

May 2009

Introduction

Breast cancer is the most common cancer in the UK^a despite the fact that it is a rare disease in men. Around 126 new cases of breast cancer are diagnosed each day in the UK. Diagnosis and treatment have improved significantly over the last thirty years and mortality has fallen consistently since 1989. Breast cancer is the third most common cause of cancer death in the UK after lung and large bowel cancer, with around 12,100 breast cancer deaths each year. This report focuses on female breast cancer.

Table One: Number of new cases and rates of breast cancer; UK, 2006

		England	Wales	Scotland	N. Ireland	UK
Cases	Males	275	18	20	1	314
	Females	38,004	2,445	4,079	980	45,508
	Persons	38,279	2,463	4,099	981	45,822
Crude rate per 100,000	Males	1.1	1.2	0.8	0.1	1.1
	Females	147.1	160.7	154.1	110.3	147.3
	Persons	75.4	83.0	80.1	56.3	75.6
European age-standardised rate per 100,000 (95% CI)	Males	0.9 (0.8-1.0)	1.0 (0.5-1.4)	0.7 (0.4-1.0)	0.1 (0.0-0.2)	0.9 (0.8-1.0)
	Females	121.4 (120.2-122.6)	124.4 (119.4-129.3)	121.7 (118.0-125.4)	99.2 (92.9-105.4)	121.0 (119.9-122.1)
	Persons	63.9 (63.2-64.5)	65.7 (63.1-68.3)	65.3 (63.3-67.3)	52.4 (49.1-55.7)	63.8 (63.2-64.4)

Incidence

In 2006 there were 45,822 new cases of breast cancer diagnosed in the UK: 45,508 (over 99%) in women and 314 (less than 1%) in men.¹ It is by far the most common cancer in women accounting for 31% of all cases: the next most common cancer in women is lung cancer, with 16,647 cases (11% of total) in 2006. So nearly a third of all new cancers in women are breast cancers and the lifetime risk of being diagnosed with breast cancer is estimated to be 1 in 9 (see **Risk factors** section for risk by age-group).

Table One shows the numbers and rates of new cases in the UK and its constituent countries.¹ The lowest rates are recorded in Northern Ireland and this has been a consistent pattern since Northern Ireland cancer registration rates became available in 1993.²

Age

Breast cancer risk is strongly related to age, with 81% of cases occurring in women aged 50 years and over. Nearly half (48%) the cases are diagnosed in the 50-69 age-group (**Figure One**): these women and those aged 70 are targeted in the national screening programme.

Although very few cases occur in women in their teens or early 20s, breast cancer is the most commonly diagnosed cancer in women under 35. Among women aged 35-39, around 1,500 cases of breast cancer are diagnosed each year. The rates generally increase with age, with the greatest rate of increase prior to the menopause, supporting a link with hormonal status.

Geographic variation

Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all new female cancer cases.³ Incidence rates vary considerably, with the highest rates in North America and the lowest rates in Africa and Asia (**Figure Two**).³ Around 429,900 new cases occur each year in Europe and 182,460 in the USA.^{4,5} The lowest European rates are in eastern and southern Europe and the highest

Figure One: Number of new cases and rates for female breast cancer, by age, UK, 2006

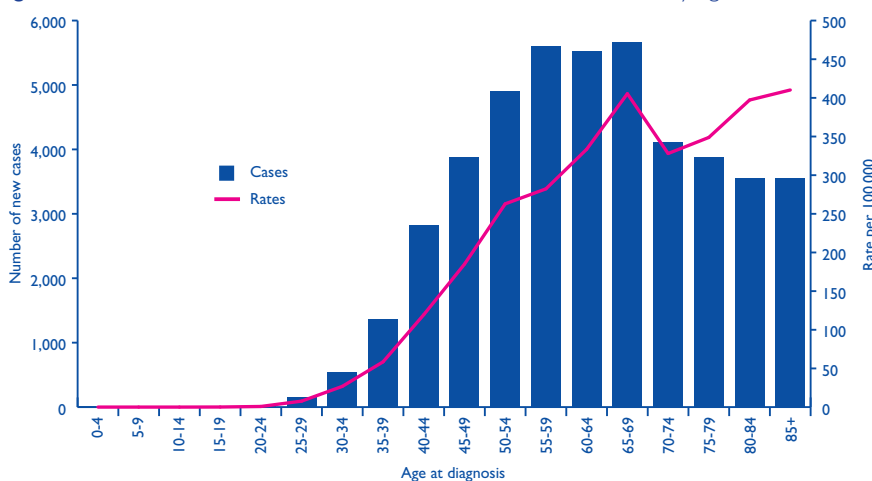
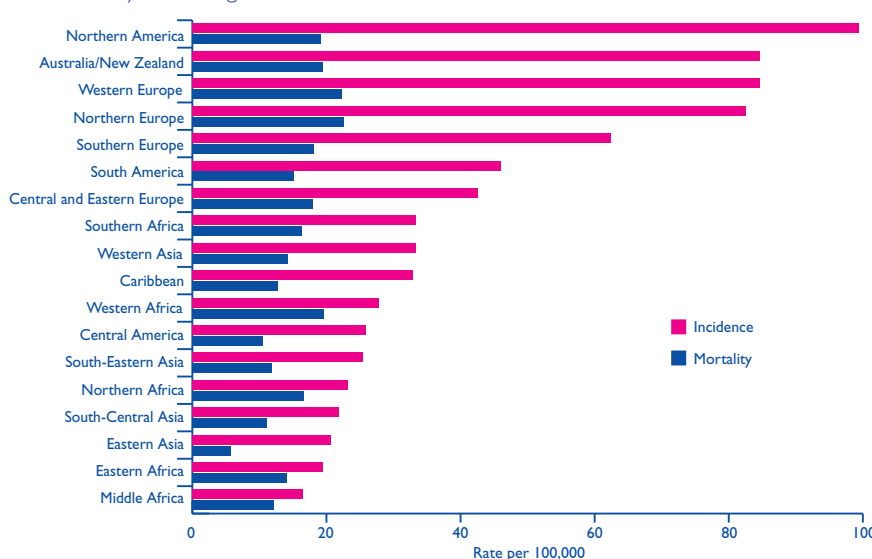


Figure Two: World age-standardised incidence and mortality rates for female breast cancer by world region, 2002 estimates



^a Excluding non-melanoma skin cancer

are in northern and western Europe (Figure Three).¹ The risk for women who migrate from low to high risk countries typically increases suggesting a strong effect for environmental or lifestyle factors. For example, Japanese migrants to the USA experience rapidly increasing breast cancer incidence rates.^{6,7}

An analysis of cancer incidence and mortality from 1991 to 2000 within the UK and Ireland reported relatively little geographical variation for either breast cancer rate.⁸ At the regional and country level, the European age-standardised rate (EASR)⁹ for breast cancer incidence ranged from 97 per 100,000 in Ireland to 116 per 100,000 in the South East of England. In England rates were slightly higher than average in the south and slightly lower than average in the north but very few areas differed by more than 10% from the average. In Ireland rates were generally more than 10% below the average. A more recent examination of incidence rates within the UK for 2005 also reported only modest variation in breast cancer incidence for the majority of cancer networks.¹⁰

Socio-economic variation

Breast cancer is one of the few cancers where incidence rates are higher for more affluent women and there is a clear trend of decreasing rates from least to most deprived groups.¹¹ An analysis of incidence rates in Scotland for patients registered from 2001-2005 showed a 6% difference between rates in the least deprived (EASR 118.7 per 100,000) and the most deprived (EASR 111.0 per 100,000) areas.¹² In England, a study of incidence for patients diagnosed between 1998 and 2003 by socio-economic group and region, also reported modest differences between socio-economic groups with the highest rates for the most affluent groups.¹³ The most recent study in England comparing deprivation for cancer patients in two time periods, 1995-99 and 2000-04, reported that rates in the most deprived groups in 2000-04 were around 20% lower than in the most affluent.¹⁴ If all groups had the rates of the most affluent, then there would be an additional 2,500 new breast cancer cases each year in England.¹⁴ These results are not unexpected as many of the risk factors for breast cancer, for example, late first pregnancy and lower parity are generally more prevalent in the more affluent groups in society.

Trends

Breast cancer incidence has been increasing since registration records began in economically developed countries.^{15,16} From the late 1970s until the introduction of breast screening, the increase in Britain was around 2% per annum.² The introduction of the national screening

programme in 1988 led to a transient additional increase in incidence as a prevalent pool of undiagnosed cancers were detected (Figure Four).¹ During the 1990s the increasing use of hormone replacement therapy (HRT) is thought to have also contributed to the increase in incidence.¹⁷ Analysis of incidence trends by deprivation group showed that incidence rose more rapidly in affluent women than among deprived women between 1986 and 1999, and the higher use of HRT in affluent women may have contributed to this.¹⁸ Over the thirty year period 1977-2006 in Britain, the EASR increased by 63% from 75 per 100,000 in 1977 to 122 per 100,000 in 2006. Over the same time period the annual number of new cases of breast cancer almost doubled from

23,463 to 44,528 in Britain. During the last ten years in the UK^b, the EASR has increased by 6% from 114 per 100,000 in 1997 to 121 per 100,000 in 2006, while the numbers of cases rose from 39,819 to 45,508, an increase of 14%.

The trends by age-group show clearly that the steep increase in incidence following 1988 was largely confined to women aged 50-64 who were invited to join the breast screening programme (Figure Five).¹ The most recent rates show a downturn for this age-group (Figure Five). A steep decrease in incidence since 2002 for women aged 50 or older has been noted in the USA and linked to the sudden drop in HRT use following publication of the Women's Health Initiative (WHI) Trial^c

Figure Three: European age-standardised incidence and mortality rates for female breast cancer, selected EU countries, 2006 estimates

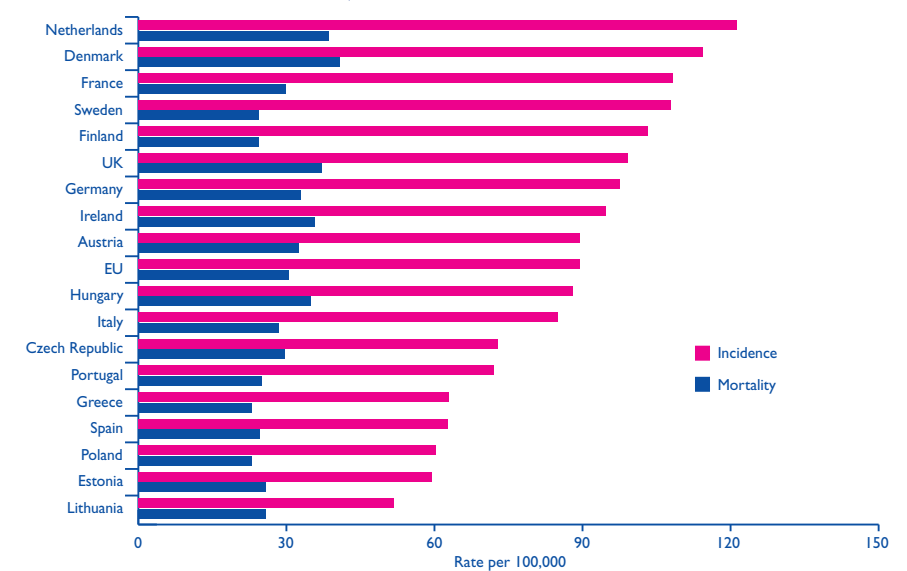


Figure Four: European age-standardised incidence and mortality rates for female breast cancer, Great Britain, 1975–2007

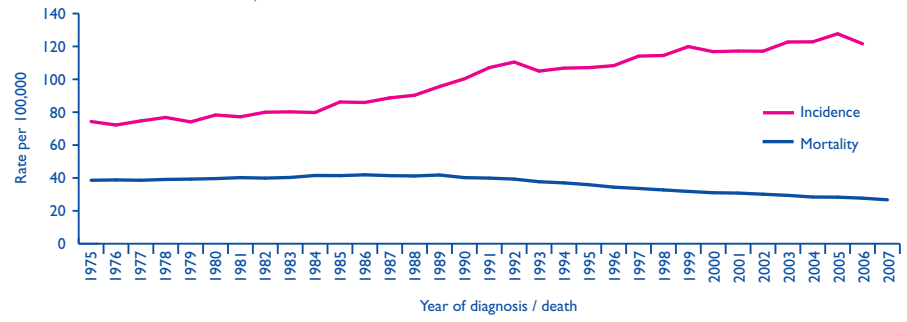
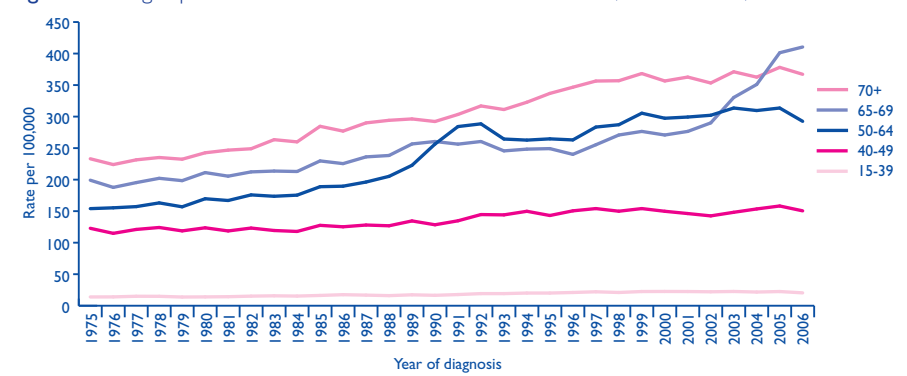


Figure Five: Age-specific incidence rates for female breast cancer, Great Britain, 1975–2006



^b Northern Ireland data is not available before 1993 and therefore long-term trends refer to Great Britain (England, Wales and Scotland) while more recent trends are for the UK (England, Wales, Scotland and Northern Ireland)

^c WHI trial was a randomised controlled trial of estrogen-plus-progestin use in post-menopausal women for prevention of chronic disease. The trial was stopped early in July 2002 because risks exceeded benefits

results.^{16, 19-21} The most recent WHI study reports that the decrease in breast cancer incidence in the over 50s is most likely to be due to reduced use of HRT rather than decreased uptake of screening, and also that the risk of breast cancer after stopping HRT seems to fall very quickly.²² Similar trends have been seen in other countries.²³ In Scotland a recent analysis of breast cancer incidence and HRT use also reports a reduction in incidence for women aged 50-64 and a dramatic decrease in HRT use (**Figure Six**) consistent with this theory.²⁴ In the UK as a whole, the use of hormonal preparations rose steeply from 1992 to reach a maximum in 2000-01 when approximately 25% of women aged 45-69 were using them; the percentage has fallen to half that in 2006.²⁵ It has been estimated that due to the fall in use of HRT, there were 1,400 fewer cases of breast cancer at ages 50-59 in the UK in 2005 than would have occurred if no such fall in use had happened.²⁵ The recent steep rise in rates for women aged 65-69 (**Figures Five and Six**) is almost certainly caused by the introduction of national breast cancer screening for this age-group (see **Prevention and screening** section).

Projections for Britain from 2005 until 2024 show that the EASR is expected to increase from 119 per 100,000 in 2000-04 to 124 per 100,000 in 2020-24. Over the same time period, the average number of cases per year will rise from 41,900 to 55,700 new cases^d, that is, more than double the number of cases registered in the late 1970s.²⁶

The historically lower rates in central and Eastern Europe and the Far East have begun to rise rapidly.²⁷⁻²⁹ For example, in Japan, where breast cancer incidence rates have more than doubled over the last 40 years, breast cancer is now the most common form of cancer in women, and rates are likely to continue rising.³⁰ China, with a fifth of the world's female population, has already seen dramatic rises in incidence in some cities such as Shanghai and if these trends spread to the rest of the country, a substantial increase in the number of cases is predicted.³¹ These increases have been linked to changes in reproductive behaviour^e and lifestyle risk factors such as weight gain, alcohol consumption and the use of hormone replacement therapy.

Prevalence

As the incidence of breast cancer is high, and five-year survival rates are over 80%, many women are alive who have been diagnosed with breast cancer. The most recent estimate based on diagnoses up to the end of 2004 applied to the population in 2008 suggests that around 550,000 women are alive in UK who have had a diagnosis of breast cancer.³² This equates to more than 2% of the total female population and nearly 12% of the population aged 65 years and older.

Figure Six: European age-standardised incidence rates of invasive breast cancer by age group in Scottish women (1980–2005), and numbers of dispensed items of HRT and raloxifene (1993–2005)

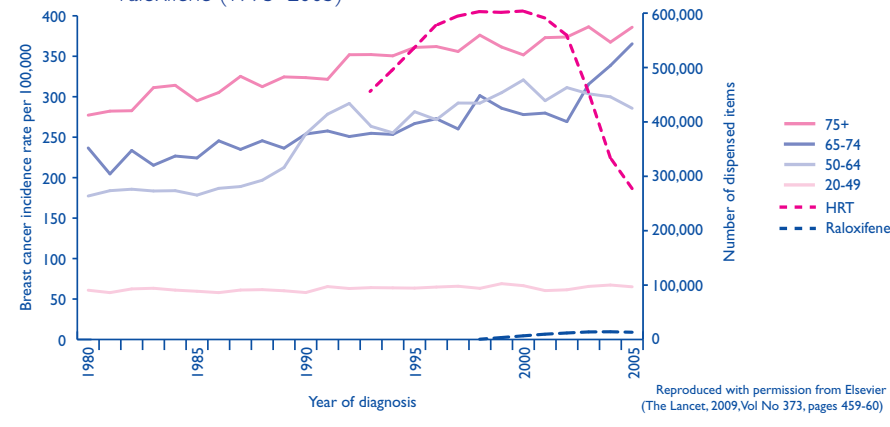


Table Two: Estimated risk of developing breast cancer by age, females, UK, 2001–2005^f

Estimated risk at birth up to and including:	UK (2001–2005)
age 24	1 in 15,300
age 29	1 in 2,300
age 39	1 in 200
age 49	1 in 52
age 59	1 in 22
age 69	1 in 14
age 79	1 in 10
age 84	1 in 9
Lifetime risk	1 in 9

Histology

Nearly all invasive breast cancers are adenocarcinomas (derived from glandular tissue), either ductal (85%) or lobular (15%). Ductal carcinoma *in situ* (DCIS), a non-invasive cancer, is now detected much more frequently because of the widespread use of mammography.

Risk factors

A substantial proportion of the breast cancer cases experienced in developed countries can be explained by factors that influence exposure to sex hormones including reproductive and exogenous hormonal factors, obesity, alcohol and physical activity.³⁴ Lifestyle factors which reduce the risk of developing breast cancer and have other health benefits include avoiding post-menopausal obesity, taking regular exercise and initiating and prolonging breastfeeding. Avoiding alcohol and exogenous hormones including HRT and oral contraceptives would lower breast cancer risk further but their risks and medical benefits, for example, the use of HRT for menopausal symptoms, need to be assessed on an individual basis. Changes in patterns of reproduction in westernised countries, for instance, having more children and doing so earlier in life, are not practicable and therefore many trials are looking at the possibility of reducing exposure to sex hormones through chemoprevention.

Age

The strongest risk factor for breast cancer (after gender) is age: the older the woman, the higher her risk. Risk by age is shown in **Table Two**.¹

Reproductive factors

Women in developed countries are at increased risk of breast cancer compared to women from less developed countries. A large part of this variation can be explained by the fact that women in developed countries have fewer children on average and a limited duration of breastfeeding. Calculations based on breast cancer incidence rates during the 1990s suggest that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100, if women had the average number of births (6.5 instead of 2.5) and the lifetime duration of breastfeeding (breastfed each child, on average, for 24 months instead of eight months) typical in developing countries around that time (**Figure Seven** (overleaf)).³⁵

The following reproductive factors influence risk:

- **Age at menarche.** Early age at menarche has been consistently associated with an increased risk of breast cancer. The estimated decrease in risk per five year delay in menarche is 22%.³⁶ Average age of menarche in developed countries fell from around 16-17 years in the mid-19th century to 12-13 today.³⁷ Good nutrition in early life reduces the age of menarche.³⁸
- **Age at first birth.** The younger the woman is when she begins childbearing, the lower her

^d Projected number of cases in the UK in 2024 is 57,000
^e In China the average birth rate fell from 5.9 births per woman in 1970 to 2.9 in 1979 and 1.7 in 2004. Hesketh T et al. NEJM 2005;353:1171-6.
^f Multiple primary breast cancers were included in this analysis which may have led to slight over-estimation of the risks

risk of breast cancer. The relative risk of developing breast cancer is estimated to increase by 3% for each year of delay.³⁵ There is evidence that the reduction in risk of breast cancer with childbirth, and higher risk with later age at first full-time birth, may be limited to oestrogen-receptor-positive tumours.³⁹

- **Parity.** Childbearing reduces the risk of breast cancer and the higher the number of full-term pregnancies, the greater the protection. Risk of breast cancer reduces by 7% with each full-term pregnancy, and overall women who have had children have a 30% lower risk than nulliparous women.^{35, 40, 41} A 15% risk reduction has been shown for women with a twin birth, compared to women giving birth to a singleton.⁴²
- **Breastfeeding.** Women who breastfeed reduce their risk compared with women who do not breastfeed. The longer a woman breastfeeds, the greater the protection: risk is reduced by 4% for every 12 months of breastfeeding.³⁵
- **Age at menopause.** Late menopause increases the risk of breast cancer. Women who have undergone the menopause have a lower risk of breast cancer than pre-menopausal women of the same age and childbearing pattern.⁴³ Risk increases by almost 3% for each year older at menopause (natural or induced by surgery), so that a woman who has the menopause at 55 rather than 45, has approximately 30% higher risk.⁴³

The evidence does not support a link between abortion and breast cancer risk.^{44,47}

Endogenous hormones

Higher levels of endogenous hormones have long been hypothesized to increase breast cancer risk. Studies generally show that post-menopausal women with the highest levels of oestrogen and testosterone have 2-3 times the risk of women with the lowest levels.⁴⁸ The link between these hormones and pre-menopausal breast cancer risk is less clear.^{49, 50} Higher levels of the hormone, prolactin, have been associated with an increased risk of breast cancer, particularly oestrogen-receptor-positive tumours.⁵¹ Having higher levels of insulin has been associated with an increased risk of post-menopausal breast cancer in women not taking hormone replacement therapy.⁵²

Exogenous hormones

- **Oral contraceptives (OCs).** The use of oral contraceptives increases the risk of breast cancer in current and recent users, but there is no significant excess risk ten or more years after stopping use (Table Three).⁵³ Cancers diagnosed in women who have used OCs tend to be less clinically advanced than those detected in never-users.⁵³ OC users are generally younger women whose breast

Figure Seven: Estimated cumulative incidence of breast cancer in developed countries if women had family sizes and breastfeeding patterns typical of developing countries.

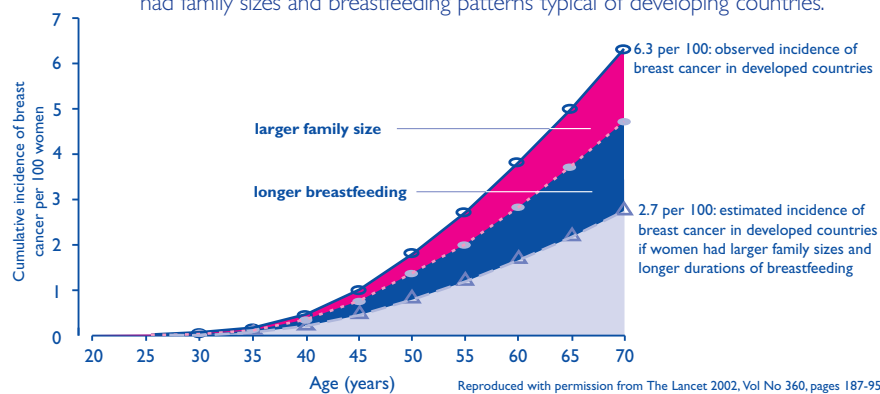


Table Three: Oral contraception and the relative risk of breast cancer

Oral contraceptive use	Relative risk (confidence interval)
Never users	1.0
Current users	1.24 (1.15-1.33)
1-4 years after stopping	1.16 (1.08-1.23)
5-9 years after stopping	1.07 (1.02-1.13)
10+ years after stopping	1.01 (0.96-1.05)

Table Four: Relative risk of invasive breast cancer in relation to recency and type of HRT used

HRT use at baseline	Relative risk (confidence interval)
Never users	1.0 (0.97-1.04)
Current users	1.66 (1.60-1.72)
Current user of oestrogen only	1.30 (1.22-1.38)
Current user of oestrogen-progestagen	2.00 (1.91-2.09)
Current users of tibolone	1.45 (1.25-1.67)
All past users	1.01 (0.95-1.08)
Last use < 5 years previously	1.04 (0.95-1.12)
Last use 5-9 years previously	1.01 (0.88-1.16)
Last use >= 10 years previously	0.9 (0.72-1.12)

cancer risk is comparatively low, so the small excess risk in current users will result in a relatively small number of additional cases.

The formulation of OCs has changed considerably since use became widespread in the 1960s, but current evidence suggests that this does not affect risk.⁵³ The risk associated with oral contraceptive use in women is similar regardless of a woman's family history, ethnic origin, years of education, age at menarche, height, menopausal status, weight and alcohol consumption.

- **Hormone replacement therapy (HRT).** Women currently taking HRT have a 66% increased risk of breast cancer compared to non-users (Table Four).⁵⁴ The risk increase is temporary, with risk returning to that of a never-user within five years. A woman's BMI modifies the effect of HRT, with a stronger effect in women with a lower BMI.^{43, 55} The risk is larger for use of oestrogen-progestagen⁸ therapy compared to oestrogen-only.⁵⁶⁻⁵⁹ In the Million Women Study, current users of oestrogen-progestagen therapy had twice the risk of never-users, while users of oestrogen-only or tibolone had smaller risk increases (Table Four).⁵⁴

It was estimated in 2003, that 20,000 extra breast cancer cases had occurred among women aged 50-64 in the UK over the previous decade as a result of HRT use and three-quarters (15,000) of these additional breast cancers are due to the use of oestrogen-progestagen HRT.⁵⁴

Breast density

Breast density is strongly and independently related to the risk of breast cancer.^{60, 61} Breast tissue is composed of fat, connective tissue and epithelial tissue. Breasts with a high proportion of fatty tissue are described as less dense. Women with the most dense breasts have almost five times higher risk of breast cancer than women with the least dense breasts.⁶² The effect of breast density is independent of endogenous hormones.⁶¹ Density is affected by menopausal status, weight and number of children, but there is some evidence that the most important determinant is inherited.⁶³

Previous breast disease

Benign breast disease is a generic term describing all non-malignant breast conditions, some of which carry an increased risk for breast cancer while others do not. Women with

⁸ Progestagen is a synthetic form of the hormone progesterone

proliferative breast disease without atypia have a two-fold increased risk, whilst those with atypical hyperplasia have a more than four-fold increased risk.⁶⁴ Women with a strong family history^h and nonproliferative breast lesions have a 60% increase in risk of breast cancer, but there is no risk increase for women without a family history.⁶⁴ Women are more likely to develop breast cancer in the same breast as the benign breast lesion than in the opposite breast.^{64, 65}

Ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) are non-invasive conditions of the breast, which can in some cases develop into invasive cancer. Although women with *in-situ* disease are more likely to develop invasive disease, it is difficult to know which are going to, although it is more likely to occur with high grade than low grade DCIS lesions.⁶⁶

A previous diagnosis of breast cancer raises the risk of developing a second primary breast cancer: Risk estimates vary from 1.4-fold^{67, 68} to 3.5-fold.⁶⁹

Family history (also see **Molecular biology and genetics** section below)

A woman with one affected first-degree relative (mother or sister) has approximately double the risk of breast cancer of a woman with no family history of the disease; if two (or more) relatives are affected, her risk increases further.⁷⁰⁻⁷¹ Risk is higher if the relative is diagnosed aged under 50. However, over 85% of women who have a close relative with breast cancer will never develop the disease, and more than 85% of women with breast cancer have no family history of it.⁷⁰ In developed countries it is estimated that hereditary factors contribute around a quarter of inter-individual differences in susceptibility to breast cancer, while environmental and lifestyle factors contribute the remaining three-quarters.³⁴

A small proportion of women have a particularly strong family history of breast cancer and are at very high risk. Mutations in the breast cancer susceptibility genes, *BRCA1* and *BRCA2*, account for the majority of families with four or more affected members and for 2-5% of all breast cancers.⁷² The estimated prevalence of *BRCA1* and *BRCA2* mutation carriers in the general population is 0.11% and 0.12% respectively, meaning that around 1 in 450 women carries a fault in one of these genes.⁷³ By the age of 70, around 60% of *BRCA1* carriers will develop breast cancer and around 50% of *BRCA2* carriers.⁷⁴ Genetic testing for faulty *BRCA* genes is available on the NHS for women with a very strong family history. An increased risk of breast cancer has also been shown in women from families without *BRCA1* or *BRCA2* mutation but with two or more breast cancers diagnosed before the age of 50, or three breast cancers diagnosed at any age.⁷⁵

Table Five: Rare familial cancer syndromes associated with breast cancer

Gene	Cancer syndrome	Associated tumours
<i>BRCA1</i>	Breast/ovarian predisposition	Breast, ovarian, bowel, prostate
<i>BRCA2</i>	Breast/ovarian predisposition	Breast (including male), ovarian, prostate, pancreatic
<i>TP53</i>	Li Fraumeni syndrome	Childhood sarcoma, brain, leukaemia, adrenocortical carcinoma, early-onset breast
<i>PTEN</i>	Cowden's syndrome	Breast, gastrointestinal, thyroid (benign and malignant)
<i>STK11/LKB1</i>	Peutz-Jeghers syndrome	Breast, gastrointestinal, pancreatic, ovarian
<i>ATM</i>	Ataxia telangiectasia	Non-Hodgkin lymphoma, ovarian, breast (in heterozygote carriers)

Table Six: Relative risk (95%CI) of breast cancer in categories of BMI, by menopausal status

BMI	Pre-menopausal	Post-menopausal*
<22.5	0.96 (0.85 to 1.08)	0.85 (0.80 to 0.91)
22.5–24.9 (reference group)	1.00 (0.90 to 1.11)	1.00 (0.95 to 1.06)
25–27.4	0.93 (0.82 to 1.05)	1.10 (1.04 to 1.16)
27.5–29.5	0.99 (0.84 to 1.16)	1.21 (1.13 to 1.29)
≥30	0.79 (0.68 to 0.92)	1.29 (1.22 to 1.36)

* Restricted to never users of hormone replacement therapy

Increased susceptibility to breast cancer is also a feature of several rare, familial cancer syndromes (Table Five). Since the lifetime risk of a woman being diagnosed with breast cancer is one in nine, there will be many women who have a mother or sister with the disease but there is only a significant likelihood of a major inherited predisposition if there are several family members on the same side of the family with early-onset breast cancer.

Non-reproductive lifestyle factors

- **Bodyweight.** Overweight and obesity, as measured by high body mass index (BMIⁱ), moderately increases the risk of post-menopausal breast cancer and is one of the few modifiable risk factors for breast cancer. Compared to lean (BMI 22.5-24.9) women, overweight post-menopausal women have a 10-20% increased risk of breast cancer, and obese post-menopausal women a 30% increase in risk. Women with a BMI under 22.5 have a 15% reduction in risk compared to women with a BMI of 22.5-24.9 (Table Six). In contrast, obese pre-menopausal women have a 20% reduction in cancer risk. Based on the results of the Million Women Study, an estimated 7% of breast cancers in post-menopausal women in the UK are due to overweight and obesity.⁷⁶

The link between BMI and breast cancer risk is likely to be due to hormones. In post-menopausal women, the main endogenous source of oestrogen is the conversion of hormones in fatty tissue. This is likely to explain the higher risk in overweight post-menopausal women.⁷⁷ The reduction in risk in obese pre-menopausal women may be due to the increased likelihood of anovulatory menstrual cycles^j in this group.⁷⁸

- **Physical activity.** Physical activity probably protects against breast cancer, with studies showing a 20-40% risk reduction for women in the highest category of physical activity.⁷⁹⁻⁸¹ Women in this category were walking or hiking for 10 or more hours per week or running for 3.5 hours. These studies suggest that the protective effect applies to both pre- and post-menopausal women. The effect of physical activity on breast cancer risk may be due to how it affects hormone levels, with a recent European Prospective Investigation of Cancer (EPIC) study showing lower levels of oestrogen and testosterone in post-menopausal women who reported higher levels of physical activity.⁸²
- **Alcohol consumption.** Epidemiological studies have consistently shown a significant association between alcohol consumption and breast cancer and a recent IARC report concluded that this association is causal.⁸³ Estimates of the relative risk associated with every additional drink (~ 10g of alcohol) consumed on a daily basis range from about 7-12%.⁸⁴⁻⁸⁶ Recent results from the largest of these studies⁸⁶ suggest that each additional drink consumed on a daily basis causes around 11 extra breast cancers before the age of 75 per 1,000 women, and that 11% of all breast cancers in the UK (5,000 cases annually) are caused by alcohol. This is possibly due to the higher levels of some sex hormones in the bloodstream of alcohol consumers than non-consumers.⁸⁷

^h In this study the criteria for a strong family history includes women with at least one first-degree relative with breast cancer before the age of 50 years or two or more relatives with breast cancer, with at least one being a first-degree relative
ⁱ BMI is calculated by dividing weight in Kg by height in metres squared. A BMI under 18.5 is classified as underweight, 18.5-24.9 as healthy weight, 25-29.9 as overweight and 30 or over as obese
^j A menstrual cycle in which ovulation fails to occur

- **Diet.** There has been a lot of research into the effects of dietary factors on breast cancer risk, but findings are generally inconsistent and inconclusive. The strongest evidence seems to be for fat intake: a meta-analysis of 45 studies⁸⁸ reported that higher total fat intake increased breast cancer risk by 13% while a recent cohort study showed a small but significant risk increase for higher intakes of saturated, monounsaturated and polyunsaturated fat.⁸⁹
- **Shift work.** There is some evidence that women who do night shift work have an increased risk of breast cancer⁹⁰ and other studies show that sleeping longer reduces risk of breast cancer.^{91,92} One theory is that disrupted or shorter duration of sleep leads to reduced levels of the hormone melatonin which has been shown to have anti-carcinogenic properties. Melatonin also suppresses the production of other hormones that have been linked to an increased risk of breast cancer. A recent study showed a 38% reduction in risk of breast cancer in women with the highest levels of the major melatonin metabolite, 6-sulfatoxymelatonin.⁹³

Other factors

- **In-utero exposure.** A meta-analysis showed that women with higher birth-weight or birth-length or older maternal age at conception had a small (30%) raised risk of breast cancer and this has been associated with higher levels of oestrogen in maternal blood.⁹⁴ Conversely, some studies suggest that breast cancer risk among offspring of mothers with pre-eclampsia or eclampsia^k may be reduced by as much as half and this has been connected to lower levels of maternal oestrogen.⁹⁴
- **Height.** Tallness is associated with an increased risk of breast cancer in post-menopausal women, with an approximate 7% increase in relative risk for each additional 5 centimetres in height.⁹⁵ The underlying mechanism for the association between height and breast cancer risk is unclear but it is likely that height is a marker for other exposures that influence breast cancer risk.
- **Medical radiation exposure.** Ionising radiation is an established risk factor for breast cancer.^{96,97} The effect is strongly related to age at exposure, that is, the younger the woman is exposed, the greater the excess risk. Studies show 12- to 25-fold increases for secondary breast cancer for women treated with mantle radiation therapy to the chest for Hodgkin's lymphoma before the age of 30.⁹⁸⁻¹⁰¹ Women who received diagnostic x-rays to the chest for tuberculosis or pneumonia between the ages of 10 to 29 have a three-fold increased risk of breast

cancer.⁹⁷ It has been estimated that exposure to diagnostic x-rays (much lower in dose than radiotherapy) may be responsible for 29 female breast cancer cases before the age of 75 each year in the UK, an attributable risk of 0.1%.¹⁰²

- **Medications.** A risk reduction of up to 25% has been shown for women regularly using aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).¹⁰³⁻¹⁰⁶ One study has shown that post-menopausal NSAID users have lower levels of oestrogen than non-users.¹⁰⁷ However, because of the potential adverse consequences of high intake of aspirin, such as gastrointestinal haemorrhage, it would not be recommended as a prophylactic measure.

Molecular biology and genetics

Inherited genetics

Intense research into the genetic basis of familial breast cancer in the 1990s led to the identification of the 'high risk' breast cancer susceptibility genes *BRCA1* and *BRCA2*.^{108,109} Increased susceptibility to breast cancer is also a feature of several other very rare, familial cancer syndromes (**Table Five**). Women carrying deleterious mutations in the *BRCA* genes have a 50-80% chance of developing breast cancer.¹¹⁰ This risk varies depending on the strength of the family history. Deleterious mutations in these genes account for the majority of multi-case, multi-generation families with four or more cases of breast cancer¹¹¹ and genetic testing for faulty *BRCA* genes is available on the NHS for women with a very strong family history. However, these mutations are rare in the population. They account for just 2-3% of all breast cancer and less than 20% of the familial or inherited genetic component of disease risk.¹¹²

Most of the unexplained inherited component of disease risk is due to gene variants that confer small or modest increases in breast cancer risk. Several variants that confer a 2- to 2.5-fold increase in risk have been found in genes such as *CHEK2*,¹¹³ *BRIPI*,¹¹⁴ and *PALB2*.¹¹⁵ These variants are all uncommon in the population (< 1% frequency) and they account for less than 5% of the genetic component of the disease. More recently eight genetic polymorphisms (population frequency of 5 percent or more) that are associated with an increased risk of breast cancer have been found^{116,117} but these increase risk by less than 1.3-fold and account for just 4% of the genetic component of the disease. It is likely that many more polymorphisms such as these will be identified in the next few years and it is possible that combinations of them could be used to identify women at high risk of the disease.¹¹⁸

Somatic mutations

Breast cancer, like all other cancer, is fundamentally caused by accumulation of

multiple genetic abnormalities in breast epithelial cells. While some of these abnormalities might be inherited, most accumulate during a woman's lifetime. These are known as 'somatic' mutations. A wide variety of genes is commonly mutated or incorrectly regulated in breast cancer cells and have been implicated in the development and progression of the disease. These include genes encoding growth factors and receptors, intracellular signalling molecules, cell cycle regulators, apoptosis (cell death) regulators and adhesion molecules. Studies of these altered molecules are identifying new diagnostic and prognostic markers and unearthing new potential targets for therapy. The best example of such a targeted therapy is trastuzumab, which has been shown to be effective in breast cancer that overexpresses the growth factor receptor ERBB2 (also known as HER2).¹¹⁹

Prevention and screening

Breast cancer screening can detect very early stage breast cancer when the tumour is too small to be seen or felt. Such tumours have an excellent prognosis and around half of all tumours detected through screening could not have been detected by hand.¹²⁰ A national screening programme for breast cancer (NHSBSP), the first of its kind in the world, was introduced by the NHS in 1988 following recommendations made by the Forrest report.¹²¹ Asymptomatic women aged 50-64 were invited for mammographic screening at three-yearly intervals as studies had estimated that if at least 70% of such women attended screening, there would be a 25% reduction in breast cancer mortality rates in women invited for screening.¹²²⁻¹²⁴ An international review confirmed that breast cancer mortality on average would be reduced by 25% for women aged 50-69 invited for screening but, for women aged 50-69 who were screened regularly, the reduction would increase to 35% – effectively one life saved for every 500 women screened.¹²⁵ A case-control study of the impact of screening in East Anglia reported a 48% breast cancer mortality reduction for women attending screening.¹²⁶

The NHSBSP has reviewed and refined its operation over the last twenty years based on research findings.¹²⁷ Originally a single view mammogram was taken at each screen, but when a randomised controlled trial showed a 24% increase in cancer detection rates for two-view mammography at the first (prevalent) screen, this was introduced in 1995.¹²⁸ Two-view mammography was extended to all screens in England from 2003 following new epidemiological evidence.¹²⁹ It was also announced in 2000 that the upper age limit for inviting women for screening would be raised

^k Pregnancy-induced high blood pressure which causes swelling, abnormal amounts of protein in urine and – in eclampsia – seizures
^l Overall 0.6% of the cumulative risk of cancer to age 75 might be attributable to radiation in the UK, approximately 700 cases of cancer each year. This is low compared to other developed countries

from 64 to 70 in England, Wales and Scotland. In England the programme will be extended further to cover women aged 47-73 by 2012.¹³⁰ Older women can request screening and there is concern, that despite their higher risk of developing breast cancer, there is a lack of awareness amongst older women.¹³¹ Initiatives are underway to increase breast cancer awareness and promote earlier diagnosis in older women.^{132,133} The cost/benefit case for women younger than 47 receiving screening is under investigation.^{134,135} Younger women have denser breasts making cancer detection more difficult and there is also the associated risk from the additional radiation to be considered.¹³⁶ However, annual screening using mammography or an MRI scan is available to young women aged under 50 with a family history of breast cancer if they are considered to be at moderate risk (17-30% lifetime risk) or high risk (>30% lifetime risk).¹³⁷⁻¹³⁹ Less than 1% of women are at high risk due to the inheritance of a faulty gene (*BRCA1*, *BRCA2* and *TP53*), and after consultation with genetic counselling services, they may have risk-reducing surgery (prophylactic bilateral mastectomy).¹⁴⁰

All women, whatever their level of risk or age, need to be fully informed about their chance of developing breast cancer and the drawbacks, such as over-diagnosis and over-treatment, as well as the benefits of screening.¹⁴¹ A key element of the screening programme is the provision of quality-assessed information so that women can make an informed choice.¹⁴² New information leaflets are in preparation.

Breast cancer screening programmes are run from separate departments in England,¹²⁷ Scotland,¹⁴³ Wales,¹⁴⁴ and Northern Ireland.¹⁴⁵ Much information, including annual results, is routinely published and widely available. A short summary of the most recent results from the audit of breast cancer detected by the NHSBSP in the UK is given in **Table Seven**.¹⁴⁶ Nearly 2 million women aged 50-70 were screened between 1st April 2006 and 31st March 2007 in the UK. 15,856 cancers were detected and 79% of these are invasive, about half of all breast cancers at those ages, with the remainder occurring in women who do not attend screening or who present symptomatically in the interval between screens. Tumours detected by screening tend to be smaller and earlier than those diagnosed outside the screening programme¹⁴⁷, and only a quarter of women diagnosed with invasive cancer by screening have mastectomies – most are treated with breast conserving surgery (lumpectomies).¹⁴⁸ As a result of screening, it is estimated that 1 in 8 women are spared mastectomies because their tumour is detected at an earlier stage.¹⁴⁹ The five-year relative survival rate for women whose invasive cancer was detected by screening between March 2000/April 2001 was 96.4%.¹⁴⁶

The NHSBSP continues to develop and explore

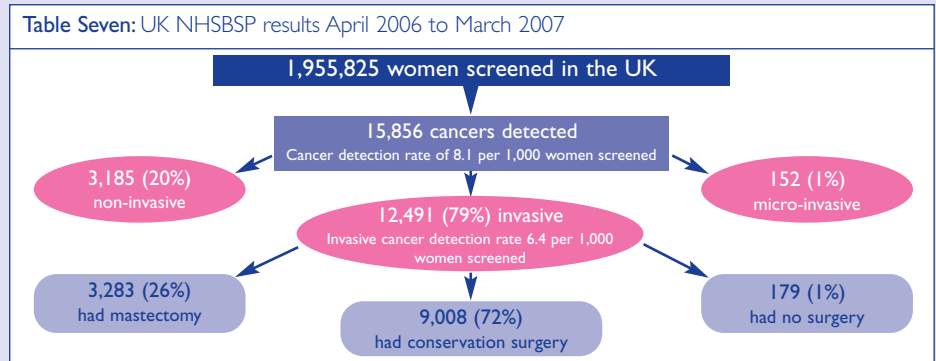


Table Eight: The main stages of breast cancer

Stage I	<ul style="list-style-type: none"> • Tumour up to 2 cm • No lymph nodes affected • No evidence of spread beyond the breast
Stage II	<ul style="list-style-type: none"> • Tumour between 2cm and 5cm, and/or: • Lymph nodes in armpit affected • No evidence of spread beyond armpit
Stage III	<ul style="list-style-type: none"> • Tumour more than 5cm • Lymph nodes in armpit affected • No evidence of spread beyond armpit
Stage IV	<ul style="list-style-type: none"> • Tumour of any size • Lymph nodes in armpit often affected • Cancer has spread to other parts of the body

better ways of delivering the service to maximise the benefits and minimise the drawbacks including false positive and false negative findings. Digital mammography, which has higher sensitivity^m for younger women and higher specificityⁿ than conventional mammography, is being introduced with the possibility of harnessing computers to help radiologists read the increasing number of mammograms.^{150,151} False positive results are an important problem as they cause anxiety and unnecessary additional assessments and may reduce attendance rates for subsequent screens.^{152,153} Around 9% of women are recalled after their first screen but less than 10% of these will have either an in situ or invasive cancer.¹⁵⁴ At subsequent screens a lower percentage of women are recalled (around 4%) but a higher number (1 in 5) will have in situ or invasive cancer.¹⁵⁴ Overall, around 95% of women attending screening have no abnormality and will be routinely invited for screening three years later. Of the 5% who are recalled, only 1 in 6 will have an in situ or invasive cancer.¹⁵⁴ However, the chance of a recalled woman having cancer has risen since the introduction of two view mammography.¹⁵⁵ Personal characteristics (use of HRT, previous breast surgery and BMI) may also affect the efficiency and possibly the effectiveness of mammography and need to be taken into consideration.¹⁵⁶ Acceptance rates are above the necessary 70% overall, but certain groups in the population, for instance minority ethnic women, have lower uptake, and strategies to encourage their attendance are being devised. About 1 in 5 cancers (around 3,000 annually) detected by the screening programme are non-invasive, the main type being ductal carcinoma *in situ* (DCIS). The natural history of these tumours is not fully

known but there is evidence that they carry a raised risk for invasive cancer. Most are treated in case they progress, inevitably leading to some over-treatment.^{149,157,158} To improve treatment for these non-invasive conditions and to help prevent over-treatment, a prospective study has been set up called the Sloane project.^{159,160}

Symptoms and treatment

Symptoms of breast cancer vary widely but include a lump that can be felt, change in the breast size or shape, altered skin texture and drawing in of the nipple. Breast lumps are, however, common, especially in younger women, and the majority are not cancerous. About 30% of women diagnosed with breast cancer have no symptoms and are detected by breast screening.

Breast cancer is diagnosed by taking a biopsy, or sample of breast tissue, and examining it under the microscope. Subsequent treatment decisions are based on the extent of the disease (**Table Eight**) and characteristics of the cancer, menopausal status and general health of the patient. Treatment is usually multimodality, requiring careful co-ordination and planning among surgeons, medical/clinical oncologists, pathologists, radiologists and other staff.¹⁶¹⁻¹⁶⁴

Carcinoma in situ

Ductal carcinoma in situ (DCIS). Breast screening has led to an increase in the detection of DCIS, where cancerous cells are found in the lining of the breast ducts. DCIS is “non-invasive” meaning that it cannot spread, but can progress and become invasive. It is treated, usually by breast conserving surgery +/- radiotherapy or, by mastectomy.

^m Proportion with condition who test positive
ⁿ Proportion without condition who test negative

Lobular carcinoma in situ (LCIS). Here abnormal cells are found in the breast lobes.¹⁶⁵ LCIS is often an incidental finding in biopsies taken for other reasons or it may be diagnosed through screening. Although not itself pre-cancerous, the presence of LCIS is associated with slightly increased risk of developing invasive cancer in the future; as such, patients are kept under surveillance. Occasionally an area of LCIS may be surgically removed if it has high grade features.

Early breast cancer

This term refers to those patients whose cancer has not spread outside the breast and the axillary lymph glands under the arm on the same side as the tumour. Treatment is given with curative intent.

Surgery. Initial treatment is usually to remove the cancer surgically, either by breast conservation followed by radiotherapy, or mastectomy, which may be followed by immediate or delayed reconstruction. The choice of operation depends on the characteristics of the cancer and the patient's preference. Prior to surgery if there is no evidence that the cancer has spread to the axillary lymph nodes, patients may be offered sentinel lymph node biopsy in which only one or two critical lymph nodes are removed; this reduces complications such as lymphoedema. If the sentinel node(s) contains cancer, or if cancer cells have already been detected in ultrasound-guided fine needle aspiration cytology/core biopsy, it is necessary to surgically remove all the lymph nodes by an axillary dissection.¹⁶³

Adjuvant treatment. Adjuvant therapy is given to reduce the risk of cancer recurrence or death from microscopic spread of the cancer that is suspected, but cannot be detected, at the time of diagnosis. Increasing size of the primary cancer; higher histological grade and the presence of tumour in the axillary nodes all increase the risk of subsequent recurrence and death.

- **Radiotherapy** to the breast is routine after breast conserving surgery; together they are as effective at treating the primary cancer as mastectomy in reducing the risk of local recurrence.¹⁶⁶ After mastectomy, radiotherapy to the chest wall and regional lymph nodes is given to patients considered at higher risk of loco-regional recurrence, for example, those with large cancers or involvement of several axillary lymph nodes.
- **Endocrine therapy** is offered only to the two-thirds of women whose cancer is oestrogen receptor (ER) positive. In such women, adjuvant endocrine therapy reduces the risk of breast cancer recurrence and death by 40% and 30%, respectively.¹⁶⁷ Oral tamoxifen given for 5 years is well established and effective in both pre- and post-

menopausal women. In pre-menopausal women removing the ovaries has a similar effect. In post-menopausal women only, the aromatase inhibitors (anastrozole, letrozole and exemestane) given orally, block oestrogen production and are more effective than tamoxifen.¹⁶⁸ They may be given in place of tamoxifen, after 5 years of tamoxifen use¹⁶⁹, or women may switch to an aromatase inhibitor after 2 or 3 years of tamoxifen.^{170,171}

- Adjuvant **chemotherapy** reduces the risk of breast cancer recurrence and death by about 30% and 20%, respectively.¹⁶⁷ Because of its side-effects, adjuvant chemotherapy is usually given to women at significant risk of recurrence, or if their cancers are ER negative. The benefits of adjuvant chemotherapy in women over 70 are not well established as this age group of patients are under-represented in clinical trials. Anthracycline-based regimens are the current standard. The addition of a taxane (Paclitaxel or docetaxel) may benefit sub-groups of women with higher risk disease.¹⁷²

- **Biological therapies.** The HER2 receptor is over-expressed in around 15–20% of invasive breast cancers and biological therapies may be used.^{161,173} The monoclonal antibody trastuzumab is given intravenously which targets the HER2 receptor in women with HER2 positive cancers. Preliminary analysis shows that the addition of trastuzumab to adjuvant chemotherapy reduces the risk of relapse and death by about 50% and 30% respectively for this subgroup of patients but with some increased risk of cardiotoxicity.¹⁷⁴⁻¹⁷⁶ As yet, the optimal duration of adjuvant trastuzumab is unclear.

Although generally well tolerated, trastuzumab can cause cardiac damage. It should not be given at the same time as anthracycline chemotherapy or to patients with pre-existing heart failure. All patients must have their cardiac function assessed before and during treatment with trastuzumab.

Clinical trials of lapatinib are underway in the adjuvant setting. Lapatinib also targets HER2 but is given orally and in addition acts on another receptor: Bevacizumab, which targets the formation of new blood vessels in tumours, is also being evaluated as adjuvant intravenous therapy.

- **Neo-adjuvant therapies.** Patients may be offered neo-adjuvant chemotherapy (or less often endocrine therapy) before definitive breast surgery. Neo-adjuvant chemotherapy may allow breast conservation surgery where otherwise mastectomy was the only choice. It also has the potential advantage of allowing the response of the primary tumour to be monitored, and alternative chemotherapy be

offered if initial chemotherapy is not working. Neo-adjuvant treatment is standard in patients with locally advanced breast cancer (see below).

Locally advanced breast cancer (LABC)

Women with LABC have substantially worse outlook than those with early breast cancer. LABC encompasses a wide range of clinical presentations including primary tumours involving the skin or chest wall (T4) and fixed axillary nodes or involvement of the internal mammary nodes (N2/3). Inflammatory breast cancer is a specific, aggressive form usually seen in younger women and characterised by inflammatory skin changes often with a diffuse underlying tumour.

Initial treatment with anthracycline-based chemotherapy is standard and may be followed by a taxane. For patients who respond, definitive local therapy may be total mastectomy and axillary nodal clearance, followed by radiotherapy to the chest wall and to the regional lymph nodes. Breast conserving surgery may be considered in those who achieve good, partial or complete response to the primary chemotherapy. Subsequent systemic therapy may include further chemotherapy, trastuzumab (if HER2 positive) and endocrine therapy (if ER positive).

Metastatic breast cancer

Occasionally patients have visible spread of the cancer, known as metastatic disease when they first present, but usually metastatic disease is a sign of disease recurrence. Treatment for patients with metastatic (stage IV) breast cancer is "palliative" in nature; the prognosis is better for women with soft tissue (e.g. bone) rather than those with visceral (e.g. liver) metastases. The aim is to control (rather than cure) the disease, prolong life, improve symptoms and maintain quality of life.

Endocrine therapy. Blocking hormones is the first option for patients with ER positive disease; the exception may be those with spread to vital organs in whom chemotherapy may be preferred. If there is a good response to first-line endocrine therapy, second and further lines of endocrine therapy may also be effective.^{177,178}

The choice of therapy depends on the menopausal status of the patient, previous adjuvant endocrine treatment, and exposure and response to prior endocrine therapy for metastatic disease. In post-menopausal women, the aromatase inhibitors are used first-line but tamoxifen remains a useful option for pre-menopausal women. Other options include ovarian ablation for pre-menopausal women and fulvestrant¹⁷⁹, which is given intra-muscularly, for post-menopausal women.

Cytotoxic chemotherapy. Chemotherapy is offered to patients whose disease is no longer sensitive to endocrine therapy and those with ER negative disease. Many chemotherapy drugs

are active in breast cancer; including the anthracyclines (epirubicin, doxorubicin), taxanes (docetaxel, paclitaxel), capecitabine, vinca alkaloids (vinorelbine) cyclophosphamide, platinum agents (carboplatin, cisplatin) and ixabepilone. With the exception of capecitabine, they are given intravenously; vinorelbine can be given either intravenously or orally. They all have significant toxicities. Prior adjuvant therapies, the rate of disease progression, general health of the patient and clinician/patient preference all influence the choice of treatment. Single agents given in sequence are often preferred to combination chemotherapy.

Biological therapies. Single agent trastuzumab can work in women whose cancers are HER2 positive, but more often it is combined with chemotherapy, improving response rates and overall survival in these patients.¹¹⁹ There is increasing evidence of benefit from continuing trastuzumab beyond disease progression when a further line of chemotherapy is initiated^{180, 181}; lapatinib also can work in this setting.¹⁸² Because trastuzumab does not cross the blood brain barrier, it is ineffective in treating brain metastases.

Other treatment modalities. Radiotherapy has an important palliative role in treating painful bone metastases, inoperable brain metastases, spinal cord compression, lung obstruction and fungating or painful breast or chest wall disease. Bisphosphonates are given to treat pain and to reduce skeletal complications in patients with bone metastases; they can be given either orally or intravenously. Surgery may be used in some patients, for example, orthopaedic interventions for fractures or weakening of bones caused by spread of the cancer; spinal surgery for spinal cord compression and pleurodesis for malignant pleural effusion.

Survival

Survival rates for breast cancer have been improving since 1971⁹ in England and Wales.¹⁸³ The most recent survival rates in England and Wales are for women diagnosed in 2001-03. For this group of women five-year relative survival rates reached 80%, compared with only 52% for women diagnosed thirty years earlier in 1971-75 (Figure Eight).¹⁸⁴⁻¹⁸⁶ Over the same time period one-year relative survival rates have increased from 82% to 94% and ten-year relative rates from 41% to a predicted 72%. The predicted twenty-year survival for patients diagnosed in 2001-03 is 64% - the same rate as the ten-year survival for women diagnosed five years earlier in 1996-98. Similar increases have occurred in Scotland.¹² The latest survival statistics are for Scottish women diagnosed in 2000-04 who had relative survival rates of 96% at one year, 84% at five years and 72% at ten years.¹²

Survival varies by age at diagnosis. For most cancers relative survival decreases with age but

Figure Eight: Age-standardised relative survival at one, five, ten and twenty years since diagnosis, female breast cancer; England and Wales, 1971–2003

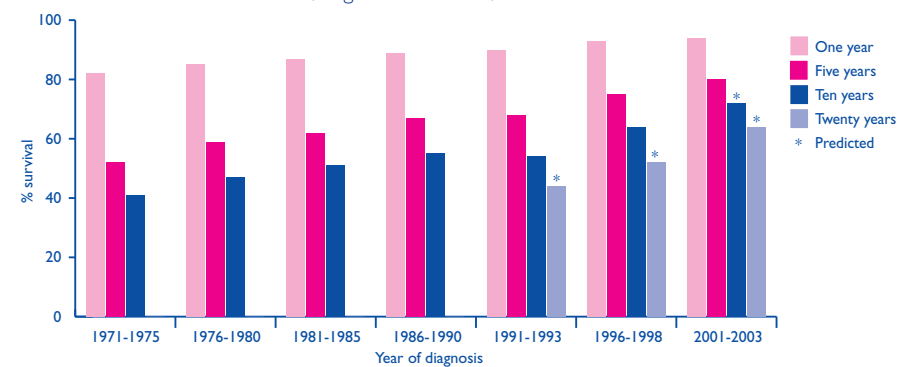


Figure Nine: Five, ten, fifteen and twenty-year relative survival for female breast cancer, by age, England, 2001–2003

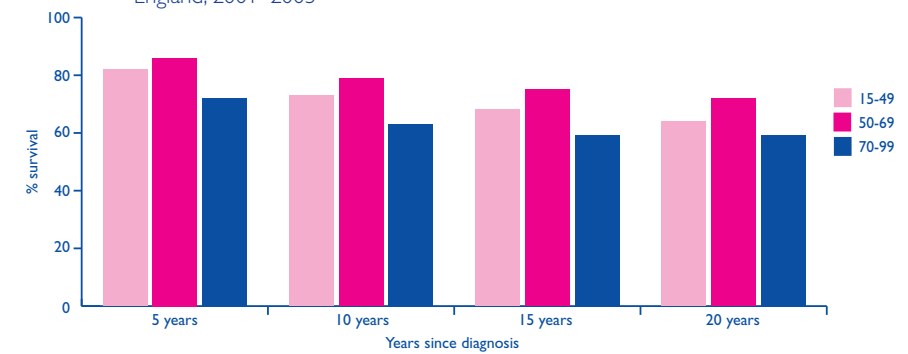
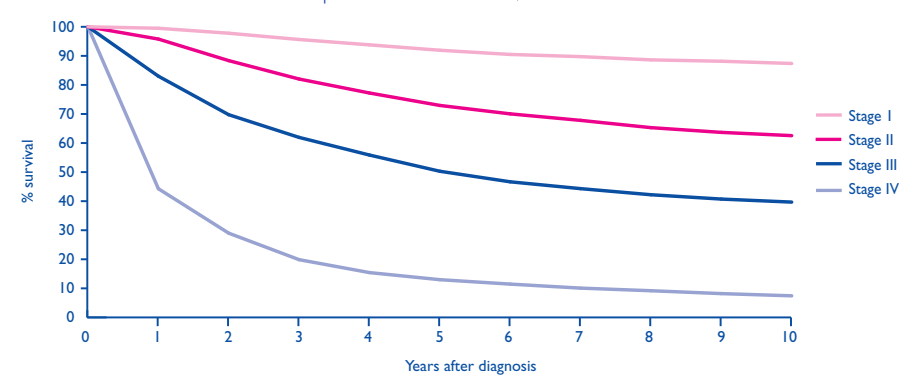


Figure Ten: 0 to ten year relative survival for breast cancer by stage, diagnosed in the West Midlands 1990–1994 followed up to the end of 2004, as at December 2008



breast cancer is unusual in that women diagnosed in their 50s and 60s have consistently higher survival rates than either younger or older women (Figure Nine).^{186, 187} Over the ten year period 1991-93 v 2001-03, survival has improved for all age groups at all end-points but the younger women had smaller improvements than women aged over 50.¹⁸⁶ For example, ten-year relative survival increased by 13% over this period for women aged 15-49 compared to 24% for women aged 50-69 and 18% for women aged 77-99.

The later the stage of disease at diagnosis, the lower the survival rate (Figure Ten).¹⁸⁸ For women diagnosed in the early 1990s in the West Midlands, 5-year relative survival rates were 92% for stage I tumours, 73% for stage II tumours, 50% for stage III tumours and 13% for stage IV tumours. The survival rates were 5% lower at

10 years for stage I and IV tumours, but for stage II and stage III tumours, they fell by a further 10%.

Analysis of survival by level of deprivation has consistently shown higher survival for more affluent women.^{184, 189} Up until the mid-1980s in England and Wales the deprivation gap was around 10%, but since then it has fallen to 6%.¹⁸ Although not directly comparable because deprivation measures are not identical, survival by deprivation in Scotland showed a similar difference.¹⁹⁰ Both countries showed no widening of the gap since the mid-1980s despite the fact that more affluent women attend screening.^{18, 190} For women diagnosed in 1987 or 1993 in Scotland, affluent women under 65 were more likely to have ER positive (good prognosis) breast cancers than their

⁹ Introduction of revised registration scheme in England and Wales

deprived counterparts (65% v 48%). This difference accounted for between 20-30% of the observed 10% survival gap between the affluent and deprived.¹⁹¹ Other factors which may contribute to the deprivation gap in survival include co-morbidity, stage at diagnosis, and access and uptake of treatments.¹⁸⁹

Cancer survival in Europe has been calculated since 1978 by the EUROCORE programme.¹⁹² Reports based on the latest data show that breast cancer survival has improved over time and inter-country survival differences are reducing.^{187, 193} However, survival in the UK is far from the best and much lower than reported in the US (**Figure Eleven**).¹⁹³ Generally breast cancer survival rates are highest in northern Europe and lowest in Eastern Europe. Comparative survival rates are difficult to interpret as they are affected by a number of factors but more detailed studies have suggested that the lower breast cancer survival rates in the UK compared to other northern European countries are largely explained by patients having more advanced disease at diagnosis.¹⁹⁴⁻¹⁹⁶

A study of cancer survival rates across the world has recently been published.¹⁹⁷ Five-year relative survival rates, standardised to the International Cancer Survival Standard, were calculated for patients aged 15-99 diagnosed during 1990-94. Breast cancer survival rates varied from over 80% in North America, Sweden, Japan, Australia and Finland to less than 60% in Brazil and Slovakia and below 40% in Algeria. Most European countries including Scotland, England, Ireland and Wales, had rates in the 70-79% range.¹⁹⁷ As with the deprivation gap, a variety of factors are likely to affect these outcomes.

Mortality

In the UK in 2007 there were 12,082 deaths from breast cancer; 11,990 (99%) of these were in women and 92 (1%) were in men. Breast cancer accounts for around 16% of female deaths from cancer in the UK and was the most common cause of cancer death in women up to and including 1998; since then there have been more deaths from lung cancer. In younger women aged 35-54, breast cancer is the most common cause of death and is responsible for 1 in 7 deaths at that age. The number of deaths from breast cancer and the rates for the constituent countries of the UK are shown in **Table Nine**.¹ Death rates from breast cancer increase with age with the highest rates occurring in the 85+ age-group (**Figure Twelve**).¹

Trends

Thirty years ago, England and Wales had the highest breast cancer mortality rates in the world, closely followed by Scotland.¹⁹⁸ Ten years later the UK still had top position with rates more than four times higher than in Japan.¹⁹⁹ The death rates had climbed inexorably since the 1950s until they reached their peak in 1989

Figure Eleven: Age-adjusted 5-year relative survival for female breast cancer; selected countries, period analysis 2000–03

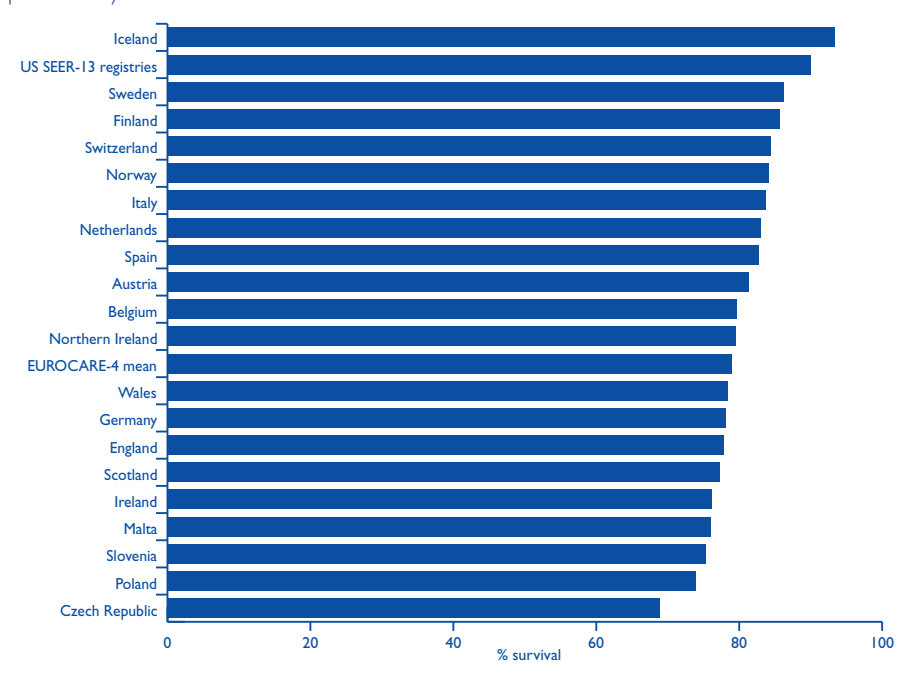
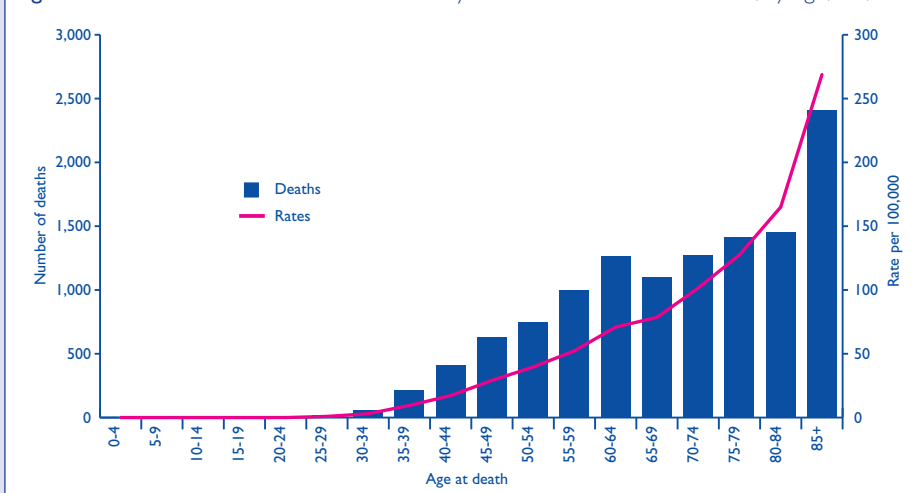


Table Nine: Number of deaths and mortality rates of breast cancer; UK, 2007

		England	Wales	Scotland	N. Ireland	UK
Number of deaths	Males	76	10	5	1	92
	Females	9,986	637	1,062	305	11,990
	Persons	10,062	647	1,067	306	12,082
Crude rate per 100,000	Males	0.30	0.69	0.20	0.12	0.31
	Females	38.44	41.74	39.95	34.00	38.60
	Persons	19.69	21.71	20.74	17.39	19.81
European age-standardised rate per 100,000 (95% CI)	Males	0.24 (0.18-0.29)	0.50 (0.19-0.81)	0.17 (0.02-0.32)	0.12 (0.11-0.35)	0.24 (0.19-0.29)
	Females	26.69 (26.16-27.21)	26.66 (24.59-28.73)	27.13 (25.50-28.76)	26.26 (23.31-29.20)	26.71 (26.23-27.19)
	Persons	14.52 (14.23-14.80)	14.69 (13.56-15.83)	15.09 (14.18-15.99)	14.54 (12.91-16.16)	14.57 (14.31-14.83)

Figure Twelve: Number of deaths and mortality rates for female breast cancer, by age, UK, 2007



(**Figure Thirteen**).²⁰⁰⁻²⁰² From 1989 onwards, the EASRs in the UK (and England and Wales) fell dramatically from 42 per 100,000 to 27 per 100,000 in 2007, a decrease of 36%. The number of deaths in the UK fell from 15,625 in 1989 to 11,990 in 2007, a decrease of 23%. Recent mortality projections for the UK until 2025, estimated that the number of women dying from breast cancer would fall by a further 6%.²⁰³ The decrease since 1989 occurred in all age-

groups (**Figure Fourteen**).²⁰⁰⁻²⁰² Between 1989 and 2007 the breast cancer mortality rate fell by 41% for women aged 40-49 and 50-64 years; by 38% for women aged 65-69; by 35% for women aged 15-39 and by 20% for women over 70. The reduction in mortality rates is likely to have several different causes including screening, increasing specialisation of care and the widespread adoption of tamoxifen treatment and other hormone therapies since 1992.

Future

Death rates from breast cancer are falling rapidly but with rising incidence rates and an ageing population, the number of women diagnosed with breast cancer in the UK is going to increase. This will have important implications for the health service and the specialist care that breast cancer patients need. The much improved survival rates, a product of both earlier stage presentation and more effective treatment, mean that breast cancer is becoming a disease which women live with rather than die from. With increasing numbers of survivors, the long-term effects of treatment, both physical and psychological, become even more important. Research needs to be directed towards achieving early diagnosis and effective treatment for all women with breast cancer; including those who are older or socio-economically deprived. New initiatives to increase early diagnosis have recently been launched by the Department of Health and Cancer Research UK as part of the Cancer Reform Strategy.¹³³

Continuing research into the genes that put some women at increased risk of breast cancer will highlight new opportunities for prevention and risk reduction. It will also enable targeting of screening and surveillance to those who most need it. Meanwhile, our knowledge of the molecular changes associated with the development of breast cancer is growing. Some of these alterations hold promise for use as molecular markers in diagnosis and early detection, or for monitoring disease progression

or response to therapy. They are also providing leads for the design of new treatments. Alongside, scientists are using the latest techniques to reveal genetic variations between breast tumours, and between patients, that

influence the outcome of radiotherapy, drug and hormone treatment. Increasingly, this will be translated into the clinic in the tailoring of treatment to the individual patient and their tumour.

Figure Thirteen: European age-standardised mortality rates for female breast cancer, England and Wales 1950–2007, UK 1971–2007

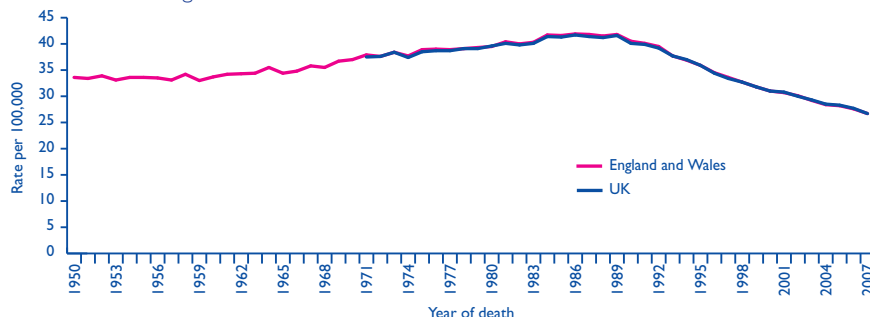
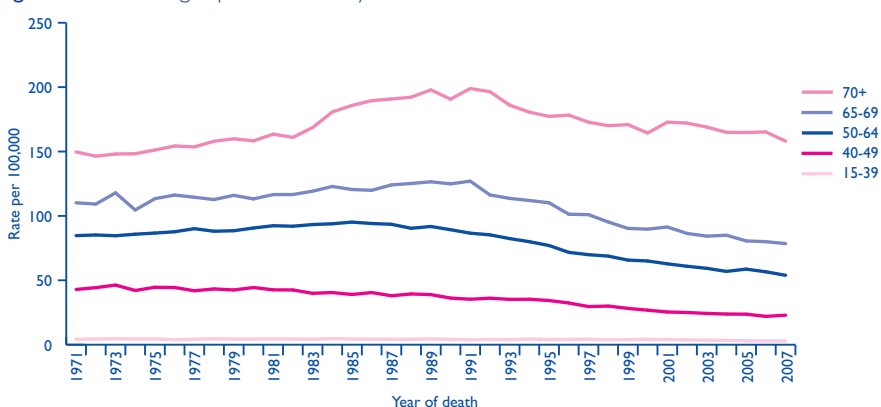


Figure Fourteen: Age-specific mortality rates for female breast cancer, UK, 1971–2007



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Further information

For a list of other CancerStats reports and PowerPoint Presentations, all freely downloadable, visit our Publications website <http://publications.cancerresearchuk.org> choose 'Browse by type' and then select from the list. Or email stats.team@cancer.org.uk for more information and help.

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