduce risk has attracted scientific and popular attention. A recent review of 18 studies reported conflicting findings.[163] Some of the case–control studies and none of the cohort studies showed reductions in risk with increased dietary intake of soy products during adulthood. A few studies have used biomarkers of phytoestrogen intake by measuring compounds in urine or blood serum, but findings from these are also inconsistent. Thus, there is little evidence to support a role for phytoestrogensinfluencing breast cancer risk, at least in adulthood. It is possible that it might be necessary to consume phytoestrogens during adolescence or at very high doses to produce a long-term reduction of breast cancer risk. More research is needed before more definitive conclusions can be drawn.

7.3.4 Other dietary components

Because foods are complex combinations of nutrients, researchers often examine specific components of food to determine their relation to disease risk. A number of vitamins, including A and C, are known to function as antioxidants, and thus might protect against DNA damage that

could result in cancer. A number of studies report that high consumption of various vitamins (including A, C and D either from diet or from supplements) is associated with a decreased risk of breast cancer, but the studies are few and the findings are inconsistent.[164] The B vitamin folate — found naturally in greens such as spinach and broccoli, and foods such as oranges and orange juice, and dried beans and peas — helps to repair damaged DNA within cells, and some small studies have suggested that women who consume more folate have a lower breast cancer risk. A recent meta-analysis concluded that there is no clear support for an overall relationship between folate intake or blood folate levels and breast cancer risk.[165] On the other hand, an adequate folate intake might reduce the increased risk of breast cancer that has been associated with moderate or high alcohol consumption, by counterbalancing the negative effect of alcohol on folate absorption (see also Section 7.4).[165]

It has been suggested that dietary fibre, obtained from vegetables, fruits and wholegrain cereal products, might reduce risk of breast cancer by altering the absorption of oestrogens by the intestines. Studies investigating the association between fibre intake and decreased breast cancer risk have produced conflicting findings. A meta-analysis of 10 case–control studies reported a statistically significant decrease in breast cancer risk with increased intake of dietary fibre (RR 0.85 for 20 g increase per day). In the UK Women's Cohort Study, a prospective study of 35,792 women, high intake of total fibre and in particular fibre from fruit was associated with a decreased risk of breast cancer for premenopausal but not postmenopausal women.[166] Breast cancer risk for postmenopausal women in the top quintile of fibre intake was 52% lower than for women in the lowest quintile (RR 0.48;95% CI: 0.24-0.96). Two other prospective studies did not show any effect of fibre intake on breast cancer risk.[167, 168]

Caffeine is a substance produced by the leaves, beans or nuts of different plants, and is contained in coffee, tea, chocolate and cola drinks. Most studies of breast cancer have shown no associations with intake of caffeine-containing beverages.[50] A recent meta-analysis examined studies of the association between consumption of either green tea or black tea and breast cancer risk.[169] For green tea, the summary relative risk was consistent with a protective effect (highest versus lowest exposure level, RR 0.78, 95% CI: 0.61-0.98) but a protective effect was only observed by one case–control study, whereas the three prospective studies that were included did not show any association. For black tea, the meta-analysis found no association with breast cancer risk (RR 0.98, 95% CI: 0.88-1.09).

7.3.5 Dietary patterns

As nutrients are not consumed in isolation but in a total dietary context, analyses have increasingly focused on dietary intake patterns. Such analyses overcome limitations of the single-food or nutrient approach, including failing to account for interaction between nutrients, intercorrelations between nutrients and the inability to detect small effects of single nutrients. Consequently, dietary patterns may be more strongly associated with disease risk than specific food or nutrients.

Few cohort studies have investigated associations between dietary intake patterns and breast cancer risk. Some have found a protective effect of a diet rich in raw vegetables and olive oil[170] or of a diet characterised by high intakes of traditional rural southern US food.[171] Others have reported increased risk associated with a pattern characterised by high consumption of alcohol[172] and yet others have found no evidence of association between dietary pattern and breast cancer risk.[173]

An intervention trial for postmenopausal women was designed to promote change in dietary patterns, with the goal of reducing total fat intake to 20% of energy and increasing consumption of vegetables and fruit.[174] In more than eight years of follow-up, breast cancer risk for women on the low-fat dietary pattern was not significantly different from that for women who were not in the intervention group (RR 0.91, 95% CI: 0.83-1.01).

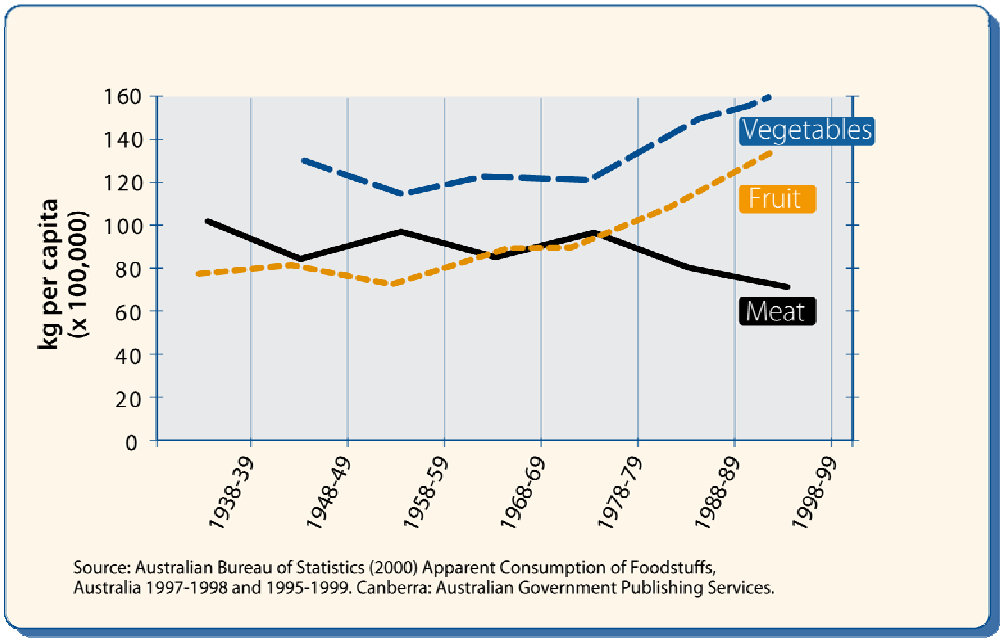
7.3.6 Dietary guidelines in Australia

Current dietary guidelines for Australian adults published by the National Health and Medical Research Council in 2003[175] recommend:

- eating a minimum of five servings of vegetables and two servings of fruits daily
- eating plenty of cereals (including breads, rice, pasta and noodles), preferably wholegrain
- limiting intake of saturated fat and moderating total fat intake by eating lean meat, fish, poultry and alternatives and choosing reduced fat varieties of milk, yoghurts and cheeses or alternatives.

An increase in consumption of vegetables and fruits and decrease in consumption of meat is apparent in Australia (see Figure 6).

Figure 6 Consumption of selected foodstuffs in Australia, 1938–1938 to 1998–1999



Source: Australian Bureau of Statistics (2000) Apparent Consumption of Foodstuffs, Australia 1997-1998 and 1995-1999. Canberra: Australian Government Publishing Services.

7.4 Alcohol

Many studies have reported alcohol intake as a risk factor for breast cancer. A collaborative reanalysis was conducted on individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without breast cancer.[176] Although there was little elevation in risk of breast cancer for low levels of alcohol consumption (ie less than one standard drink per day), compared with women who reported drinking no alcohol, the relative risk was 1.13 for about two drinks per day, 1.21 for about three drinks per day, 1.32 for about four

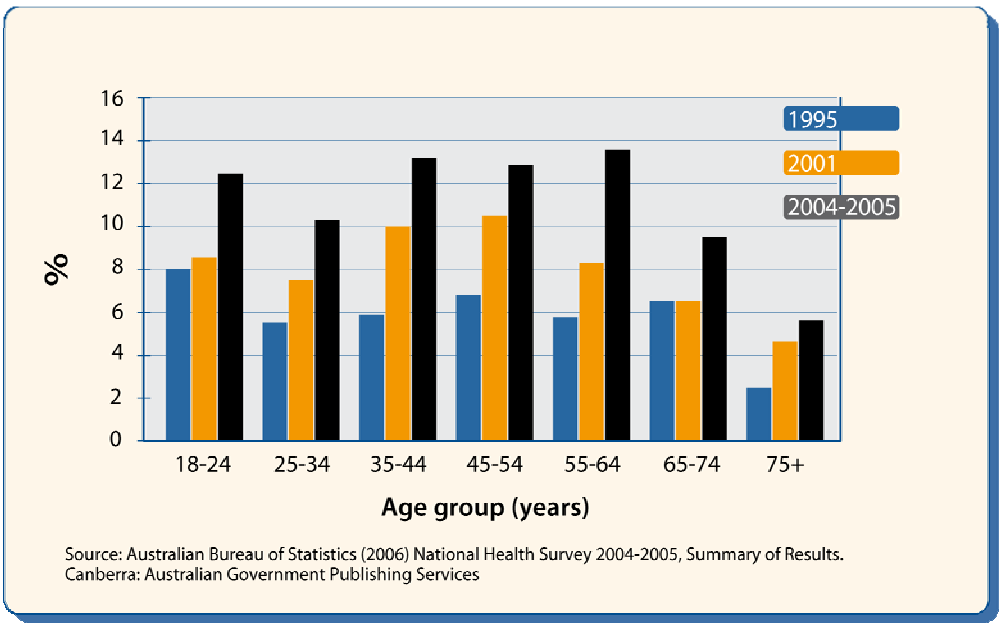
drinks per day and 1.46 for more than four drinks per day. Overall, the relative risk of breast cancer increased by 7% (RR 1.07, 95% CI: 5.5-8.7%) for each additional standard drink per day (ie ~10 g of alcohol per day).

Similar findings were obtained from a pooled analysis of six prospective cohort studies of 322,647 women followed for up to 11 years, including 4335 women with breast cancer.[177] The relative risk for breast cancer increased by 9% (RR 1.09, 95% CI: 1.04-1.13) for every additional standard drink per day. Adjustment for a range of breast cancer risk factors did not modify the findings of either study, and findings differed minimally by study design characteristics.[178] Consumption of beer, wine and spirits and liquor all contribute to the positive association [176-178] Some studies, including EPIC, found that only recent consumption of alcohol, and not lifetime intake, was associated with breast cancer risk. The relative risk for each additional standard drink per day reported by the EPIC cohort of 274,688 women, (RR 1.03, 95% CI: 1.02-1.05) was smaller than those from previous studies.

The mechanism underlying this association remains uncertain. Increased levels of circulating oestrogens and androgens have been suggested as the most likely mechanism.[179] Alcohol might also act negatively on folate absorption and metabolism and evidence from epidemiological studies discussed in Section 7.3.4 suggests that adequate folate intake might mitigate the increased risk of breast cancer associated with alcohol consumption.[165]

In 2004–2005, 54% of Australian women aged 18 or older reported consuming alcoholic beverages in the previous week. In the past 10 years, the proportion of adult women aged under 65 drinking more than two standard drinks of alcohol per day increased from around 6% to 13% (see Figure 7).[122] The average consumption of alcohol in Australia is somewhat higher than the 6 g/day (about half a drink) reported by the pooled analysis.[176] Assuming that the relationship is causal, approximately 2–5% of breast cancers in Australia could be attributed to alcohol consumption.

Figure 7 Percentage of Australian women reporting drinking more than two standard drinks of alcohol per day



Source: Australian Bureau of Statistics (2006) National Health Survey 2004-2005, Summary of Results. Canberra: Australian Government Publishing Services

7.5 Cigarettes

The relationship between cigarette smoking and breast cancer risk is complicated. Epidemiological studies have reported positive, inverse and null associations between cigarette smoking and breast cancer.

At least three critical reviews that examined the published literature on smoking and breast cancer concluded that cigarette smoking might be associated with a small increase in breast cancer risk, particularly for smoking of long duration.[180-182] A meta-analysis of 44 studies published between 1984 and 2001 reported a combined relative risk of 1.10 (95% CI: 1.02-1.18) comparing ever smokers with never smokers.[180] The combined relative risk increased with increasing intensity of exposure (cigarettes smoked per day) and increasing duration of smoking (years). A recent update from a Canadian prospective study including over 89,000 women found that breast cancer risk was associated with the duration (40 years versus 0: RR 1.50, 95% CI: 1.19-1.89), intensity (40 cigarettes per day versus 0: RR 1.20, 95% CI:1.00-1.44), cumulative exposure (40 pack-years versus 0: RR 1.17, 95% CI: 1.02-1.34) and time since commencement of cigarette smoking (40 years versus 0: RR 1.28, 95% CI:1.06-1.55).[183]

Evidence of positive associations between breast cancer and cigarette smoking was also published in a report where non-smoking women who were exposed to passive, second-hand smoke were excluded from the comparison group.[181] In addition, studies suggest that the risk of breast cancer associated with smoking might be increased for premenopausal women[180] or women who started smoking in their mid-teens or earlier, or before their first full-term pregnancy.[180,182-184] Similarly, women who inherited specific variants in genes involved in the metabolism of carcinogens found in tobacco might experience higher risks associated with smoking cigarettes.[181,182,185]

The hypothesis that cigarette smoking is associated with breast cancer risk was not confirmed by Collaborative Group on Hormonal Factors in Breast Cancer, which reported in 2002 the findings from a pooled analysis of data from 53 epidemiological studies that compared ever smokers with never smokers, using 22,255 women with breast cancer and 40,832 controls. Women who reported drinking alcohol were excluded from the analysis to examine the association with cigarette smoking alone. No association was found between smoking and breast cancer risk (RR 1.03, 95% CI: 0.98-1.07).[176]

Tobacco is known to contain a variety of compounds that are carcinogens.[181,182] These are transported by the blood stream to the breast, as shown by studies of fluids expressed from the breast, of adipose tissue surrounding the epithelial cell ducts and of p53 mutations found in breast tissue of smokers compared with non-smokers. Tobacco smoke also has possible “anti-oestrogenic” properties, as suggested by smokers having earlier menopause, lower breast-density measures, higher rates of osteoporosis and lower risks of other hormone-dependent gynaecological conditions compared with non-smokers.[182] If the carcinogenic effects of smoking are counterbalanced by the anti-oestrogenic effects, the result might be no net effect or a very small effect on the overall risk of breast cancer. On the other hand, it is possible in an overall analysis that strong effects might be obscured for important subgroups of women based on the timing of their exposure to tobacco smoke in relation to breast development, or their genetic makeup or exposure to other factors.

Despite years of educational campaigns describing the health hazards of cigarette smoking, one in four Australian adults smoke. Overall, 20% of adult women smoke; but in the 18–34 age

bracket 26% of women are smokers.[122] From 1995 to 2004, the proportion of women aged 18–34 who smoked decreased, but increased for women aged 35–54.[122]

7.6 Summary

In addition to reproductive history and use of exogenous hormones, other lifestyle behaviours are associated with breast cancer risk, often as a consequence of altering levels of either circulating or tissue hormone. With respect to body size, women who are taller than 175 cm have a breast cancer risk 30–40% higher than women shorter than 160 cm. For reasons that are still unclear, obese women (BMI ≥31 kg/m^2) seem to have a premenopausal breast cancer risk almost 50% lower than lean women (BMI <21 kg/m^2). It is also clear that overweight and obese women (BMI >25 kg/m^2) have a postmenopausal breast cancer risk 20–40% higher than lean women (BMI <21 kg/m^2). Regular physical activity appears to decrease postmenopausal breast cancer risk, mainly through weight control. There is limited evidence that physical activity is associated with decreased premenopausal breast cancer risk.

The role of diet in the development of breast cancer is probably less important than for some other cancers (eg head and neck). The evidence regarding an association between high consumption of fat or red meat and increased risk of breast cancer is still limited and the effect, if any, is likely to be small. Women with the highest consumption of fat or red meat would have a breast cancer risk 10–20% higher than that for women with the lowest consumption. It is possible that high consumption of vegetables or fruit is associated with a small decrease in breast cancer risk, but the evidence is limited. Consumption of dairy products appear unrelated to breast cancer risk. Studies have investigated several other foods, beverages, nutrients and vitamins, but the data are either of too low quality, too inconsistent, or based on too few studies to allow conclusions to be reached.

In contrast, drinking alcoholic beverages, whether beer, wine or spirits, is associated with breast cancer risk. For each additional standard drink per day, breast cancer risk increases by around 7%. Intake of folate found in green vegetables such as spinach and broccoli, oranges and other foods can reduce the risk of breast cancer associated with drinking alcohol.

There is no consistent evidence of an association between cigarette smoking and breast cancer risk, but recent research raises the possibility that cigarette smoking might increase risk for subgroups of women defined by stage of breast development when smoking started or by genetic status related to metabolism of carcinogenic compounds in tobacco smoke.

8 Medical history

A variety of diseases, medical treatments and medications have been associated with breast cancer, although frequently the mechanism underlying these associations is poorly understood. The increased risk of breast cancer associated with a previous personal history of breast cancer is discussed here, while breast cancer risk associated with personal history of other breast conditions has been discussed in Chapter 4.

8.1 Prior health conditions

8.1.1 Prior personal history of breast cancer

For women with a prior personal history of breast cancer, the increased risk of developing a second breast primary, compared with the general population, is up to two-fold.[186] The risk seems to be particularly high for women who have their first primary breast cancer before the age of 40, and decreases significantly with increasing age at diagnosis of first breast primary.[186-188] It has been estimated that 2–11% of women diagnosed with breast cancer will develop contralateral breast cancer in their lifetime.[188] Several factors have been investigated in relation to the risk of a second primary breast cancer, including genetic predisposition and family history, reproductive history, histology of the first breast cancer, treatment, anthropometry and race.[189]

Second primary breast cancers are an increasing public health issue because of the increased incidence rates for primary breast cancer, and the increased average length of survival from breast cancer.

8.1.2 Previous cancer other than breast cancer

A recent report on second primary cancers from the Victorian Cancer Registry shows that women with an initial breast malignancy appear to be at increased risk for subsequent cancers of the stomach, uterus, ovary and soft tissue, as well as melanoma of the skin and acute myeloid leukaemia.[190] These findings are consistent with those from a similar survey in the US that also found increased risks for second cancers of the salivary glands, thyroid and oesophagus, and a small increase in the risk of colon cancer.[186] Both the Victorian and American survey reported a decreased risk of lung cancer after breast cancer, and the American survey reported a decreased risk of pancreas and cervix cancer and non-Hodgkin's lymphoma after breast cancer. Some of these decreased risks are probably due to a lower prevalence of tobacco smoking in women with breast cancer. Other associations have been found to be reciprocal; that is, women with an initial cancer at one of these sites are at increased risk of developing a cancer in the breast.[186, 191] Women with a first primary of cancers of the uterus (endometrium), ovary, renal pelvis or ureter, or thyroid, as well as women with a prior history of melanoma of the skin and Hodgkin's lymphoma, are at increased risk for a second primary cancer of the breast. Childhood cancer survivors also appear to be at increased risk of breast cancer.

Shared hormonal influences are assumed to underlie the associations with endometrial and ovarian cancers, despite the fact that risk factor profiles are not always similar. Possible dietary

and hormonal links have been suggested to explain the associations observed with malignant melanoma and colon cancer. However, similar genetic susceptibilities cannot be excluded, because many of these cancers also cluster in families and comprise familial cancer syndromes.

Some studies have shown that premenopausal women with thyroid cancer are 40% more likely to develop breast cancer 5–20 years later than women without thyroid cancer (RR 1.42, 95% CI: 1.19-1.67) but the same was not true for postmenopausal women (RR 0.97, 95% CI: 0.80-1.17).[192] However, since not all reports show an increased risk of thyroid cancer following breast cancer,[186] it is possible that treatment for thyroid cancer, which involves use of radioactive iodine, is the relevant exposure influencing breast cancer risk, rather than the disease itself.

For women treated for Hodgkin's lymphoma, breast cancer is the most common second malignancy.[186,193] For women diagnosed with Hodgkin's lymphoma at age 60 or more, breast cancer risk is up to two-fold that of the general population, and increases to more than four-fold for women diagnosed with Hogkin's lymphoma at age less than 30.[186,194] When diagnosed with breast cancer, women with prior Hodgkin's lymphoma were more likely to be younger than the average breast cancer patient, and to have bilateral disease. The excess breast cancer risk associated with Hodgkin's lymphoma appears to be lower for patients receiving new treatment regimens.[194]

8.1.3 Non-insulin dependent diabetes mellitus

Non-insulin dependent diabetes (or type 2 diabetes mellitus), subclinical diabetes or hyperinsulinemia with insulin resistance have been implicated as potential risk factors for breast cancer, generally showing rather modest increases in risk (~20%) that are independent of body weight.[50]

It has been hypothesised that hyperinsulinemia is associated with increased risk of breast cancer because excessive levels of insulin in circulation would promote cell growth in breast tissues and increase circulating levels of oestrogens, testosterone and insulin-like growth factors.[195] A meta-analysis including five case–control studies and 15 cohort studies that had been published up to the beginning of 2007 showed that breast cancer risk for women with diabetes mellitus was 20% higher than for women without diabetes mellitus (RR 1.20, 95% CI: 1.12-1.28). The summary estimates were similar for case–control and cohort studies.[196]

The association between hyperinsulinemia and breast cancer risk represents a public health challenge, due to the high and increasing prevalence of insulin resistance in most developed countries, including Australia. However, it would also represent a modifiable risk factor that could be controlled by physical activity and weight control.

8.2 Medications

8.2.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) include aspirin and other medications used to reduce pain associated with headache, arthritis, menstrual cramps, etc. They are available in a range of strengths and are available by prescription, pharmacist release or purchase "over the counter".

Aspirin and NSAIDs are thought to influence breast cancer risk by blocking cyclooxygenase (COX) a major enzyme involved in the body's inflammatory response. The expression of COX is abnormally high in breast cancer, and it is hypothesised that it plays a role in tumour growth and in angiogenesis.[197] It is therefore conceivable that aspirin and NSAIDs could reduce the risk of developing breast cancer. Aspirin might also have a preventive effect because of its antioxidative properties, or because it can modulate oestrogen biosynthesis.[197]

Studies that have investigated the possible association between NSAIDs and breast cancer risk have been summarised by two meta-analyses that have each reported an approximately 20% reduced risk of breast cancer with regular use of aspirin or other NSAIDs.[198,199] Similar findings were observed for cohort studies and for case–control studies using either general population controls or controls with diagnoses other than cancer. The definition of regular use varied across studies, but generally involved at least two tablets per week for some extended period of time. In the most recent cohort studies, the evidence of an inverse association between use of NSAIDs and breast cancer risk is less convincing. Some studies did not find a protective effect of NSAIDs or aspirin use,[200-202] one reported a protective effect associated with long-term moderate use, but an increased risk associated with frequent use of high doses,[202] one reported a protective effect only for current long-term users of NSAIDs,[203] one found an increased risk of breast cancer for NSAID users.[204]

Data from a randomized controlled trial showed that low-dose aspirin administered every other day for an average follow-up of 10.1 years was not associated with a reduced risk of breast cancer (RR 0.98, 95% CI: 0.87-1.09), or cancer at any other site.[197]

8.2.2 Antidepressants

Prescriptions for antidepressant medications have increased dramatically in the past two decades. As a consequence, evidence from animal studies that some antidepressants increase mammary tumour growth raised concern about the potential effect of antidepressant use by women. The two agents of greatest concern are known as tricyclic antidepressant (TCAs) and selective serotonin reuptake inhibitor antidepressants (SSRIs). A number of studies have been published in the past few years on antidepressant use and breast cancer, but so far epidemiological data have shown conflicting and inconsistent findings for any association between antidepressant use and breast cancer risk.[205] Some studies suggested a possible increased risk of breast cancer associated with the use of antidepressants possibly due to increased levels of prolactin. Other studies did not find any evidence of increased breast cancer risk regardless of duration of use, daily dose and type of drug used (SSRIs, TCAs).

Due to inconsistencies in findings across studies, limited availability of data on specific formulations and relatively short follow-up for SSRIs (which have become increasingly used during the past 10 years), continuing research is necessary. In addition, it will be important to try to determine whether any observed associations are due to the medication used or the underlying condition for which it was prescribed and other possibly associated behaviours.

8.2.3 Infertility drugs

Women with infertility now may choose to undergo treatment with a range of medications designed to stimulate ovulation and to alter levels of endogenous reproductive hormones. The use of fertility drugs has become increasingly frequent for infertility treatment over the past 30

years and research about the association between their use and breast cancer risk is only now becoming available.

Epidemiological studies published to date have reported contradictory findings. Most studies have found no association between use of fertility drugs and risk of breast cancer, two studies found that fertility drugs increased the risk of breast cancer, whereas two other studies found that use of fertility drugs decreased the risk.[206] A recent report from a Danish cohort study reported no association between breast cancer risk and use of fertility drugs[206] but a recent update of the findings showed that breast cancer risk for this cohort of 54,362 infertile women was slightly higher than for the general female population of Denmark after adjusting for age and parity (RR 1.08, 95% CI: 1.01-1.16).[207] This association could be explained by a small effect of infertility drugs or by a genetic/biologic susceptibility shared by this group of infertile women.

Although presented here because of potential interest, it is generally considered too early to confirm an association between treatment for infertility and breast cancer risk.

8.2.4 Antibiotics

There is little evidence to implicate the use of antibiotics in the aetiology of breast cancer. A Finnish cohort study of 9633 women explored self-reported use of antibiotics for bacterial urinary tract infections and estimated an increased risk of breast cancer for women younger than 50 years (RR 1.74, 95% CI: 1.13-2.68).[208] There was no association between breast cancer risk and use of antibiotics for urinary tract infections by women 50 or older. A case–control study of 2266 women with breast cancer and 7953 control women was conducted in the Seattle area of the US[209] and reported statistically significant increased risks of breast cancer with use of antibiotics (RRs ranging from 1.5–2.3, depending on whether analyses used the number of days treated or the number of prescriptions). Findings were consistent for all types of antibiotics under study with evidence of a dose response relationship. In a study of 3099 breast cancer cases and 12,396 matched controls using the Saskatchewan Prescription Drug Plan (Canada) the incidence of breast cancer was higher for subjects who had more antibiotic prescriptions during the 1 to 15 years prior to the index date (RRs 1.50, 1.63, 1.71 and 1.79 for the four quartiles, respectively, p trend = 0.0001). However, the authors conclude that the lack of temporal trends and the absence of class specific effects suggest a non-causal relationship between antibiotics and breast cancer risk.[210] Other studies have not or at most only weakly supported increased risk of breast cancer following antibiotic use.[211]

It is premature to draw conclusions about the relationship, if any, between use of antibiotics and breast cancer risk. There were important limitations noted within the studies. However, researchers remain interested in the possibility of an association because it is considered biologically plausible. Antibiotics might disrupt the natural intestinal microflora, thereby altering metabolism of endogenous oestrogens and/or phytoestrogens from food, or they might have effects on the immune system and inflammatory responses.[212] Also, there are a range of antibiotics to consider which might affect breast cancer risk in different ways and it will be important to separate the effects of the antibiotics from the effects of the condition for which the antibiotics are used. This will be an active area for further research.

8.2.5 Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic form of oestrogen that was administered to several million pregnant women in the United States, Europe and Australia to prevent spontaneous abortion and premature delivery between the early 1940s and early 1970s. when a strong association was reported between in utero exposure to DES and clear cell adenocarcinoma of the vagina and cervix in young women.[213] Animal studies suggested that the teratogenic and carcinogenic effects of prenatally administered DES might be due to changes in the expression of genes involved in the development of the reproductive tract.[214]

In the early 1990s, the National Cancer Institute assembled new and previously established cohorts of women exposed in utero to DES and unexposed women for combined follow-up (DES Combined Cohort Follow-up Study). Baseline findings limited to analysis of the previously established cohorts showed DES was associated with an excess risk of clear cell adenocarcinoma and possibly with elevated breast cancer risk for older women.[215] More recent follow-up of the cohort for breast cancer incidence showed that after age 40, daughters of women who took DES during pregnancy had an increased risk of breast cancer compared with unexposed women but the estimate was based on a relatively small number of cases (RR 1.8, 95% CI: 1.1-3.2).[216]

The findings support the hypothesis that prenatal DES exposure influences breast cancer risk. The increase in risk for mothers who took DES is around 30% and does not appear to depend on age.

8.3 Summary

Breast cancer risk has been associated with the diagnosis of or treatment for a range of medical conditions. For women with a prior personal history of breast cancer the increased risk of developing a second primary in the breast compared with the general population is up to two-fold. Women with a first primary cancer of the uterus (endometrium), ovary, renal pelvis/ureter and thyroid and women with a prior history of melanoma of the skin and Hodgkin's lymphoma have an increased risk of a second breast primary. Childhood cancer survivors appear to be at increased risk of breast cancer. The increased risk of breast cancer following Hodgkin's lymphoma, about three to four-fold compared with the general population, appears to be restricted to women treated for Hodgkin's lymphoma with radiotherapy before the age of 40 years. A history of non-insulin dependent diabetes or insulin resistance also has been associated with an increased risk of breast cancer.

The effect of regular use of aspirin or other NSAIDs on the risk of breast cancer is unclear and further trials are underway to examine this question more fully. No association between breast cancer and antidepressant use has been established. It is possible that infertile women are at a slightly increased risk of breast cancer but it is still unclear whether drugs used to treat infertility increase that risk. Findings that prolonged or recurrent use of antibiotics, or the conditions for which they are used, are associated with increased risk of breast cancer require confirmation by further large studies before any conclusions can be drawn. Finally, in utero exposure to DES increases the risk of breast cancer by 80% for women older than 40 years of age and for mothers who took DES during pregnancy by 30%.

9 Environmental exposures

The rising incidence of breast cancer during the 20th century, as well as distinct geographic patterns of risk, with migrants and their offspring gradually assuming risks characteristic of their adopted homelands, support the notion that environmental exposures contribute to the development of breast cancer. Some of these trends might be due to differences in lifestyles or other personal behaviours. Exposures that are generally more under individual control, for example exogenous hormone related exposures, diet, alcohol consumption and cigarette smoking, have been addressed in previous sections. Many of these are considered "environmental" exposures to the extent that they are non-genetic. This section addresses exposures that occur in the environments surrounding our homes, work and leisure activities.

9.1 Radiation

9.1.1 Ionising radiation

The term radiation indicates the emission of energy in the form of waves or particles. Radiation powerful enough to remove electrons from atoms is termed ionising. Examples of ionising radiation are X-rays from medical machines and gamma rays from radioactive substances. Ionising radiation is an established cause of breast cancer, with evidence from studies of atomic bomb survivors, women exposed to radiation for medical purposes related to diagnosis or treatment of health conditions and women working with radiation in occupational settings.[47, 50] Generally, the risk of breast cancer increases with higher doses (dose–effect relationship) and with earlier age at exposure. Breast cancer risk associated with ionising radiation appears to be highest for exposure before age 20, particularly during infancy, childhood and puberty. In contrast, exposure at ages older than 40 or 45 years appears associated with a small, if any, excess risk. Young children exposed to high doses of ionising radiation do not show a detectable elevation in breast cancer occurrence for some 35 to 40 years after exposure. The time between radiation exposure and breast cancer development is shortest for older women, with a minimum of five to 10 years. For high-level exposures (mean dose of 0.4–2.5 Gray), the relative risk for breast cancer has been estimated at 1.4 to 2.2. Much of the research about ionising radiation and breast cancer risk is based on historical exposures, as increased awareness of health risks associated with ionising radiation has led to improved workplace conditions and changes in medical practice and technology.

Commonly performed medical procedures, such as chest radiography and mammography, result in very low exposure to ionising radiation (mean doses to breast tissue around 0.002–0.0002 Gray). The effect of exposure to such low-dose radiation, if any, is likely to be very small.

A study of women carrying mutations in BRCA1 and BRCA2 raises the possibility that some subgroups of women are at higher risk of ionising radiation exposure because of increased susceptibility due to inherited variants in genes involved in DNA repair.[217] Further research is needed in this area to confirm and extend these findings to variants in other genes of similar function.

9.1.2 Electromagnetic fields

Electromagnetic fields (EMFs) are invisible areas of low energy that result from the flow of electric current. Sources include power lines, electric appliances, radio waves and microwaves, among others. It is also called electromagnetic radiation. Associations between exposure to EMFs and a number of cancers have been reported, but, to date, a causal link has not been established. The scientific literature on EMFs exposure and breast cancer risk was reviewed by the International Agency for Research on Cancer (IARC), in 2002[218] and updated in 2006 in a review paper that concluded that the weight of the evidence available today does not suggest an increased risk of breast cancer related to EMF exposure.[219]

Some early studies suggested effects for premenopausal women, particularly for ER positive breast tumours. These studies were often limited by small numbers of cases, crude exposure information and lack of information on confounding factors.[220] Epidemiological research about the health effects of electromagnetic fields is generally based on studies investigating high levels of exposure in occupational settings. Research about breast cancer is therefore limited because of the rarity of women in electrical occupations. An alternative to occupational studies is studies of residential exposures (eg from transmission lines) but these exposures are difficult to determine and the findings of these studies are conflicting.

9.2 Light at night and night shift work

An emerging issue in breast cancer is the role of disruption of the daily sleep/wake cycles (i.e. circadian rhythm) in increasing the risk of the disease. Experimental studies show that melatonin, a hormone produced primarily at night, inhibits cancer cell grow in rats and a growing number of epidemiologic studies show that night workers have lower nightly melatonin levels.[221] This leads to hypothesise an association between shift or night work and cancer risk.

The possible association between high melatonin levels measured in urine samples and decreased breast cancer risk was investigated in four case–control studies nested in prospective cohorts.[222-225] Three of them supported the hypothesis[222-224] and one reported no association.[225] A few studies investigated breast cancer risk for night shift workers.[226-229] A record-linkage case-control study of Danish employees and a case-control study from Seattle, U.S. found an association between night shift work and increased risk of breast cancer[226,227] while a recent record-linkage study of Swedish workers found no association.[229] A major limitation of the American study was the retrospective case-control design while the major limitations of the two record-linkage studies were the imprecise classification of the exposure based on grouped data and job classifications and the lack of data on some potential confounders. An analysis of the U.S. Nurses' Health Study, a prospective cohort study of more than 115,000 nurses that were asked how many years in total they had worked rotating night shifts with at least three nights per month found that nurses who reported more than 20 years of rotating night shift work had an 80% increase in breast cancer risk compared with nurses who did not report any rotating shift work (RR 1.8; 95% CI: 1.1-3.0).[228] This analysis found that there was no association with breast cancer risk for fewer years of rotating night work. A few other studies reported associations between occupations with typical shift work and breast cancer risk but they were designed for other purposes than evaluating the association with night shift work and information on exposure and potential confounders was very limited.

On the basis of the current evidence the International Agency for Research on Cancer Expert Working Group concluded that "shift work that involves circadian rhythm disruption is probably

carcinogenic to humans".[230] This conclusion was based on consistent and substantial evidence from experimental animal studies that constant light at night and simulated chronic jet lag can increase cancer incidence but there is still limited evidence of an association with increased breast cancer risk in humans.

9.3 Chemicals

9.3.1 Environmental tobacco smoke (ETS)

In addition to personal smoking habits (addressed previously in section 7.5), exposure to environmental tobacco smoke (ETS; also known as second-hand or passive cigarette smoke) has also been investigated with respect to breast cancer risk. Although it might seem counterintuitive for a causal relationship to be entertained for exposure to ETS when the evidence is considered inconclusive for exposure to active smoking, the hypothesis is plausible. Sidestream smoke contains a cocktail of potential carcinogens in much greater concentration than direct smoke, because of incomplete combustion when tobacco burns at a lower temperature (eg when not being inhaled) and because exposure to ETS is unfiltered. Also, the anti-oestrogenic effect of active cigarette smoking might not occur with ETS, hence no counterbalancing takes place against the carcinogenic effects. This could have important implications for the majority of women who are not current smokers but who find themselves exposed to ETS at home, work or during leisure activities.

In late 2003, a report by the California Environmental Protection Agency declared ETS a toxic air contaminant associated with a range of developmental, respiratory, cardiovascular and cancer conditions; the Agency judged ETS to be a cause of breast cancer.[231] The evidence for an association between ETS and breast cancer had been mounting for the past decade.[181,231,232]. Based on 11 epidemiological studies of exposure to ETS, the combined relative risk for breast cancer was 1.41 (95% CI: 1.14-1.75).[232] Higher estimates were obtained from six studies with more complete information on ETS exposure, such as childhood residential, adult residential and occupational sources, providing a combined relative risk for breast cancer of 1.92 (95% CI: 1.54-2.39).[231] The association was stronger for premenopausal women: RR 2.20 (95% CI: 1.70-2.85). A recent report suggests that passive smoking is associated with an increased risk of premenopausal breast cancer and that this risk might be influenced by underlying genetic susceptibility.[185]

The evidence of an association between ETS and breast cancer risk weakened significantly when a large prospective study of 224,917 never smokers participating in the UK Million Women Study showed that breast cancer risk for women who reported passive exposure to smoking was similar to the risk for women not exposed (RR 0.98, 95% CI: 0.88-1.09).[233] This report also included a meta-analysis of published studies on passive smoking that showed that the increase in risk reported in previous studies was mainly limited to retrospective studies that are more prone to bias, ie differential recall of exposure between cases and controls compared with prospective studies.

9.3.2 Environmental pollutants

More than 200 chemicals have been shown in animal studies to damage DNA, promote tumour development and growth, or alter mammary gland development.[234] These chemicals include benzene from gasoline, polychlorinated biphenyls used as coolants, insulating fluids and additives, dioxins, by-products of incineration and manufacturing processes, organic solvents, drinking water disinfection by-products, some pesticides such as DDT and DDE and polycyclic aromatic hydrocarbons. Epidemiological and occupational studies with respect to chemicals and breast cancer risk have been recently reviewed by Brody et al.[235]

Polychlorinated biphenyls DDT and DDE are by far the most studied environmental pollutants in relation to breast cancer risk. Polychlorinated biphenyls were produced commercially in large quantities up until the late 1970s when their importation for most purposes was banned in Australia. Twenty-seven case–control studies and nested case–control studies have examined associations between polychlorinated biphenyls and breast cancer risk and have produced inconsistent findings.

Tetrachlorodibenzo-p-dioxin is classified by the IARC as a human carcinogen. Studies have investigated the risk of cancer in residents of the region around Seveso, Italy exposed to tetrachlorodibenzo-p-dioxin after an industrial accident in 1976, in residents of the region around Chapaevsk, Russia contaminated by a chemical plant and workers exposed to tetrachlorodibenzo-p-dioxin during the production of herbicides. The only statistically significant association was found for women living near the chemical plant in Chapaevsk who were reported to have a two-fold increase in breast cancer mortality compared with women living in surrounding regions. A major problem with this study and with occupational studies generally, is that any association with breast cancer might be due to other chemical and occupational exposures. Women exposed to high doses of dioxin from the Seveso accident did not show an excess risk of breast cancer or breast cancer mortality but to date the number of breast cancer cases and deaths recorded in the cohort is very small.

Twenty-five reports from case–control studies and nested case–control studies published between 2000 and June 2006 examined associations between serum or adipose levels of DDT or DDE and breast cancer. Although a few studies showed elevated risks, most did not support an association between DDE and breast cancer overall or when stratified by menopausal status, tumour hormone receptor status, parity, breastfeeding, or body mass index.

Polycyclic aromatic hydrocarbons are products of combustion. Major sources of exposure for general populations are smoking, air pollution, auto exhaust, diesel and diet, including smoked and grilled foods and foods such as grains that are contaminated by ambient air pollution. The Long Island breast cancer study found that the prevalence of markers of DNA damage induced by polycyclic aromatic hydrocarbons was slightly higher for breast cancer cases than for controls but these markers were measured after diagnosis of the cases and might not be relevant to determine the causes of the disease. Although a few studies using indicators of industrial and traffic density, occupational exposure to gasoline and vehicular exhaust and high consumption of meat cooked at high temperature reported small elevations in breast cancer risk for exposed versus unexposed women, an effect on disease risk, if any, cannot be attributed to polycyclic aromatic hydrocarbons.

9.4 Limitations of the literature

Epidemiological studies of environmental exposures are extremely challenging to conduct, because of difficulties in exposure assessment and for many pollutants, finding women who are unexposed. Although workplace exposures represent a high-dose model and are easier to study, relatively few studies include women because they are underrepresented in the workforces of relevant industries. Moreover, new findings relevant to environmental epidemiology of breast cancer, including possible associations with metals, cosmic or solar radiation and viral infections, require additional research before even preliminary conclusions can be drawn.[235,236] We are thus in the very early days with respect to understanding the role of environmental chemicals and other agents in the development of breast cancer.

9.5 Summary

Research about relationships between environmental exposures and breast cancer risk is more difficult than research about exposures related to individual lifestyle, the main difficulty being exposure assessment.

To date there is evidence that exposure to high doses of ionising radiation increases the risk of breast cancer, while exposure to low-dose radiation from sources including medical machines is likely to have a small effect, if any. Avoidance of unnecessary medical X-rays is one of the best ways to reduce exposure to ionising radiation but in many instances, the benefits outweigh the risks, as in mammographic screening for the early detection of breast cancer for women aged older than 50 and for women at high risk of breast cancer; as a tool for diagnosis of various diseases or injuries and as an effective way to treat some cancers.

There is no convincing evidence that exposure to electromagnetic fields, including radio waves, is associated with breast cancer risk.

A number of epidemiologic studies show growing evidence of an association between high melatonin levels and decreased breast cancer risk. On average, night shift workers have lower melatonin levels but there is still limited evidence to support the hypothesis that night shift workers have an increased risk of breast cancer. The strongest evidence comes from a cohort of American nurses but the reported association is limited to more than 20 years of shift work and relatively modest and imprecise (RR relative to women who did not report any shift work = 1.8; 95% CI: 1.1-3.0). This finding needs to be replicated in other professions and in other large cohort studies with accurate and detailed information on both shift and night work and with extensive data on potential confounders.

For virtually all chemicals investigated to date there is no convincing evidence of an association with breast cancer risk, nor is there convincing evidence that passive smoking is associated with breast cancer risk. To investigate the possible role of chemicals classified as carcinogenic, or potentially carcinogenic, it is necessary to conduct large, well-designed studies with longer follow-up of existing cohorts of women exposed to high doses of environmental pollutants.

10 Psychosocial stressors

A link between psychosocial stress and cancer is biologically plausible, since stress might induce disturbances in the immune system that might increase predisposition to malignant growth.[237,238] It is also considered that psychosocial factors might influence hormone levels or the nervous system, either directly or indirectly, through changes in behaviours such as diet, exercise, sleep, etc.[239] Nevertheless, the epidemiological evidence for an association between psychosocial stress and breast cancer risk is weak.

The NBOCC supported a systematic literature review that included 38 studies, seven methodological articles and 13 review papers about the relationship between psychosocial factors and risk of breast cancer.[239,240] The findings from this review and from more recent studies are summarised below in three categories: life events, short-term coping with life events and long-term emotional and personality factors.

10.1 Life events (either positive or negative)

Life events are considered occurrences, positive or negative, that disrupt normal life activities over a prolonged period of time. Examples of life events include marriage, birth of a child, moving house, loss of a job, or death of a loved one. Overall, the 17 studies reviewed did not support a significant association with breast cancer risk, although few studies had followed sufficiently rigorous methods. To assess life events, most investigators attempted to count the number and type of stressful events and to obtain an objective or subjective rating of their intensity. Most studies reported no difference in the number of life events experienced by women with and without breast cancer. Two small studies using one particular scale, the Brown and Harris Life Events and Difficulties Scale (LEDS), reported an association between severe life events and breast cancer risk. The only other studies to report an association between significant life events and breast cancer risk had significant design flaws to the extent that the reviewers considered their findings invalid.

The relationship between stressful life events and breast cancer risk has also been evaluated in a meta-analysis including several studies published between 1966 and 2002. Overall, the meta-analysis did not find a significant association between stressful life events and breast cancer risk. Only a modest association was observed between death of spouse and breast cancer risk (OR = 1.37, 95% CI 1.10–1.71).[241] The meta-analysis went on to report evidence of publication bias with small studies reporting evidence of association that were not confirmed by larger studies.

10.2 Short-term coping with life events and social support

Coping refers to the efforts made to reduce external and internal demands and the conflicts amongst them, whereas social support is generally defined in terms of the number or availability of trusted individuals within one's social network. The evidence for an influence of short-term coping with life events and the development of breast cancer was sparse and inconsistent. The reviewers concluded it was unlikely that this factor played a significant role in determining breast cancer risk. There also was no evidence from the studies reviewed that social support had a significant impact on breast cancer risk.

10.3 Long-term emotional and personality factors

The studies exploring long-term emotional and personality factors were classified into one of three categories, as follows:

10.3.1 Emotional repression/alexithymia/low "type A" behaviour

The association between breast cancer risk and emotional repression, particularly of anger, was uncertain. Six of 13 studies reported no association between breast cancer and anger repression, self awareness or absence of "type A" personality. This "type A" personality is commonly defined as including characteristics such as being impatient, excessively time conscious, insecure about one's status, highly competitive, hostile and aggressive and incapable of relaxation. However, seven studies reported an association between breast cancer and emotional factors. Three of these studies were considered to be of high quality. These findings suggest that repression of anger might be a breast cancer risk factor, particularly for women younger than 50 years.[239] On the other hand, a study reported that emotional repression, including suppression of anger, was not associated with breast cancer for a large group of women attending a mammography screening clinic in Australia.[242] Results from the Melbourne Collaborative Cohort Study suggest that anger control and negative affect are not associated with breast cancer.[243]

10.3.2 Chronic anxiety and depression

Few studies measured negative emotions and life events together, so it was difficult to separate independent and interdependent effects. Evidence for a link between breast cancer and chronic anxiety and depression was poor.[239]

10.3.3 Other personality features

Breast cancer risk has been studied in relation to a range of other personality traits, including extroversion/introversion, authoritarianism, dependence, external locus of control, religiosity, commitment and a tendency to behave in socially desirable ways. All were found to be unrelated to breast cancer risk. Two of seven studies reported significant findings: rationality/anti-emotionality (mistrust of feelings) was associated with a small increase in risk in one study. The other finding was that women with excessive self-esteem, unresolved recent grief or a hysterical disposition were more likely to develop breast cancer, although these psychological ratings were based on subjective judgements with no inter or intrarater reliabilities reported. None of these features is currently accepted as a breast cancer risk factor.

10.4 Stress and breast cancer risk

The majority of studies have investigated associations between stressful life events and breast cancer risk, but only a few have looked at the effect of stress itself.

A Swedish cohort of 1462 women aged 38–60 and followed up for 24 years found that women who reported experience of stress had an almost doubled risk of breast cancer.[244] The opposite conclusion was reached by the Copenhagen City Heart Study, which included 6689 mostly

postmenopausal women and showed that women with a high level of stress had a 40% lower risk of breast cancer compared to women with a low level of stress.[245] Another prospective study of 10,519 Finnish mainly premenopausal women followed for 20 years published a null association between self-reported stress related to daily activities and breast cancer risk.[246]

The association between stress at work and breast cancer risk has been studied in two large prospective studies. In the Nurses' Health Study, no increased risk of breast cancer was found to be associated with stress from care-giving or job strain, defined as the condition of simultaneous high demands and low control at work.[247,248] Recent findings from the prospective Swedish cohort of the Women's Lifestyle and Health Cohort Study reported a small increased risk of breast cancer for women in full-time employment who experienced job strain, but not for part-time workers.[249]

10.5 Limitations of the literature

Reports published before the late 1980s were often produced by methodologically flawed studies. For example, psychological factors were generally assessed after a diagnosis of cancer had been given and hence no distinction between cancer related and pre-cancer factors could be made. Some studies addressed this problem by interviewing women while under investigation for breast cancer and before they knew their diagnosis. It is possible, however, that women subsequently diagnosed with breast cancer had more pre-test cues that a cancer diagnosis was likely (eg age, family history of breast cancer or physical symptoms) than those with benign disease.

Additional problems found in early papers included a failure to deal adequately with the confounding effects of non-psychosocial factors, the most important of which was age. Older women have had more time to experience severe life events and might be more depressed, or conversely, they might be less emotionally volatile. In addition, the effects of psychosocial factors might differ between younger and older women. Finally, despite the clear inter-relationships among the psychosocial factors investigated, they were rarely measured together.

A small number of prospective studies have investigated the association between stress itself and breast cancer risk, but the lack of consistent data and biological plausibility of an association limits the interpretation of the findings.

10.6 Summary

Evidence for a relationship between psychosocial factors and risk of breast cancer is very weak. Findings with regard to emotional repression, especially of anger and the loss of a significant other, reported to be associated with breast cancer risk by some studies were not confirmed by others. The majority of studies have investigated associations between stressful life events and breast cancer risk but only a few have examined stress itself and their findings were inconsistent. On the other hand, few studies have been performed with sufficient rigour to definitively rule out a minor role for psychosocial stressors.

11 Other possible causes

A variety of other possible risk factors have captured the attention of the media and breast cancer survivors themselves. We address several of these below.

11.1 Bras

The wearing of bras, particularly underwire types or those that fit tightly, has been proposed to increase risk of breast cancer. Two anthropologists made this claim in a book called *Dressed to Kill,* which describes a study they conducted.[250] A number of websites have also promoted this hypothesis, which is based on a theory that bras cause physical constriction that reduces lymphatic circulation, resulting in the retention of carcinogenic toxins. However, the anthropologists' study fails to meet current scientific standards for rigorous hypothesis testing. To date, there have been no scientifically valid studies that support the claim that wearing bras causes breast cancer.

The association between breast cancer risk and bra cup size has been discussed in Chapter 7.

11.2 Silicone breast implants

Concerns about the safety of silicone breast implants were raised in the early 1990's. Epidemiological evidence has indicated breast implants do not lead to increased risk of breast cancer.[50,253] Some studies reported decreased breast cancer risk, which may reflect favourable breast cancer risk profiles of women who tend to undergo breast augmentation.[50]

Breast implants were cleared of causing ill health by a UK Government review in 1998.[254]

More recent data from large studies, including extended follow up for almost four decades,[266] provide no evidence of increased risk of breast cancer for women with breast implants.[255-257, 267] In 2011, the FDA released a report about a possible association between breast implants and a very rare type of cancer (anaplastic large cell lymphoma).[268] There were 34 cases identified worldwide in the literature[268] and this is an area of ongoing research interest.

11.3 Underarm deodorant

Articles in the press and on the internet have reported the possibility of underarm deodorants or antiperspirants increasing the risk of breast cancer.

Some toxicologists have reported that these products involve a variety of chemical constituents, including some with oestrogenic and other hormone activity.[258,259] In particular, it is asserted that the aluminium salts used as the active antiperspirant agent in underarm cosmetics are capable of interfering with oestrogen action and that their absorption is facilitated by shaving.[260,261] The biological activity of the chemicals is stronger when absorbed through the skin than by other routes. Moreover, evidence of the presence of these compounds has been detected in tissue samples of breast tumours.[262] The high proportion of carcinomas arising in the upper outer quadrant of the breasts is argued to support the hypothesis that underarm cosmetics cause breast cancer; however, it might be a reflection of the greater amount of breast tissue in this quadrant.[263]

There is no conclusive evidence of an association between underarm deodorants and breast cancer risk. The first study evaluating this hypothesis showed no association between breast cancer and current antiperspirant or deodorant use.[264] In another report, frequency and earlier onset of antiperspirant/deodorant usage with underarm shaving were associated with an earlier age of breast cancer diagnosis for women diagnosed with breast cancer.[261] Because studies of antiperspirants and deodorants and breast cancer risk are so limited and have provided conflicting findings, further work is needed to clarify this relationship.

11.4 Summary

The evidence to date does not support a link between breast cancer and wearing a bra, using silicone breast implants, or underarm deodorants or antiperspirants.

12 What does this mean for the individual woman?

Epidemiological analyses describe population averages. While our statistical models can tell us quite accurately that the average five-year risk in a group is 2% (or, equivalently, that two women out of 100 with a certain profile will develop disease in five years), our models and knowledge of the risk factors cannot tell us which two women will be affected. A statistical model of probability will tell us with great accuracy that, if we flip a coin 1000 times, we can expect very close to 500 heads, but the model can tell us nothing about the outcome of a single flip (where we have a 50% chance of being right or of being wrong). Similarly, most statistical models in epidemiology are very good at providing information on group averages but cannot speak to the individual level.

Knowledge of risk factors might provide accurate information about an individual's future if the risk factors are associated with very large increases in risk above the "background" risk. Relative risks in the order of 50 or higher comparing exposed to unexposed are usually necessary to allow fairly accurate prediction of individuals' futures.[265] For example, knowledge of a high-risk genetic mutation, as in BRCA1 or BRCA2, allows for a more informed (although not nearly perfect) prediction that a woman might develop breast or ovarian cancer sometime in the future and might consider prophylaxis. (Note that the flip side is not true — knowledge that a woman does not have such a mutation does not allow for accurate statements that a woman will not get breast cancer.)

There are not many breast cancer risk factors with such high relative risks as BRCA1/2, and those few that have been found (eg high doses of ionising radiation to the chest during puberty) are very rare in terms of their prevalence in the population. After decades of epidemiological research into breast cancer, a consistent picture of the underlying biology is emerging. But the measurable risk factors thought to convey information on the underlying biology (that is, on lifetime exposure to endogenous oestrogens and other hormones) are associated with only modest increases in risk. This is because they are probably relatively poor surrogates of the true exposures of interest. Most breast cancer risk factors have relative risks in the range of 1.5–2.0 comparing exposed to unexposed women, far from the relative risks of 50 or greater needed to allow individual-level discrimination and accurate screening and targeting.

In addition to being associated with only modest relative risks, most of the established breast cancer risk factors, especially the reproductive factors, have been defined by scientists in such a way that a large proportion of women in developed countries such as Australia have at least one. For instance, many women either have had menarche before age 13; have had their first child after age 30; are nulliparous; or have at least one female relative with the disease. In other words, the established breast cancer risk factors, at least as they are conventionally defined, are highly prevalent. This means that:

- most women who do get breast cancer look very much like those who remain free from the disease, in terms of their risk factor profile
- the majority (90% or so) of women with established breast cancer risk factors (excepting the high-risk genetic mutations) will remain free from the disease for their lifetime
- knowing a woman's status on the established reproductive and lifestyle risk factors does not convey much information about her future with respect to breast cancer.

Many of the risk factors for breast cancer, including some of the strongest, are not readily modifiable; for example, age, family history of breast cancer, genetic status. Others, although potentially modifiable, might require choices that compromise life goals or other important considerations related to how a woman lives her life, for example, whether or not to have children, how to manage fertility, how long to breastfeed for, how much alcohol to drink. Making this even more complex is the fact that some modifiable risk factors for breast cancer are actually beneficial for other health conditions, suggesting the necessity of considering a woman's stage of life and competing causes of disease and quality of life.

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Funded by the Australian Government Department of Health and Ageing

RFRW 08/09