BCUK Background Briefing | Breast Cancer risk factors

Introduction
Breast cancer is the most common cancer in women globally. In the UK in 2015 there were 54,751 new diagnoses of invasive breast cancer in women and 371 in men. Current estimates predict 1 in 7 women living in the UK will be diagnosed with breast cancer at some point in their lifetime.

This briefing provides an overview of the major risk factors that are known or suspected of being associated with the development of primary breast cancer in women. A separate male breast cancer brief describes the main risk factors for men, although many are common to both sexes.

SUMMARY

Risk factors you have no control over
Ageing, being female, inheriting certain single gene mutations (e.g. BRCA mutations), genetic pre-disposition (based on inheriting variation in many genes), family history of breast cancer, tall stature, heavy birthweight, benign breast disease, previous breast cancer diagnosis, high mammographic density (this is partly genetic and partly environmental (e.g. increased by alcohol & poor diet). It changes over a lifetime and can only be determined by a mammogram).

Risk factors you have some control over
Weight: being obese or overweight increases risk; try to reduce your weight.
Diet: poor diet (high in fat & sugar, low in vegetables) increases risk; adopt a healthy diet e.g. a Mediterranean-style diet.
Physical activity: physical activity reduces risk; do at least 150 minutes of moderate or 75 minutes of vigorous physical activity weekly.
Alcohol: consider reducing your alcohol intake to government guidelines of less than 14 units (e.g. 6 glasses of wine) per week or stop drinking alcohol altogether.
Vitamin D: ensure enough exposure to sunlight for adequate Vitamin D production (9 minutes of daily sunlight at lunchtime from March to September).
Having children and Breastfeeding: Having children young and breastfeeding reduce risk.
Smoking: smoking may increase risk, especially if you begin early or have smoked for many years; stop smoking.
Hormonal contraception (e.g. the pill): consider alternative forms of contraception.
Hormone Replacement Therapy: consider alternative approaches for managing menopausal symptoms.
Radiation: Exposure to high level ionising radiation from medical treatment, especially during puberty, increases your risk of breast cancer. Practically, it is not possible to avoid, as it is used as an effective cancer treatment.

Environmental risk factors you may have some control over
Endocrine Disrupting Chemicals (EDCs): avoid exposure to EDCs where possible.
Night Shift Work/Light at Night: avoid shift work if possible; ensure good quality sleep in a dark room.
Residence: those who live in urban (rather than rural) areas and in areas of higher socio-economic status have an increased risk of breast cancer.

Check breasts regularly, especially if you’ve had a high-risk benign breast disease diagnosis or carry a faulty BRCA (or other) gene that’s known to increase breast cancer risk.
Ageing is the most significant risk factor for female breast cancer, with 25% of new cases of invasive breast cancer in women aged over 75\textsuperscript{4} and only 19% in women under 50\textsuperscript{5}. Nonetheless in the UK between 2013-15 there were still 10,176\textsuperscript{6} cases diagnosed in the under 50 age group, demonstrating there are important causes other than ageing.

A “risk factor” for breast cancer is anything that might cause us to be more likely to develop the disease. For some of these risk factors we can do nothing to change them and they are referred to as “non-modifiable”. One UK study\textsuperscript{7} estimates that 23% of breast cancer cases in the UK are attributable to “modifiable” risk factors and may be preventable through changes to the way we lead our lives. This is equivalent to over 12,500 cases of breast cancer in the UK female population. Other studies suggest this figure is an underestimate, for example a recent French study\textsuperscript{8} concluded that 37% of breast cancer cases may be preventable (equivalent to over 20,000 breast cancer cases in UK women). Regardless of the precise figure, a large number of breast cancers can be prevented, especially if multiple risk factors are addressed simultaneously.

Breast Cancer UK’s approach to risk is informed by “the precautionary principle” which states that “in cases of serious or irreversible threats to the health of humans or ecosystems, acknowledged scientific uncertainty should not be used as a reason to postpone preventive measures”\textsuperscript{9}.

Not all the risk factors included here are universally acknowledged”. Nonetheless we believe strongly they should be included, based on scientific evidence (including \textit{in vitro} and \textit{in vivo} studies) that suggests they are likely to increase the risk of developing breast cancer.

The types of risk discussed in this brief are:

- Intrinsic risks
- Lifestyle risks
- Dietary risks
- Environmental risks

**Intrinsic risks**

Intrinsic risk factors are those we are born with and cannot directly change. In some cases we can try to mitigate a proportion of risk with surgery or pharmacological intervention (see NHS booklet for advice in this area relating to inherited \textit{BRCA} gene mutations) or by adopting risk-reducing strategies such as favourable alterations to diet and lifestyle.

Risk varies according to sub-types of breast cancer and by sub-groups of women, such as those in a specific age group\textsuperscript{10}.

1) Ageing

The main contributing factor for breast cancer is advancing age. Breast cancer risk increases as a woman ages, with incidence peaking for UK women in the 85 to 89 year age group\textsuperscript{11}. As time passes and cells undergo more divisions, DNA mutations accumulate and there is an increased chance that mutations associated with breast cancer will arise.

Ageing is also associated with gradual changes to breast tissue that affect its tumour-suppressive ability as a result of “epigenetic changes” that happen with ageing and following exposure to environmental factors. Epigenetic changes refer to changes in gene expression (whether genes are switched on or off) that do...
not involve changes to the underlying DNA sequence itself. These changes in gene expression – caused by processes such as DNA methylation or histone modification – can be passed down through generations and are therefore said to be “heritable”. For example changes to DNA methylation of tumour suppressor genes resulting in lack of tumour suppressor proteins increase risk of breast cancer\textsuperscript{12,13}.

\textbf{2) Genetics and family history}

The risk of developing breast cancer is increased when particular genetic mutations in single or multiple genes are inherited. Such “familial” breast cancer accounts for around 18\% of all breast cancers\textsuperscript{14}.

(i) Single gene mutations and hereditary breast cancer

Around a fifth of familial breast cancers (~4\% of all breast cancers)\textsuperscript{15} arise from inheriting a single dominant gene mutation (e.g. in a \textit{BRCA1} gene). Children of a parent who carries such a mutation have a 50\% chance of inheriting the mutated gene. Breast cancers associated with single dominant mutations are referred to as “hereditary breast cancers”.

Mutations in \textit{BRCA1} or \textit{BRCA2} genes are the most common single gene mutations linked to increased breast cancer susceptibility and have the most impact in terms of increased risk. Whilst many different mutations in \textit{BRCA} genes have been identified, only some are detrimental; these are commonly referred to as “faulty genes”. Inherited faulty \textit{BRCA} genes are not common; in the U.S. around 1 in 400 people carry a faulty \textit{BRCA1} or \textit{BRCA2} mutation\textsuperscript{16}.

Prevalence does vary by ethnic group; for example in the U.S. Ashkenazi Jewish population faulty \textit{BRCA1} or \textit{BRCA2} genes are present in 1 in 40 individuals\textsuperscript{17}.

Recent studies suggest the risk of breast cancer to age 80 for women carrying a faulty \textit{BRCA1} gene is 72\% and for those carrying a faulty \textit{BRCA2} gene is 69\%\textsuperscript{18}. This compares to around 13\% for the general population. Those carrying a faulty \textit{BRCA} gene tend to develop breast cancer at a relatively young age. This is reflected in the incidence data showing that cumulative risk rises rapidly up to age 40 for \textit{BRCA1} and age 50 for \textit{BRCA2} and less rapidly thereafter. Faulty \textit{BRCA1} or \textit{BRCA2} genes also increase the risk of developing ovarian cancer; such cancers are described as hereditary breast/ovarian cancer syndrome\textsuperscript{19}. This syndrome and some of the less common single gene mutations that are linked to breast cancer susceptibility are described in \textbf{Table 1}.

(ii) Multiple genes and genetic variations and breast cancer

Variations in other genes and non-coding regions of DNA known as “single nucleotide polymorphisms” (SNPs) are also associated with an increased breast cancer risk. DNA sequencing of entire genomes has detected more than 177 genomic loci (discrete regions of DNA) harboring common variants associated with increased breast cancer risk\textsuperscript{20}. Inheriting one of these loci may have very little impact, but certain combinations contribute significantly to increased risk.

(iii) Family history

As breast cancer is relatively common, having a relative with the disease doesn’t necessarily indicate you have a genetic pre-disposition.
When considering family history with no knowledge of genetic make-up, the most significant risk of breast cancer is associated with having a first degree relative (mother, sibling or daughter) who has developed breast cancer; this approximately doubles your risk. When you have more close relatives who have the disease or if they develop breast cancer at a young age, risk increases. For details of family history that is indicative of a higher risk, see here, and for comprehensive advice about genetic testing see the NHS website.

### Table 1: Altered genes & syndromes associated with breast cancer risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Abnormal gene and associated syndromes</th>
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| BRCA1     | Single dominant mutation Suppress tumour development (involved in DNA repair) | Hereditary Breast and Ovarian cancer syndrome  
Lifetime breast cancer risk is 65-85%  
Lifetime ovarian cancer risk is 39-46% |
| BRCA2     | Single dominant mutation Suppress tumour development (involved in DNA repair) | Hereditary Breast and Ovarian cancer syndrome  
Lifetime breast cancer risk is to 40-79%  
Lifetime ovarian cancer risk is 10-27%  
Increased risk of pancreatic cancer, melanoma, (prostate in males) |
| TPS3 (p53) | Single dominant mutation Codes for a protein that helps control cell division (tumour suppressor gene) | Li-Fraumeni syndrome  
Causes soft tissue cancers at a young age. People with this syndrome have a higher than average risk of breast cancer and many other cancers.  
No reliable estimate of breast cancer risk  
Risk of any cancer by age 70 is 90% |
| PALB2     | Single dominant mutation Codes for a protein that works with BRCA2 protein, stops tumour growth (involved in DNA repair) | Risk of breast cancer by age 80 is 45%  
May also increase risk of ovarian cancer. |
| PTEN      | Single dominant mutation Codes for a protein that helps control cell division (tumour suppressor gene) | Cowden syndrome, a rare disorder in which people have a higher risk of benign and cancerous breast tumours as well as growths in other tissues  
Lifetime risk of uterine cancer 19-28%  
No reliable estimate of breast cancer risk |
| CHEK2     | Single dominant mutation Codes for a kinase; which is activated upon DNA damage (involved in apoptosis and DNA repair) | Risk of breast cancer is 29% by age 80 |
| STK11     | Codes for serine/threonine kinase (involved in DNA repair) | Peutz-Jeghers syndrome  
Lifetime risk of breast cancer is 45-50%  
Lifetime risk of ovarian cancer is 18-21%  
Increased risk of many other cancers |
| CDH1      | Codes for a glycoprotein involved in cell to cell adhesion (tumour suppressor gene) | Risk of lobular breast cancer is 53% by age 80  
Also increases risk of gastric cancer |
| ATM       | (recessive mutation found in both genes) Codes for a protein kinase (involved in apoptosis; DNA repair) | Ataxia telangiectasia is a rare inherited disorder that affects the nervous system  
Risk of breast cancer is 27% by age 80 |
3) **Being female:** Women are at much higher risk of breast cancer compared to men, mainly because of their breast development and lifelong exposure to oestrogens. Oestrogens are natural hormones important for sexual development and other bodily functions. Their role in breast development includes highly regulated tissue replication, growth and differentiation, ultimately to enable breastfeeding should a pregnancy arise. Lifetime exposure to high concentrations of oestrogens is positively associated with the risk of developing breast cancer. The influence of naturally occurring hormones and their contribution to a woman’s risk level does vary at different times in a woman’s life, mainly due to the different sources and levels of circulating oestrogen before and after the menopause. For this reason, it is important to look at whether a woman is pre- or postmenopausal when considering breast cancer risk. Higher blood oestrogen levels may modestly increase breast cancer risk before menopause, whilst risk is doubled in post-menopausal women with higher blood levels of oestradiol (one of four types of oestrogen) compared to those with lower levels.

**Early menarche and late menopause:** There is a correlation between early onset of periods or menarche (before age 12) and late onset of natural menopause (after age 55 years) and higher risk of breast cancer. Both scenarios increase the overall time a woman’s breast tissue has been exposed to circulating oestrogens.

**Levels of other sex hormones:** Hormones other than oestrogen, including progesterone, testosterone and prolactin, can also affect breast cancer risk. Elevated levels of circulating prolactin associated with lactation and other functions, and testosterone (precursor of oestradiol) are known to increase risk. Progesterone’s role in normal breast tissue is less well understood. Studies suggest it controls replication of breast epithelial cells, which line breast ducts and lobes. It is triggered into action during the menstrual cycle in pre-menopausal women by rising levels of oestrogen. This cyclic reactivation of progesterone may be tumour promoting or, under some circumstances, prevent tumours spreading. Whether or not progesterone is a risk factor for breast cancer is dependent on factors such as concentration and duration of exposure, oestrogen levels and age. However, alterations in normal progesterone/progesterone receptor signalling pathways do contribute to early-stage breast cancer progression and any substance or change - for example exposure to endocrine disrupting chemicals such as bisphenol A (found in polycarbonate plastic) - that can enhance receptor sensitivity to progesterone is likely to increase its effect, contributing to increased risk of cancer development.

4) **Tall stature, growth hormone and insulin-like growth factor:** Increased height is a risk factor for breast cancer. A recent meta-analysis estimated that a 10cm increase in height is associated with a 17% elevated risk of breast cancer. The biological explanation may be linked to the influence of higher levels of growth hormone (also called somatotropin) and one of its downstream effectors, insulin-like growth factor (IGF-1), during foetal growth and at
puberty, when significant changes in breast tissue occur\(^7\). Higher levels of circulating IGF-1 are found in taller, compared to shorter women. IGF-1 promotes epithelial cell proliferation and inhibits apoptosis (programmed cell death). An elevated level of circulating IGF-1 is correlated with increased risk of oestrogen receptor positive breast cancer\(^38\). Higher levels of growth hormone are also correlated with increased breast cancer risk\(^39\).

5) **Heavy birth weight & large early body size:** There is strong evidence that a heavy birth weight (above 4kg) and large early body size (at age 18 or under) are strong surrogate markers for increased lifetime risk of developing breast cancer, in the same way adult attained height is a marker\(^40,41\).

6) **Mammographic breast density:** Mammographic breast density is partly inherited, partly influenced by the environment, and changes over a women’s lifetime\(^42\). A dense breast is defined via a mammogram image and cannot be determined by visually or by manual examination. Four categorisations are used to describe breast density\(^43\): “heterogeneously dense” (C) or “extremely dense” (D) represent dense breasts (Table 2). High breast density is the most significant breast cancer risk factor for women after ageing\(^44\). Those with a high breast density have a 4-5 times greater risk compared to those with low breast density\(^45\).

Breast density increases in response to hormones such as oestrogen although how this occurs at the cellular level is not fully understood. Dense breasts are common and normal especially among younger women.

Typically, breast density decreases with parity (the number of times a woman has given birth) and age; post-menopausal women, who have less circulating oestrogen, have lower density. Those with a high body mass index (BMI) also tend to have lower breast density\(^46\). Paradoxically a high BMI is associated with a higher breast risk cancer (see Lifestyle risks, section 3). This may be explained because obese individuals tend to have more fat cells in their breast tissue. Environmental factors that increase breast density may include alcohol and diet\(^47\), including consumption of sweet foods\(^48\), and possibly air pollution\(^49\). Use of certain synthetic hormones, including combined hormone replacement therapy (HRT), increases breast density and cessation of use lowers it\(^50\).

<table>
<thead>
<tr>
<th>Categories of breast tissue density</th>
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<tr>
<td>(A) Almost entirely fatty breast tissue, found in about 10% of women</td>
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<tr>
<td>(B) Scattered areas of dense glandular tissue and fibrous connective tissue (scattered fibro-glandular breast tissue) found in about 40% of women</td>
</tr>
<tr>
<td>(C) Heterogeneously dense breast tissue with many areas of glandular tissue and fibrous connective tissue, found in about 40% of women</td>
</tr>
<tr>
<td>(D) Extremely dense breast tissue, found in about 10% of women</td>
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7) **Benign breast disease and previous breast cancer diagnosis:** Women with a history of certain types of benign breast disease (BBD) have an increased risk of breast cancer, independent of familial or genetic risk. Around 30% of breast cancers occur in women
diagnosed with BBD\textsuperscript{61}. Two types of BBD, atypical hyperplasia and proliferative disease without atypia, are associated with increased risk. It is estimated that those who have had atypical hyperplasia have an almost fourfold increased relative risk. The most common type of BBD, non proliferative disease, is not associated with increased risk\textsuperscript{62}.

Diagnosis of lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) – both types of non-invasive breast cancer - is associated with increased risk of breast cancer. A previous diagnosis of a primary invasive breast cancer is associated with an increased risk of a second primary breast cancer\textsuperscript{63}.

**Lifestyle risks**

Lifestyle risks are those that we encounter through our daily life. They may be avoidable by altering our lifestyle choices, or modifiable by removing them from our environment or reducing our contact with them in our environment.

1) **Pregnancy and births:** Women who have their first child at a younger age (under 30 years) have a reduced risk of developing breast cancer\textsuperscript{64}. Having more children, at a younger age, also reduces risk. Reasons for this are not clear; it may be associated with pregnancy-induced changes to mammary tissue resulting in differentiation of breast cells that are less susceptible to carcinogenesis, changes in levels of circulating sex hormones, or changes to epithelial stem cell composition\textsuperscript{65,66}. Recent findings from a Danish cohort study (see Table 3)\textsuperscript{57} showed that risk is also affected by pregnancy length, and whether it is a first, second or third pregnancy.

![Table 3: Danish Cohort study: link between risk reduction and pregnancy](image)

<table>
<thead>
<tr>
<th>Women's circumstances</th>
<th>Risk reduction (average)</th>
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<tbody>
<tr>
<td>Pregnancies lasting 33 weeks</td>
<td>reduced by 2.4%</td>
</tr>
<tr>
<td>Pregnancy lasted 34 weeks or more</td>
<td>reduced by 13.6%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} pregnancy reached 34 weeks</td>
<td>reduced by 16.9%</td>
</tr>
<tr>
<td>By 3\textsuperscript{rd} pregnancy and after pregnancy reached 34 weeks</td>
<td>reduced by 37.7%</td>
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The link between reduced cancer risk and a pregnancy that reaches 34 weeks occurred no matter whether the pregnancy resulted in a live or a stillbirth.

There is a transient increase in breast cancer risk following full-term births, which peaks around 5 years after child-birth and continues for about 20 years\textsuperscript{59}. The reasons for this are not fully clear; it has been suggested that proliferation of breast cells during pregnancy might promote accelerated development of latent initiated tumour cells and changes associated with the breast microenvironment may facilitate cancer migration and metastasis.

2) **Breastfeeding:** Breastfeeding is strongly associated with a decrease in breast cancer risk, especially hormone receptor negative breast cancer, and this decrease is positively correlated with total time spent breastfeeding\textsuperscript{60}. Again, reasons are not fully understood although like parity, breastfeeding is associated with permanent alteration of breast tissue, characterised by maturation of
terminal ductal units, which is known to be associated with reduced risk. Shorter exposure to hormones such as oestrogen and non-hormonal mechanisms such as changes in immune response and apoptosis may also contribute.\textsuperscript{61,62}

3) Weight and body fat: Higher body fat and adult weight gain are well-recognised risk factors for breast cancer in post-menopausal women.\textsuperscript{63} Body mass index (BMI) is the most common measure of body fat and refers to weight in kg divided by height in metres squared.

<table>
<thead>
<tr>
<th>Weight classification</th>
<th>BMI</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>Below 18.5</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>30+</td>
</tr>
<tr>
<td>Severely obese</td>
<td>40+</td>
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Although many studies use BMI, there are other measurements, including waist to hip ratio and the percentage of lean vs. fat mass, which are considered more accurate measurements. You can have a healthy BMI and still have excess fat around the waist – meaning you’re still at increased risk of breast cancer.

In the UK it is estimated that around 8.3% of all post-menopausal breast cancers can be attributed to being obese or overweight.\textsuperscript{64} In contrast, higher body fatness in pre-menopausal women is “probably” associated with a reduced risk of breast cancer, before and after menopause.\textsuperscript{65}

A possible explanation for these differences may relate to the different hormonal drivers of cellular activity in breast tissue before and after menopause.\textsuperscript{66} Oestrogen is mainly produced by the ovaries in pre-menopausal women and by adipose (fat) tissue in women following menopause. In pre-menopausal women excess fat tissue may cause ovarian dysfunction resulting in a reduction in menstrual cycles and as a result, reduced exposure to hormones, including oestrogen. After menopause excess adiposity results in increased levels of circulating oestrogens which increase risk.

Obesity and excess body fat are also associated with low-grade inflammation in tissues, including breast tissue. Fat cells secrete numerous compounds, such as leptin, pro-inflammatory cytokines, insulin, IGF-1 and IGF-1 receptor, and a hormone called leptin, which mediate cancer development.\textsuperscript{67} Indeed a meta-analysis found a positive association between increased levels of leptin – a hormone produced by fat cells that regulates energy balance through modulating hunger levels – and breast cancer incidence and spread in post-menopausal women. This suggests leptin may have a role as a biomarker for breast cancer risk in overweight and post-menopausal women.\textsuperscript{68}

4) Insufficient physical activity: Failing to undertake recommended levels of physical activity is linked to an increased risk of breast cancer. The World Health Organisation (WHO) recommends adults should undertake at least 150 minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity each week.\textsuperscript{69} The risk of insufficient physical activity is especially strong in post-menopausal women and the intensity of physical activity undertaken is very important.
when considering risk reduction in pre-menopausal women\textsuperscript{70/71}. According to the World Cancer Research Fund (WCRF):

- There is strong evidence that total physical activity can reduce the risk of post-menopausal breast cancer, but only limited evidence that it reduces the risk of pre-menopausal breast cancer.

- There is strong evidence that vigorous-intensity physical activity can reduce the risk of pre-menopausal breast cancer.

Physical activity also improves survival rates for women who have breast cancer. One study found as little as an hour of walking per week was beneficial, with maximum benefits found in women who did 3-5 hours per week\textsuperscript{72}.

Forms of physical activity, including structured exercise lowers levels of hormones, such as oestrogen, androgen, insulin and leptin\textsuperscript{73} and certain growth factors; all of these have been associated with cancer development and progression. Being active also helps to prevent obesity including the development of insulin resistance and type II diabetes. Moreover, being active improves the capacity of the immune system to protect us from cancer, and limits damaging processes such as oxidative stress and inflammation which increase cancer risk\textsuperscript{24}.

5) Hormonal contraception: Most studies examining hormonal contraception investigate the link between breast cancer risk and combined oral contraceptives, which contain synthetic oestrogen and progesterone (see Table 3). A Danish cohort study of nearly two million women found a 20% increase in risk of breast cancer among current or recent users compared to non-users\textsuperscript{75}. Risk increased with longer use and decreased following cessation of use. This is consistent with most data which suggest a small increase in risk of developing breast cancer from using the combined oral contraceptive pill, with risk no longer apparent five years after use has stopped\textsuperscript{76}. A systematic review of epidemiological studies on oral contraception containing progestin (synthetic progesterone) and breast cancer risk showed no association\textsuperscript{77}, in contrast to results from the Danish study (above) which found women who currently or recently used a progestin-only intrauterine system had an elevated risk of breast cancer, compared to those who had never used hormonal contraceptives. Any risk associated with hormonal contraceptives should be considered in context following discussion with a health professional, as combined oral contraception is associated with various health risks and benefits\textsuperscript{78}.

6) Hormone replacement therapy: Hormone Replacement Therapy (HRT) is used to relieve symptoms of menopause and involves the administration of oestrogens with or without progesterone, or their synthetic derivatives. Breast cancer risk is increased when combined HRT (oestrogen and progesterone) is taken, and

<table>
<thead>
<tr>
<th>Table 3: Forms of hormonal contraception</th>
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<tbody>
<tr>
<td>Combined and progesterone*</td>
</tr>
<tr>
<td>oral contraceptive patch</td>
</tr>
<tr>
<td>vaginal ring</td>
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<tr>
<td>depo-injection</td>
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\textit{*in the form of progestin, a synthetic progesterone}
Risk increases with increasing duration of treatment, and is higher for women who started taking HRT close to menopause. HRT with oestrogen alone is associated with little or no change in risk, however it may be associated with cancer of the endometrium and ovary. When combined HRT treatment ceases, risk reduces considerably and returns to normal after about five years, although for some combinations elevated risk continues for up to ten years.

7) Sleep patterns, light at night and circadian rhythm disruption: In 2007, shift work that involves circadian disruption was classed by the International Agency for Research on Cancer (IARC) as “probably carcinogenic to humans” based on limited evidence from eight epidemiological studies on breast cancer, and evidence from animal experiments. Since then many new and extended clinical studies and meta-analyses have been published. Most studies have found evidence that night shift work and light at night exposure are risk factors for breast cancer, although not all studies demonstrate a link. Different assessments of what constitutes night shift work or different amounts of night light exposure may help explain the disparity in findings.

Low melatonin levels have been linked to elevated breast cancer risk. Produced by the pineal gland during darkness, melatonin regulates our internal body clock, controlling multiple bodily processes as well as exerting beneficial anti-oxidant, immune-enhancing and anti-tumour activity. This suggests that night-time shift work and increased breast cancer may be due to lower melatonin production.

Some research has shown that poor sleep increases breast cancer risk (e.g. Results of studies vary and more data are needed to confirm this.

8) Smoking: Most recent studies and meta-analyses conclude there is a modest increase in breast cancer risk for women who smoke, mainly in pre-menopausal women and those who started smoking at an early age. Limited evidence suggests passive smoking may also increases risk.

Tobacco smoke contains a number of carcinogens, several of which are known to induce mammary cancers. There is also evidence that it can exert an anti-oestrogenic effect, which may help explain the less detrimental effect in women post-menopause. Smoking increases the risk of at least 15 types of cancers.

9) Radiation from medical treatment, population screening & diagnostics:

Ionising radiation damages DNA, which then needs to be repaired. During DNA repair mutations can be randomly introduced, which increase the risk of cancers, including breast cancer. Exposure to ionizing radiation to the chest or face area from medical treatment, particularly during puberty, significantly increases the risk of breast cancer.

Mammograms deliver radiation to the breast tissue but at a much lower level than a standard chest X-ray and the introduction of digital mammograms has reduced that radiation exposure further. The NHS mammography screening information booklet states that
having mammograms every 3 years for 20 years very slightly increases the chance of getting cancer over a woman’s lifetime. Currently the screening service in the UK is exploring a move towards more targeted use of mammograms by stratifying the screening population by risk profile using combined risk data. This would mean fewer mammograms for the low risk individuals and more for those at high risk.

10) Low vitamin D: Low levels of vitamin D are correlated with an increased risk of breast cancer, but it is unclear whether it is a direct causative factor or marker of risk. Vitamin D represents a group of fat-soluble vitamins that come in various forms; the most important include vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Between 80-100% of vitamin D3 is produced in the skin after exposure to UV in sunlight. Dietary vitamin D3 comes from animal-based food and vitamin D2 is from certain plants and yeast. Another source of vitamin D may be obtained from dietary supplements.

The key function of vitamin D is the regulation of the body’s metabolism of calcium, magnesium and phosphate associated with bone health. It also acts as a hormone affecting many organs including the heart, lungs, intestine, skeletal system and mammary glands. Research has found that lower than normal circulating levels are linked to a range of diseases, including breast cancer. At present it is unclear whether vitamin D supplementation could help reduce breast cancer risk with different meta-studies reaching different conclusions.

One recent study suggests white Caucasians living in the UK need nine minutes of daily sunlight at lunchtime from March to September for vitamin D levels to remain at an adequate level throughout the winter. This assumes forearms and lower legs are exposed during Summer months and only hands and face need be exposed during cooler months.

11) Residence: Breast cancer incidence varies globally. The highest rates occur in North and Western Europe (including the UK), Australia, New Zealand, Canada and the US; the lowest rates are found in Eastern Asia and South America. Differences are partly associated with reproductive factors, such as earlier age at menarche, later age at first childbirth, having fewer children, less breastfeeding and other lifestyle factors such as obesity.

In the UK and other countries, living in urban areas, as opposed to rural areas, is associated with increased risk of breast cancer. This may be partly due to less screening and detection (in remote rural areas), as well as differences in lifestyle and certain reproductive factors, such as parity and age at first birth. Women who live in areas of higher socioeconomic status have an increased risk of breast cancer compared to those who live in more disadvantaged areas. Reasons may be similar to those associated with living in urban areas.

Dietary risks

1) Overall diet: The World Cancer Research Fund’s Continuous Update Project’s Third Expert Report 2018 on diet and cancer offers an up to date and comprehensive meta-analysis.
of all studies that have looked at the impact of different dietary components and breast cancer incidence. Another report published subsequently by Cancer Australia\textsuperscript{104} also examines all aspects of diet and breast cancer risk. Both reports conclude that a diet high in non-starchy vegetables reduces breast cancer risk, especially oestrogen receptor negative (ER-) breast cancer.

One example of this is the Mediterranean-type diet. The broad health benefits of the Mediterranean-type diet are well accepted, although both WCRF and Cancer Australia classify evidence for reduced breast cancer risk as inconclusive. A meta-analysis\textsuperscript{105} involving over 4 million participants, confirmed an incremental beneficial effect with increasing adherence to the diet, resulting in an 8% decrease in overall mortality and a 4% risk reduction for all cancer deaths. Another meta-analysis\textsuperscript{106} supported these findings and suggested extra virgin olive oil may also be associated with risk reduction; both WCRF and Cancer Australia concluded the data were too limited to support this.

Both WCRF and Cancer Australia found suggestive evidence that consumption of foods containing carotenoids (plant pigments responsible for bright red, yellow and orange hues in many fruits and vegetables and are found in e.g. carrots, melons and sweet potatoes) decreases the risk of breast cancer. Cancer Australia also found suggestive evidence that dairy and dietary calcium (from e.g. dairy, certain vegetables, fish and nuts, though not calcium supplements) may be associated with decreased breast cancer risk\textsuperscript{107}.

2) Alcohol: The relationship between alcohol and breast cancer is clear: drinking alcoholic beverages is a risk factor for breast cancer, as well as some other forms of cancer\textsuperscript{108}. Alcohol is attributed as the cause for more than 100,000 cases of breast cancer worldwide every year\textsuperscript{109}. A woman drinking a daily average of two units of alcohol (e.g. 500ml of lager or 175ml glass of wine) has an 8% higher risk of developing breast cancer than a woman who drinks an average of one unit of alcohol per day. Even light consumption of alcohol (one drink per week) increases the risk of breast cancer\textsuperscript{110}. Also, the more alcohol a woman consumes, the more likely she is to be diagnosed with a recurrence after initial treatment\textsuperscript{111}. Drinking alcohol during pregnancy may raise the lifetime risk of breast cancer in daughters\textsuperscript{112}.

UK government guidelines recommend less than 14 units of alcohol per week.

The mechanisms by which alcohol increases breast cancer risk are not fully understood\textsuperscript{113}. Alcohol interferes with hormones and growth factors and studies have shown it may increase oestrogen levels, an established breast cancer risk factor. Alcohol is metabolised by the liver and has the potential to affect metabolism of other nutrients, which may make an individual more susceptible to breast cancer. Alcohol is also metabolised in breast tissue to acetaldehyde, potentially producing chemically reactive by-products (reactive oxygen species and free radicals) that can cause DNA damage and breast cancer initiation. An in vitro study examining the effects of alcohol on breast cancer cells found that alcohol increased oestrogen-induced cell proliferation and
promoted the sustained expression of a cancer promoting gene (BRAF) without oestrogen present, suggesting another possible mechanism of action.\textsuperscript{114}

3) Processed meats
A 2016 report by the WHO classified processed meat in the Group 1 risk category, which means there is convincing evidence that eating processed meat causes cancer.\textsuperscript{115} Although, breast cancer is not mentioned specifically. A recent meta-analysis published in 2018,\textsuperscript{116} that examined associations between eating red and processed meats and breast cancer incidence, suggests that eating processed meat is linked to increased risk of breast cancer. The researchers found that compared to people who ate the lowest amounts of processed meats, those who ate the highest amounts had a 9\% higher risk of breast cancer compared to the normal population. The Cancer Australia report conclude there is suggestive evidence that processed meat increases risk.\textsuperscript{117}

4) Phytoestrogens: Phytoestrogens are plant-derived molecules in foods such as cruciferous vegetables, soy, berries, seeds and grains, nuts, fruit and wine. Many are structurally similar to oestrogen and can mimic the effect of oestrogen in the body by binding weakly to oestrogen receptors (termed “oestrogenic”). Some have both oestrogenic and anti-oestrogenic activity. Phytoestrogens may also inhibit cell growth and proliferation, interact with cell signalling pathways and have anti-oxidant and anti-inflammatory effects. Currently, scientific research does not support increasing average phytoestrogen intake among women to higher levels in order to protect against breast cancer, nor does it suggest that phytoestrogen intake increases breast cancer risk.\textsuperscript{118}

Environmental chemical exposures
We are exposed to numerous potentially harmful chemicals in our air, water and soil and via products we use or consume. Occupational exposures also occur, although in health and safety regulations have reduced these considerably. Harmful chemicals associated with breast cancer risk include carcinogens and endocrine disrupting chemicals - commonly known as hormone disrupting chemicals or EDCs.

1) Endocrine disrupting chemicals are chemicals that mimic, block, or interfere with hormones in the body's endocrine system.\textsuperscript{119} The mechanisms of disruption are complex often acting at multiple levels. A number of EDCs have been shown to increase breast cancer risk; some, such as the anti-miscarriage pill, Diethystilboestrol, and the plastics component, bisphenol A, have been banned or are restricted; others, for example synthetic hormones used in HRT, are still in use. Endocrine disrupting chemicals are found throughout our environment and recorded at various levels in bodily tissues and fluids. Of the numerous products used daily, many contain known or suspected EDCs. Those that may be associated with increased breast cancer risk include for example parabens, used as preservatives, phthalates, used as plasticisers and fragrances, bisphenols used in manufacture of polycarbonate plastics and certain types of flame retardants. For more details see our brief on EDCs.
2) **Chemical carcinogens** are chemicals that cause cancer. Most known chemical carcinogens have been banned from everyday use however exposures may still occur as a result of legacy use (e.g. polychlorinated biphenyls were banned several decades ago but are still present in the environment), occupational exposure (some carcinogens are still used in industry or medicine) or exposure to polluted air, water or soil. Polluted air is the most common source of chemical carcinogens. A recent review that examined breast cancer risk associated with air pollution found exposure to traffic-related nitrogen oxides was associated with increased incidence\(^{125}\), and several other studies suggest an association between long-term exposure to particulate matter, polycyclic aromatic hydrocarbons, or certain metals (e.g. lead and cobalt) in polluted air and a higher risk of breast cancer\(^{126,127}\). However, not all studies demonstrate a link between breast cancer and air pollution\(^{128}\). Differences may relate partly to timing of exposure, with early exposures potentially more significant.

**Combined risks**

Breast cancer is recognised as a heterogeneous disease with several subtypes based on hormone receptor status and other cellular and molecular tumour characteristics. It is possible that these subtypes have different causes. However, it is combined risk brought about by interaction between multiple factors that is likely to be most important, and risk needs to be viewed holistically. Consistent with this approach new UK research has suggested that for women with dense breasts, a screening strategy that takes into account a woman’s other risk factors (e.g. hormones, diet and lifestyle) may be a more reliable predictor of breast cancer risk and how frequently invitations for mammographic screening are sent\(^{129}\).

Indeed measurements such as breast density, need to be examined in the context of all other factors linked to breast cancer. These considerations highlight the need for a multi- and interdisciplinary approach to understanding breast cancer risk, including awareness of cultural, genetic and lifestyle and behavioural factors.

**Reducing risks**

Refining risk estimates for individuals relies on continued epidemiological and prospective studies, which due to the long-term nature of developing cancer, means that such studies take a long time to come to fruition. People generally want to know which risk is the most important one to reduce or avoid. Assigning a broad guideline for the relative ordering of risks for breast cancer is a challenge, partly because of the interplay between absolute risks and markers of risk and partly due to unknown factors for any individual or population. Breast cancer risk is driven by multiple components, genetic/hereditary, diet/lifestyle and environmental. Although some risk factors are independent from one another, many known risk factors and markers of risk reflect complex interaction of the myriad cancer-supporting protagonists we encounter as we go about our daily lives. The more positive actions we take to protect ourselves the more impact we may have of reducing risk.
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UK’s leaflet “Reduce your risk of breast Cancer: a guide” is a good introduction to the first steps to a healthier lifestyle. Exposure to risk starts in the womb and continues throughout childhood leading to higher risk as adults (for further information see our brief on in utero exposures and breast cancer). It is therefore important for young women as well as older ones to take measures to help reduce their risk.

About Breast Cancer UK

Who are we?
Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them.

For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk
To view this information in a more accessible format or to provide feedback, please contact us.

Disclaimer
This brief is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

Thanks to Dr James Turner and Dr Vasanta Subramanian for reviewing this document

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Last updated June 11 2019 (Version 1.0)
Glossary

Atypia: state of not being normal or typical, indicating an abnormality on cells in tissue.

Atypical hyperplasia: a benign (not cancer) condition in which cells look abnormal under a microscope and are increased in number.

Body mass index (BMI): value derived from the mass (weight) and height of an individual. The BMI is defined as the body mass divided by the square of the body height and is universally expressed in units of kg/m², resulting from mass in kilograms and height in metres.

Carcinogen: a substance or agent that can cause cancer.

Cohort study: a study that compares a particular outcome (such as breast cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke).

Cumulative risk: a measure of the total risk that a certain event will happen during a given period of time. In cancer research, it is the likelihood that a person who is free of a certain type of cancer will develop that cancer by a specific age.

Dominant (gene) mutation: every cell has two copies of each gene, one inherited from the mother and one from the father. A dominant inheritance pattern is where a mutation needs to be present in only one copy of the gene for an individual to have an increased risk of getting that disease associated with that mutation.

Epigenetic change: refers to a change which alters the properties of a gene and affects its expression, but does not alter the primary DNA sequence. An example is methylation of DNA resulting in reduced expression of a gene. This is in contrast to a genetic change (or gene mutation) where the primary sequence of a gene is changed.

Faulty gene: refers to a gene mutation which is harmful to an individual. Gene mutations can occur spontaneously or may be inherited.

Gene mutation: a change in the usual DNA sequence at a particular gene locus. Mutations can be harmful, beneficial, or neutral in their effects on cell function. The term variant is sometimes used as a synonym for the term mutation.

Germ-line mutation: a gene change in a reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. A variant contained within the germline can be passed from parent to offspring, and so is hereditary.

Hyperplasia: an increase in the number of cells in an organ or tissue that appear normal under a microscope. They are not cancer, but may become cancerous.

In vitro: in the laboratory (outside the body). The opposite of in vivo (in the body).

In vivo: in the body. The opposite of in vitro (outside the body or in the laboratory).

Meta-analysis: a meta-analysis combines and analyses the results of multiple studies.

Parity: the number of times a women has given birth.

Pathogenic variant: a genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a variant (or mutation) is inherited, development of symptoms is more likely, although not certain. Also called deleterious mutation, disease-causing mutation, predisposing mutation, and susceptibility gene mutation.
Processed meats: meat that has been salted, cured, smoked, fermented, or processed in another way to enhance its flavour or preserve it.

Proliferative disease without atypia: proliferative tissue describes the rate of cell division, faster growing and replicating cells than normal tissue, but these cells do not look abnormal.

Protective factor: something that may decrease the chance of getting a certain disease. Some examples of protective factors for breast cancer are getting regular physical activity, staying at a healthy weight, and having a healthy diet.

Retrospective study: a study that compares two groups of people, those with a disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls); also called a case-controlled study.

Precautionary principle: the precautionary principle generally defines actions on issues considered to be uncertain, for instance applied in assessing risk management. The principle is used by policy makers to justify discretionary decisions in situations where there is the possibility of harm from making a certain decision when extensive scientific knowledge on the matter is lacking. The principle implies that there is a social responsibility to protect the public from exposure to harm, when scientific investigation has found a plausible risk. These protections can be relaxed only if further scientific findings emerge that provide sound evidence that no harm will result.

Prospective study: a study or clinical trial in which participants are identified and then followed forward in time.

Risk factor: something that increases the chance of developing a disease. Some examples of risk factors for breast cancer are age, a family history of breast cancer, being exposed to radiation or being exposed to certain chemicals.

Risk ratio: used in the statistical analysis of data to estimate the strength of the association between treatments or risk factors, and outcome. For example, it is used to compare the risk of an adverse outcome when receiving a medical treatment versus no treatment (or placebo), or when exposed to an environmental risk factor versus not exposed. Assuming the causal effect between the exposure and the outcome, values of RR can be interpreted as follows:

- $RR = 1$ means that exposure does not affect the outcome;
- $RR < 1$ means that the risk of the outcome is decreased by the exposure;
- $RR > 1$ means that the risk of the outcome is increased by the exposure.

The amount it increases or decreases is always relative to the control value being 1, whatever that is – for example if the general population has a 1 in 10 (10%) lifetime risk and the RR is 1.2 for exposure to something then the lifetime risk is increased by 20%, making it a 12% lifetime risk.

Recessive mutation: with this type of gene mutation an individual needs to inherit two mutated copies of the gene to develop the disease. Those who carry a single copy are called heterozygous carriers and those with two copies homozygous carriers.

Somatic mutation: an alteration in DNA that occurs after conception. Can occur in any of the cells of the body, except the germ cells (eggs and sperm), and are therefore not passed on to the next generation. Somatic mutations can (but do not always) lead to cancer or other diseases.

Tumour suppressor gene: a type of gene that makes a protein called a tumour suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumour suppressor genes may lead to cancer.
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