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Summary

Ovarian cancer is the fifth most common cancer and the fourth most common cause of cancer death in women in the UK. Survival has improved due to increased use of platinum-based therapy and a greater determination to treat recurrent disease.

However, around 6,500 cases are diagnosed each year and most of these patients are detected at a late stage. The majority of patients will respond to chemotherapy, but most will relapse, contributing to around 4,400 deaths annually. We urgently need better

diagnostics (there is some hope of a screening test in the next 10 years), we need better first line therapies and we need to reduce the numbers of recurrences. Many trials are in progress and some promising new treatments are currently being investigated.

Introduction

Ovarian cancer is the fifth most common cancer and the fourth most common cause of cancer death in women in the UK. This report provides a snapshot of the most recent statistical information on ovarian cancer for the UK (or Great Britain where UK data are not available), Europe and rest of the world. The latest information on risk factors, molecular biology and genetics, diagnosis and treatment is summarised, and the future possibilities of screening are discussed.

Statistics

Incidence

In 2008, around 6,500 women were diagnosed with ovarian cancer in the UK (Table One), making it the second most common gynaecological cancer (Table Two) and the fifth most common cancer in women.^a The crude rate^a shows that this equates to around 21 cases for every 100,000 women. The European age-standardised rate^b for the UK was 16 per 100,000 women, ranging from 16 per 100,000 in England to 20 per 100,000 in Wales. The lifetime risk of developing ovarian cancer is approximately 1 in 50 for UK women.¹

Age

Ovarian cancer is predominantly a disease of older, post-menopausal women with more than 80% of cases being diagnosed in women aged over 50 years.¹ There is a steep increase in incidence after the menopause (Figure One). The highest age-specific incidence rates are seen for women aged 80-84 years at diagnosis (69 per 100,000), dropping to 64 per 100,000 in women aged 85 and over.¹

Trends

The incidence of ovarian cancer in British women increased steadily for 25 years, with European age-standardised incidence rates increasing from 15 per 100,000 women in 1975 to around 19 per 100,000 in the late 1990s (Figure Two).¹ The incidence rate has

been decreasing since the early 2000s, reaching 16 per 100,000 in 2008. Trends in ovarian cancer incidence vary by age (Figure Three [page 2]), and it can be seen that much of the early increase in incidence occurred in women aged 65 and over; between 1975 and 1999, the incidence rate for women aged 65+ rose from

Table One: Ovarian Cancer (C56-C57), Number of New Cases and European Age-Standardised Incidence Rates, Countries of the UK, 2008

	England	Wales	Scotland	N. Ireland	UK
Number of new cases	5,304	400	648	185	6,537
Crude rate per 100,000	20.3	26.1	24.3	20.5	20.9
European age-standardised rate per 100,000 (95% CI)	15.8 (15.4 - 16.2)	19.6 (17.7 - 21.5)	18.0 (16.6 - 19.4)	17.6 (15.0 - 20.1)	16.2 (15.9 - 16.6)

Table Two: Gynaecological Cancers, Numbers of New Cases and Deaths and European Age-Standardised Incidence and Mortality Rates, UK, 2008

Site	Incidence		Mortality	
	Number of cases	European age-standardised rate per 100,000 (95% CI)	Number of deaths	European age-standardised rate per 100,000 (95% CI)
Ovary	6,537	16.2 (19.9-16.6)	4,373	9.7 (9.4-10.0)
Uterus	7,703	19.4 (18.9-19.8)	1,741	3.6 (3.4-3.8)
Cervix	2,938	8.7 (8.4-9.0)	957	2.4 (2.2-2.5)
Vulva	1,157	2.5 (2.4-2.7)	400	0.7 (0.6-0.7)
Vagina	258	0.6 (0.4-0.7)	77	0.1 (0.1-0.2)

Figure One: Ovarian Cancer (C56-C57), Number of New Cases and Age-Specific Incidence Rates, UK, 2008

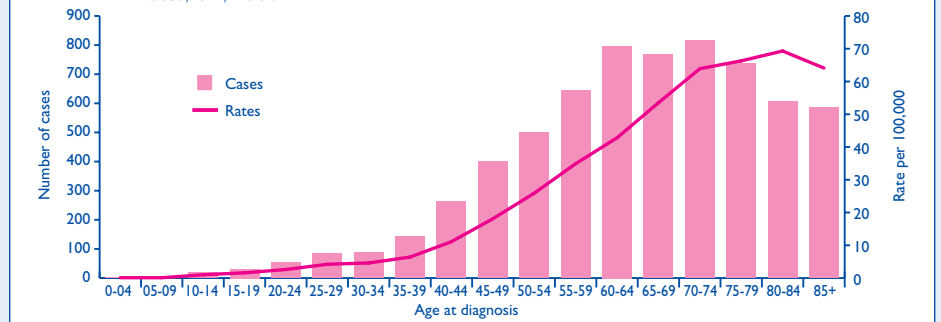
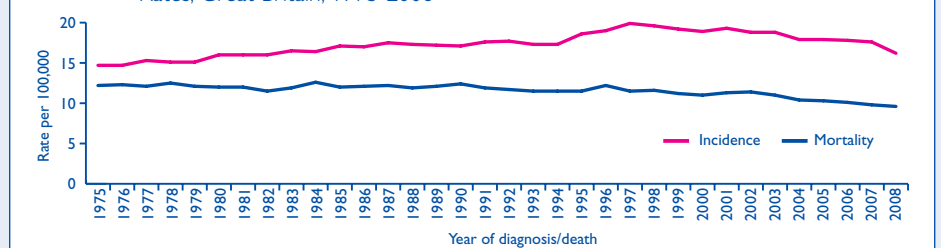


Figure Two: Ovarian Cancer (C56-C57), European Age-Standardised Incidence and Mortality Rates, Great Britain, 1975-2008



^a Crude rates are calculated using a simple formula in which the number of cases is divided by the corresponding population and multiplied by 100,000.
^b Since cancer is generally more common in older people, crude rates are greatly influenced by the proportions of older people in the populations being studied. Age-standardised rates take account of age differences in the underlying populations, and hence provide unbiased comparisons of incidence rates with respect to age (for example, over time, between sexes or between geographical areas). Age-standardised rates are calculated by multiplying individual age-specific rates by corresponding proportions (or weights) in a standard population and then summing to create an overall rate per 100,000. In this report we express incidence and mortality rates using the European age-standardised rate.

43 to 68 per 100,000, an increase of more than 50%.¹ The decrease in incidence since the early 2000s has occurred in all age groups, but women aged 50-64 have shown the biggest decrease (from 44 per 100,000 in 2001 to 34 per 100,000 in 2008). Widespread use of the contraceptive pill, which reduces risk, is one possible explanation for the stability of rates in younger women and possibly the recent fall in the 65 and over age group (see **Risk factors** section). Coding changes to the classification of ovarian cancer^c may also affect comparisons over time and between different populations.

A study of incidence and mortality trends in 28 European countries showed similar recent declines in incidence, especially in younger women, for most countries in Northern and Western Europe (but not in the rest of Europe). Some of this variation may be explained by geographical differences in the uptake of oral contraception across Europe.²

Geographic variation

Ovarian cancer incidence varies by around 40% across the four regions of Europe, with estimated European age-standardised rates ranging from 12 per 100,000 women in Southern Europe to 17 per 100,000 in Northern Europe in 2008.³ The countries with the highest incidence rates (**Figure Four**) were Latvia, Lithuania and Bulgaria (all around 19 per 100,000), and the lowest were Cyprus and Portugal (7 per 100,000). The UK ranked 6th out of the 27 countries in the European Union.³

There were estimated to be 225,000 new cases of ovarian cancer worldwide in 2008, accounting for around 4% of all cancers diagnosed in women.⁴ Incidence rates vary considerably across the world, with World age-standardised rates in more developed countries being nearly twice as high as those in less developed countries^d. The highest rates are recorded in Northern, Central and Eastern Europe, followed by Western Europe and the USA, and the lowest rates in Africa and parts of Asia. Over 65,000 cases were estimated to be diagnosed in Europe in 2008 (45,000 in the EU27) and more than 21,500 in the USA.^{4,5}

Deprivation

In a comprehensive study of incidence and mortality variation within the UK and Ireland, little geographical variation was reported for ovarian cancer.⁶ Incidence tends to be slightly higher among women in more affluent groups

Figure Three: Ovarian Cancer (C56-C57), Age-Specific Incidence Rates, Great Britain, 1975-2008

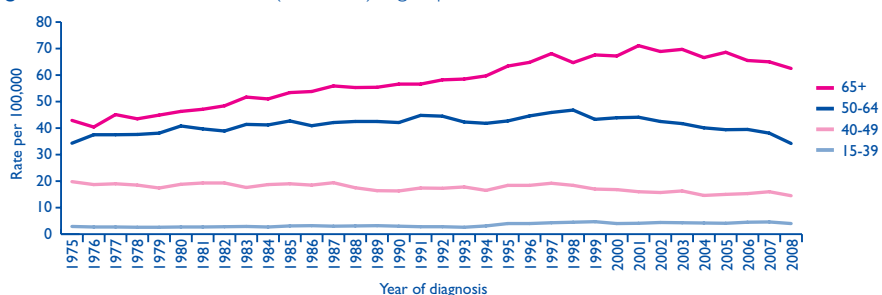


Figure Four: Ovarian Cancer; European Age-Standardised Incidence and Mortality Rates, EU27 Countries, 2008 Estimates

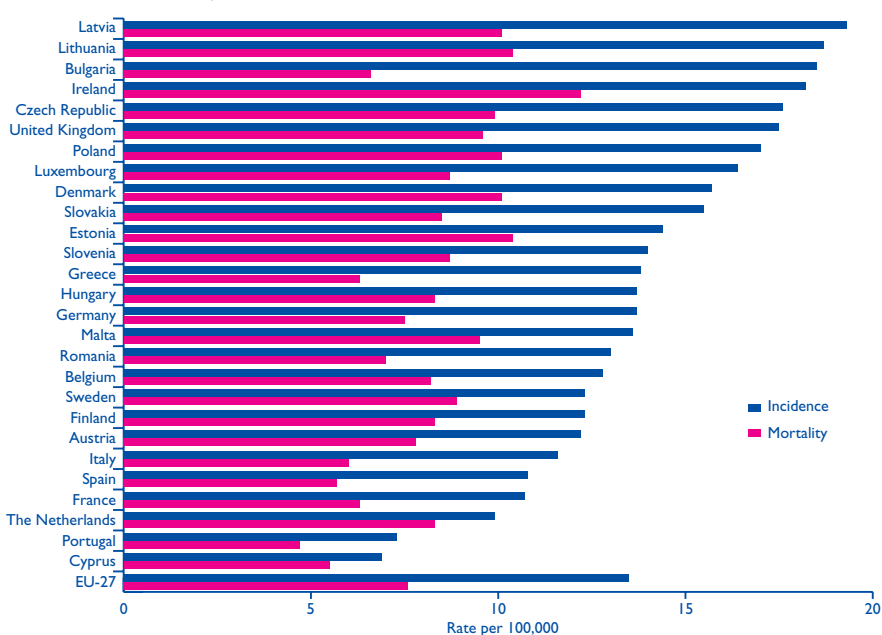


Table Three: Ovarian Cancer (C56-C57), Number of Deaths and European Age-Standardised Mortality Rates, Countries of the UK, 2008

	England	Wales	Scotland	N. Ireland	UK
Number of deaths	3,609	215	423	126	4,373
Crude rate per 100,000	13.8	14.0	15.9	13.9	14.0
European age-standardised rate per 100,000 (95% CI)	9.6 (9.3 - 9.9)	9.3 (8.1 - 10.5)	10.4 (9.4 - 11.4)	11.0 (9.1 - 12.9)	9.7 (9.4 - 10.0)

than in the most deprived groups, which is not unexpected as risk factors such as low parity are more common in more affluent women.^{7,8}

Histology

The majority of ovarian malignancies are epithelial in origin (estimated to be around 50-60%), with the most common type in the UK being serous carcinomas.^{9,10} Other rarer subtypes include germ cell tumours, which tend to occur in pre-menopausal women and are very chemo-sensitive (and hence treatable). It is thought that most histologies share common risk factors, with the probable exception of mucinous carcinomas.^{9,11} The most striking international difference occurs in Japan, which has lower rates of ovarian cancer than in Europe.⁴ Some of this variation may be explained by geographical differences in histologies, since Japan has a higher percentage of clear cell adenocarcinomas (20-25%) compared with other Asian or Western countries (5-10%).¹²

Mortality

Ovarian cancer accounts for more deaths than all the other gynaecological cancers combined (**Table Two**).¹ In 2008, there were around 4,400 deaths from ovarian cancer in the UK (**Table Three**), accounting for 6% of all female deaths from cancer. The crude mortality rate^a shows that this equates to around 14 deaths for every 100,000 women. There was very little variation in European age-standardised mortality rates^b across the UK.¹

During the 1970s and 1980s, while incidence rates rose steadily, European age-standardised mortality rates remained stable at between 11 and 12 per 100,000 women (**Figure Two**). More recently, mortality rates have shown a small but consistent decline, mirroring the recent fall in incidence. In 2008, the mortality rate was less than 10 per 100,000 women, compared with 12 per 100,000 in 1975, a fall of 21%. The relative stability in overall mortality rates masks the marked variation in mortality

^c A change in the classification of some tumours of borderline malignancy from invasive, malignant behaviour (code 3) in ICD-O-2 to uncertain behaviour (code 1) in ICD-O-3 may have contributed to a decrease in incidence since 2000. UK Association of Cancer Registries. Library of recommendations on cancer coding and classification policy and practice. <http://www.ukacr.org/content/library-recommendations>.

^d The estimated World age-standardised incidence rate for the more developed regions of the world was 9 per 100,000 in 2008, and 5 per 100,000 for the less developed countries (Ferlay et al., GLOBOCAN 2008 [version 1.2]. <http://globocan.iarc.fr>). Please note that World age-standardised incidence rates are not comparable to the European age-standardised incidence rates presented elsewhere in this report.

trends at different ages (**Figure Five**). Over the last twenty years, mortality rates have decreased by 40% for UK women aged 45-64 (from 25 per 100,000 in 1989 to 15 per 100,000 in 2008), but increased by around 25% for women aged 75-84 and 85+ (around 49-52 per 100,000 in 1989 and 62-64 per 100,000 in 2008).

The overall decline in mortality, particularly amongst younger women, is a feature of most countries in Northern and Western Europe, while mortality is still increasing in some Southern and Eastern European countries.² Part of the fall in mortality may be attributed to improved treatment for germ-cell ovarian cancers (which affect young women), which was introduced earlier in Northern European countries compared with Southern and Eastern European countries.

Survival

Survival for ovarian cancer has improved over the last 35 years, but long-term rates are still low (**Figure Six**). For women diagnosed in England during 2003-07, the one- and five-year age-standardised relative survival rates were 70% and 41%, respectively, compared to 42% and 21%, respectively, for women diagnosed in England and Wales during 1971-75.¹³ Similar estimates have also been reported for Scotland.⁶ Much of the increase occurred during the 1980s and 1990s, and appears to be levelling off in the 2000s. The significant increase in one-year survival is likely to be the result of greater use of platinum-based chemotherapy, while the increase in five-year survival may be due to both wider access to optimal primary treatment and greater determination to treat recurrent disease.¹⁴ The difference between five- and ten-year survival rates is relatively small (38% vs 35% in 2001-03) indicating that women who survive for five years after diagnosis have a good chance of being cured. Comparative studies of ovarian cancer mortality in Scotland also indicate this.¹⁵

There is a steep gradient in survival by age, with younger women having a better prognosis (**Figure Seven**). For women diagnosed in England during 2003-07, five-year relative survival rates were over 80% for women aged 15-39 and over 60% for women aged 40-49; the disease is more difficult to treat for older women, often because it is widespread at diagnosis, and rates steadily decrease with increasing age. However, survival has improved in all but the very oldest ages since the early 1990s. A recent UK study using the General Practice Research Database concluded that GPs were less likely 'to recognise and to refer patients presenting with ovarian cancer as they get older': this could be a contributory factor

Figure Five: Ovarian Cancer (C56-C57), Age-Specific Mortality Rates, UK, 1971-2008

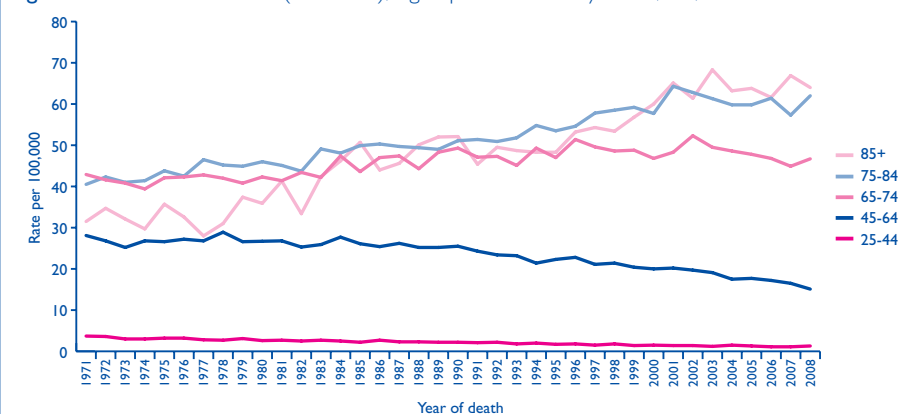


Figure Six: Ovarian Cancer, One-, Five- and Ten-Year Age-Standardised Relative Survival Rates, Adults (Ages 15-99), England and Wales, 1971-1995, and England, 1996-2007

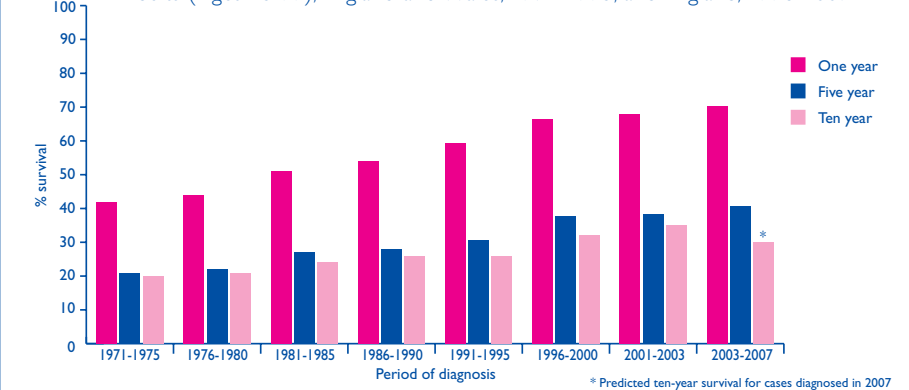


Figure Seven: Ovarian Cancer, Five-Year Age-Specific Relative Survival Rates, England and Wales, 1991-1995, and England, 2003-2007

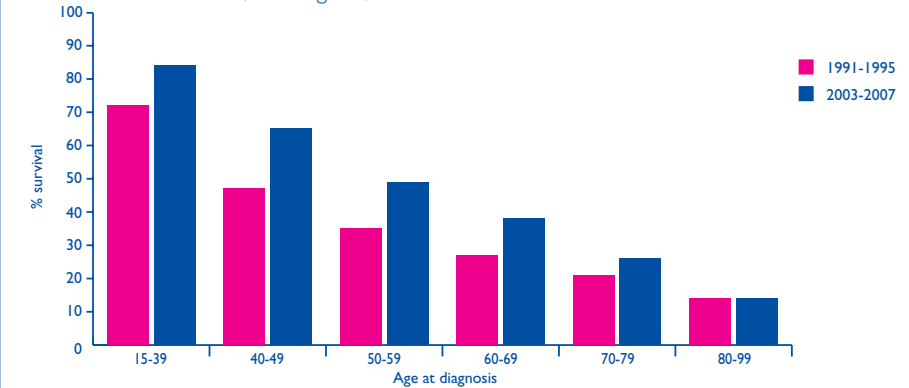


Table Four: Ovarian Cancer, Five-Year Stage-Specific Relative Survival Rates, Adults (Ages 15-99), Anglia Cancer Network, 2004-2008

Stage at diagnosis	No. of cases	% of all cases	5-year relative survival (%)	95% Confidence Interval
Stage I	424	29	92.0	(86.5-97.6)
Stage II	62	4	55.1	(36.8-73.5)
Stage III	652	45	21.9	(17.3-26.4)
Stage IV	216	15	5.6	(1.9-9.4)
Unstaged	89	6	27.6	(16.0-39.3)
All stages	1443	100	43.5	(39.9-47.0)

towards the lower survival rates in older women.¹⁸

An important determinant of ovarian cancer survival is the stage of the disease at diagnosis. Data from the Anglia Cancer Network area for women diagnosed during 2004-08 has shown that five-year relative survival rates are more than 90% for early stage disease, but fall very sharply to less than 10% for late stage cases (**Table Four**).¹⁶ The majority (60%) of women

are diagnosed with stage III or IV disease, and only around 30% of women are diagnosed at the earliest stage.¹⁶ There has been a clear improvement in five-year survival for stage I patients since the late 1980s, with rates increasing from around 80% in 1987-91 to 92% in 2004-08 (**Figure Eight** [page 4]).¹⁶ Less than 5% of patients are diagnosed with stage II disease, and although five-year survival rates have increased since the late 1980s, the confidence intervals are wide (**Table Four**)

⁶ One- and five-year relative survival increased from 52% and 30%, respectively, for women diagnosed during 1980-84 to 67% and 38%, respectively, for women diagnosed during 2000-04. Trends in Cancer Survival in Scotland, 1980-2004. www.isdscotland.com/cancer

making it difficult to draw firm conclusions about any improvement. Five-year survival for women with stage III disease has shown a small but consistent improvement since the early 1980s, and there has been very little change in prognosis for stage IV patients. A study from the Munich area in Germany has also indicated that most of the long-term improvement in ovarian cancer survival has occurred among women presenting with stage I or II disease.¹⁷

When UK survival rates for ovarian cancer are compared with those of other countries, including Australia, Canada, Norway, and Sweden, they are significantly worse. Differences in data quality and coding practices across Europe may contribute to some of the variation, but the consistently lower levels for UK countries suggest real differences in survival. More detailed studies to investigate the factors underlying these differences within Europe are being undertaken.¹⁹⁻²²

It has been estimated that if survival from ovarian cancer in Britain equalled the best in Europe, then almost 2,400 deaths could be avoided within five years of diagnosis.²³

Risk factors

The aetiology of ovarian cancer is not yet completely clear. The strongest known risk factors are increasing age (Figure One) and the presence of certain gene mutations (see Molecular biology and genetics section), the latter accounting for around 10% of cases. As more research is carried out into the histological diversity and origin of ovarian cancers, so it may become more fruitful to examine risk factors by histological subtype.^{11,24} A summary of the most well-researched factors which may raise or lower risk is given below.

Family history

Women who have a first-degree relative diagnosed with ovarian cancer have a three- to four-fold increased risk of developing the disease compared with women with no family history, although only about 10% of ovarian cancer cases occur in women with a family history.^{9,25} The known susceptibility genes (e.g. BRCA1 and BRCA2) explain less than 40% of the excess risk of familial ovarian cancer.²⁵ These estimates suggest that more research is needed (see Molecular biology and genetics section).

Reproductive factors

Ovarian cancer risk tends to be reduced by factors which interrupt ovulation such as pregnancy, breastfeeding, and oral contraceptive use, while those that prolong exposure to ovulation such as nulliparity and infertility increase risk.^{24,26-28} While the epidemiological evidence is less consistent for some of these factors, there is good evidence that both pregnancy and oral contraceptive use lower risk.

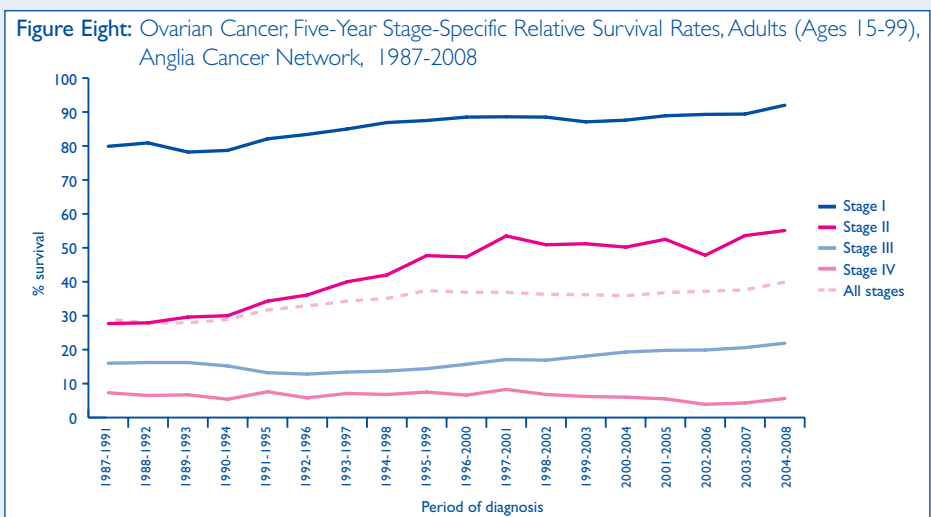


Table Five: Ovarian Cancer, Relative Risk by Parity and Duration of Oral Contraceptive Use

Relative risk for ovarian cancer by parity	Number of children	Relative risk (95% CI)
	3+	1
	2	1.21 (1.10-1.32)
	1	1.60 (1.43-1.79)
	0	2.12 (1.81-2.48)
Relative risk for ovarian cancer by duration of oral contraceptive (OC) use (mean)	OC use	Relative risk (99% CI)*
	Never	1.00 (0.96-1.04)
	Less than 1 year (0.4 years)	1.00 (0.91-1.10)
	1-4 years (2.4 years)	0.78 (0.73-0.83)
	5-9 years (6.8 years)	0.64 (0.59-0.69)
	10-14 years (11.6 years)	0.56 (0.50-0.62)
	15 years or more (18.3 years)	0.42 (0.36-0.49)
Risk reduction for ovarian cancer by time elapsed since cease of OC use (per five years of OC use)	Time elapsed since cease	Proportional risk reduction
	Less than 10 years	29%
	10-19 years	19%
	20-29 years	15%

* Relative risk stratified by study, age, parity and hysterectomy.
Data sources: Beral et al. Lancet 2008;371:303-14; Granstrom C et al. BJG

Pregnancy

Women who have given birth have a lower risk of ovarian cancer than women who have not.²⁹ There is a dose response relationship between increasing risk and a lower number of children (Table Five).⁹ Studies have also shown a risk reduction for incomplete pregnancies.^{30,31}

Breastfeeding

Evidence for a protective effect of breastfeeding is conflicting. Results from a combined analysis of two cohorts of parous women showed that breastfeeding for 18 or more months reduced the women's risk by 34%.³² However, a large case-control study showed no effect of breastfeeding after parity when other potential confounders were taken into account.³³ One study found little evidence of reduced risk for those who breast-fed some children when the last born child was not breast-fed.^{33,34}

Infertility

There is some evidence to suggest that infertility increases risk. Two cohort studies have shown a 36-46% risk increase for ovarian cancer in infertile women which was not the effect of fertility drugs.^{35,36} Research suggests that neither assisted reproductive technology nor fertility drugs has an impact on risk of ovarian cancer overall, although one study found a 67% risk increase for serous tumours after use of clomifene citrate.^{f,37,38}

Exogenous hormones

- **Oral contraceptives**
Oral contraceptives (OCs) are an established protective factor for ovarian cancer. A re-analysis of 45 separate studies conducted in 21 countries showed that the longer a woman has used OCs, the greater her reduction in risk (Table Five).³⁹ Women who have used OCs for 15 years or more halved their risk of ovarian cancer. The risk reduction was shown to be long-term, persisting for 30 or more years after OC use had ceased. In high income countries such as the UK, an estimated 13% of ovarian cancers were prevented in the 2000s in women aged under 75 years old, and an estimated 9% of cancers in the 1990s. The increase in cancers prevented by OCs is due to two factors: an increased number of women ever using OCs, and increased age of past users.³⁹ Use of OCs has also been shown to reduce the risk of ovarian cancer in women with a BRCA1 or BRCA2 mutation.⁴⁰
- **Hormone replacement therapy**
A systematic review of published case-control and cohort studies and randomised trials has studied the effect of oestrogen-only and combined oestrogen-progestin hormone replacement therapy (HRT) in relation to ovarian cancer risk. It reported that five years' use of oestrogen-only HRT increased

^f Clomifene citrate is a drug used to treat infertility. It blocks the effect of oestrogen in the body.

the risk by 22% - significantly more than the 10% risk increase with use of oestrogen-progestin HRT.⁴² According to the UK Million Women Study, risk was increased for current users of HRT and the risk increased with duration of use becoming significant after seven or more years of use. Past or short-term use of HRT was unlikely to increase the risk of ovarian cancer.⁴³

Lifestyle

Smoking

IARC recently stated that there is sufficient evidence that smoking causes ovarian cancer.⁴⁴ A systematic review showed a doubling in risk of mucinous tumours in current smokers, no effect on serous and endometrioid cancers and a 40% reduction in risk of clear cell tumours.⁴⁵ A similar risk increase for mucinous tumours for current and past smoking was subsequently shown in the Nurses' Health Study.⁴⁶

Physical activity

Evidence is mixed. A meta-analysis of case-control studies showed a 21% risk reduction for women with the highest versus the lowest levels of recreational physical activity, but the combined results of cohort studies did not show any risk reduction.⁴⁷ Subsequently, the European Prospective Investigation into Cancer and Nutrition (EPIC) found no risk reduction for women with the highest levels of total, occupational, recreational or household physical activity,⁴⁸ while a case-control study showed a 60% risk reduction for serous tumours for women doing the most recreational physical activity, but an increase in risk of clear cell and endometrioid tumours.⁴⁹

Height and bodyweight

Height

Studies show a risk increase of approximately 40% for women measuring 1.7m or over compared to women of less than 1.6m in height.^{50,51}

Body mass index

The evidence points to a probable link between body mass index (BMI) and ovarian cancer. A pooled analysis of 12 prospective studies showed a 75% increase in risk of ovarian cancer in premenopausal women who were obese (BMI of 30 or higher) compared to women of a healthy weight (BMI of 18.5-23). There was no risk increase with the same comparison in postmenopausal women.⁵⁰ However, results from EPIC and the UK Million Women Study indicate that being obese after the menopause may also increase the risk of ovarian cancer.^{52,53}

Diet

The epidemiological evidence is not strong enough to make any dietary recommendations as a means of reducing the risk of developing ovarian cancer. Fruit and vegetables do not appear to affect risk^{54,56} nor does alcohol.⁵⁷ The

evidence for other dietary factors, such as meat, fat, fish, dairy products, tea and phytoestrogens, is inconclusive.

Medical conditions, procedures and medications

Previous cancer

Studies have shown a doubling in ovarian cancer risk for women with a previous breast cancer.⁵⁸ For women whose breast cancer was diagnosed before the age of 40, a four-fold risk increase has been shown. Risk is even higher for women in this group with a family history of ovarian or breast cancer.⁵⁸ Long term risk from radiotherapy is an issue - women treated for cervical cancer 30-39 years ago had a 73% higher risk, and those treated 40 or more years ago had a 172% higher risk of ovarian cancer.⁵⁹

Endometriosis

Endometriosis is a common condition in which endometrial tissue is found outside the uterus, for instance, on the fallopian tubes and ovaries. Women with endometriosis have been shown to have a 30-66% increased risk of ovarian cancer.^{60,61}

Ovarian cysts

Young women (15-29 years old) with ovarian cysts and functional cysts (harmless, short-lived cysts that are formed as a part of the menstrual cycle) have been shown to have a doubling in ovarian cancer risk later in life, and women who had cysts surgically removed, or unilateral oophorectomy, have a nine-fold risk increase.⁶²

Hysterectomy

Hysterectomy may reduce ovarian cancer risk, with case-control studies reporting a 30-40% risk reduction regardless of age at time of surgery, and a 50% risk reduction for women whose hysterectomy was 15 or more years before the study.^{63,64}

Tubal sterilisation

Results from the Nurses' Health Study showed a 34% risk reduction for ovarian cancer in women reporting a history of tubal ligation.⁶⁵ A recent meta analysis showed a similar result, though other cohort studies have not shown an effect and results of case-control studies have been conflicting.^{41,65-70}

Intrauterine device

The Nurses' Health Study showed a 76% increased risk for women reporting use of an intrauterine device, compared to women who had not used an intrauterine device. Results were adjusted for duration of OC use.⁶⁵

Non-steroidal anti-inflammatory drugs

Studies of anti-inflammatory drugs in relation to ovarian cancer are conflicting. A 2005 meta-analysis showed no effect of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) on risk.⁷¹ A recent large cohort study

of almost 200,000 women found no effect of regular use of NSAIDs, or aspirin specifically, on risk.⁷² A subsequent, much smaller cohort study showed a 39% risk reduction for women taking aspirin six or more times per week.⁷³ Results of recent case-control studies have varied between showing a reduction in risk, no effect on risk or an increase in risk in relation to use of NSAIDs.⁷⁴⁻⁷⁶

Paracetamol

Evidence is conflicting. A meta-analysis showed a 30% risk reduction with regular use of paracetamol.⁷⁷ However, a recent large cohort study of almost 200,000 women found no effect of regular use of paracetamol on risk,⁷² while a case-control study showed an 80% increase in risk with long-term use.⁷⁸

Talcum Powder

A 2003 meta-analysis of 16 individual studies showed a 33% risk increase for ovarian cancer in relation to perineal talcum powder application.⁷⁸ One study, which looked at use of talc both in the perineal and non-perineal area, showed a doubling in risk for long-duration (>20 years), with at least daily use, compared to women who never used talc.⁷⁵

Before the mid-1970s, contamination of talc with asbestos fibres was known to occur, and in 1975 guidelines were introduced to prevent this.⁷⁹ One study, which examined year of talc use, showed that use before 1975 was associated with an increase in risk, whereas use after 1975 was not.⁷⁵ This may explain some of the risk increase shown (see below).

Asbestos

The International Agency for Research on Cancer (IARC) classifies asbestos exposure as an ovarian carcinogen.⁸⁰ Studies from the 1970s and 1980s have shown that risk of ovarian cancer death is increased by around three-five times in women with "severe" occupational asbestos exposure, compared with background mortality rates.⁸¹⁻⁸³ More recent studies of women employed in the asbestos industry before the 1980s also show an association with long-term occupational exposure to asbestos.^{84,85} Asbestos fibres have been found in ovarian tissue, and at higher rates among women living with men with documented asbestos exposure than those living with men with no documented asbestos exposure.⁸⁶

Molecular biology and genetics

Germline (inherited) mutations

Mutations in BRCA1, BRCA2 or a DNA mismatch repair gene are associated with a greatly increased risk of ovarian cancer. Around 5-15% of ovarian carcinomas occur in those known to carry BRCA mutations, depending on the population or ethnic group.^{25,87} In women with a family history of breast or ovarian cancer and a known BRCA mutation, the cumulative lifetime risk of developing ovarian

cancer has been estimated to be approximately 40-50% for BRCA1 and 20-30% for BRCA2⁸⁷, compared with an approximate 2% lifetime risk in the general UK population. In hereditary nonpolyposis colorectal cancer (HNPCC) families (also known as Lynch II families) the lifetime risk of ovarian cancer in carriers of a mismatch repair gene mutation is about 7%.⁸⁸

However these known gene faults do not account for all of the inherited risk that is found in women with a family history of ovarian cancer. Other 'high risk' ovarian cancer genes may exist, although mutations in these genes are likely to be less common than BRCA1 and BRCA2. It is likely that much of the remaining familial risk is due to a combination of several genes that each gives rise to a low or moderate increase risk. Recent studies have found new 'low-risk' genetic variations associated with ovarian cancer.^{89,90} Researchers are now looking for other genetic alterations that can contribute to a woman's risk of the disease.⁸⁹ A better understanding of these genetic alterations could lead to more accurate ways to estimate a woman's risk of developing ovarian cancer. In the future it may be possible to target screening to women with an increased risk. Knowledge of the genetic changes that contribute to ovarian cancer should also lead to better treatments for the disease.

Somatic (acquired) mutations

Most genetic abnormalities that contribute to ovarian cancer are not inherited, but are acquired during a woman's lifetime. These are known as 'somatic' or acquired mutations. Many different somatic mutations have been observed in epithelial ovarian cancer, but only a small number are known to be relatively common in the disease. These include mutations in tumour suppressor genes (such as p53 and PTEN), and genes for signalling molecules such as KRAS and the kinases.²⁷

It has also been proposed that epithelial ovarian cancers can be divided into two categories, type I and type II.⁹¹ These two tumour types develop in different ways and show different patterns of mutation. Type I tumours develop slowly and are associated with mutations in genes including KRAS, BRAF and PTEN. Type II tumours develop rapidly and spread early in development, and often show mutations in p53 and high levels of chromosomal instability, meaning that the copy numbers of particular genes are increased or decreased. Several of these genes may be possible targets for new drugs, or could hold potential for use as biomarkers for earlier diagnosis of the disease.²⁷

Stage I	Tumour confined to the ovaries
IA	Tumour limited to one ovary; no tumour on external surface; capsule intact. No malignant cells in ascites or peritoneal washings
IB	As above, but tumour limited to both ovaries
IC	Tumour limited to one or both ovaries with any of the following: tumour on external surface; ruptured capsule; malignant cells in ascites or peritoneal washings
Stage II	Tumour involving one or both ovaries with pelvic extension
IIA	Extension and/or implants in uterus and/or fallopian tubes. No malignant cells in ascites or peritoneal washings
IIB	Extension to other pelvic organs. No malignant cells in ascites or peritoneal washings
IIC	Tumour staged either IIA or IIB with malignant cells in ascites or peritoneal washings
Stage III	Tumour involving one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis. Liver capsule metastasis equals Stage III
IIIA	Microscopic peritoneal metastasis beyond the pelvis
IIIB	Macroscopic peritoneal metastasis beyond the pelvis, none exceeding 2cm in diameter
IIIC	Peritoneal metastasis beyond the pelvis greater than 2cm in diameter and/or regional lymph node metastasis
Stage IV	Distant metastasis

Diagnosis and treatment

Symptoms

A recent consensus statement reported the following symptoms to be frequent in ovarian cancer patients: persistent pelvic and abdominal pain; increased abdominal size/persistent bloating; loss of appetite and feeling full quickly.⁹² Other symptoms include urinary symptoms, change in bowel habits, extreme fatigue, back pain, postmenopausal bleeding and rectal bleeding.⁹³ All these symptoms have positive predictive values (PPV)⁸ of less than 1% except for persistent abdominal distension which has the highest PPV of 2.5.⁹³ Symptoms that are frequent, persistent and severe may help to pinpoint women with ovarian cancer.⁹⁴ If ovarian cancer is suspected, Department of Health advice to health professionals is to request a serum CA125 assay and a pelvic ultrasound scan.⁹⁵ While it is hoped that 'earlier recognition and referral will translate into earlier stage at diagnosis', no studies have yet proved this.⁹⁵ The imprecision of symptoms, and indeed of serum CA125 levels and pelvic ultrasound, underline the need for more accurate diagnostic tests to detect disease at an earlier, more treatable, stage.⁹⁶

Ovarian cancer is neither an asymptomatic disease nor a so-called 'silent killer'. Symptoms do not only become apparent when the disease is advanced. Recent studies have demonstrated that patients with *all* stages of the disease have symptoms.^{93,97,98} However, the symptoms reported by patients to their primary carers are vague and easily confused with other conditions, especially abdominal and gastrointestinal disorders. A case-control study found that 95% of women (in general) presenting to primary care reported at least one symptom annually, and 72% reported symptoms occurring at least once per month.⁹⁸ Raising awareness is one line of attack while another is the development of a symptom index.^{97,92,99} A key task is how the general practitioner, who sees on average one case of ovarian cancer every five years, can efficiently refer women with suspected ovarian cancer -

half of whom are not being referred directly to gynaecological cancer clinics.⁹⁷

Diagnosis and staging

If ovarian cancer is suspected, an urgent referral should be made to a dedicated diagnostic centre.¹⁰⁰

A risk of malignancy index (RMI) has been developed which combines the results of transvaginal ultrasound examination, menopausal status and blood levels of the ovarian cancer marker CA125 (measured in U/ml).¹⁰¹ Use of measures such as the RMI and clinical examination enables the gynaecologist to refer patients with likely ovarian cancer to a specialist gynaecological oncologist who should undertake surgery for suspected ovarian cancer.^{100,102}

The primary procedure in a woman with suspected ovarian cancer is to obtain histological confirmation of the disease. This is generally undertaken at a laparotomy, whereby the disease can also be staged. The International Federation of Obstetricians and Gynaecologists (FIGO) staging system is shown in **Table Six**.¹⁰³

Treatment

Prophylactic surgery

Prophylactic oophorectomy has been shown to decrease the risk of BRCA-mutation-related gynaecological cancers and breast cancer in BRCA1 and BRCA2 mutation carriers.^{104,105} Prophylactic bilateral salpingo-oophorectomy, with or without hysterectomy, in women with Lynch syndrome (HNPCC) was found to be effective in preventing ovarian cancer.¹⁰⁶ It is important that women have access to the appropriate specialists, as such a procedure can have extensive psychological consequences.¹⁰⁷

Surgical treatment of early disease according to menopausal status

In younger patients, where fertility is an issue, the appropriate surgery is to diagnose and stage the disease while, importantly, retaining the woman's fertility. This is because, in many

⁸The positive predictive value (PPV) is the probability that an individual with a positive test result has been correctly diagnosed with the disease in question.

cases, the cancer will be a germ cell tumour or early ovarian cancer (Stage IA), which are amenable to non-radical surgical interventions.¹⁰⁸⁻¹¹¹ In women who have completed their families, or are post-menopausal, it is recommended that the uterus, fallopian tubes and ovaries are removed and relevant biopsies performed.¹⁰³

Adjuvant chemotherapy in early disease

Immediately following surgery, many women are given adjuvant chemotherapy, normally using a platinum compound. In women with no residual disease, the recent randomised controlled trial (RCT) ICON1 indicated that platinum-based chemotherapy does improve survival.¹¹² Another RCT, ACTION, found that disease-free survival was improved in women receiving adjuvant chemotherapy.¹¹³ A meta-analysis of five trials of adjuvant chemotherapy compared with no further treatment in early ovarian cancer (including the two mentioned above) showed an improvement in both overall survival and disease-free survival (hazards ratios of 0.71 [95% CIs 0.63 to 0.80] and 0.68, [95% CIs 0.59 to 0.79], respectively).¹¹⁴ A pre-planned combined analysis of the ICON1 and ACTION trials also came to the same conclusion.¹¹⁵

Surgical treatment of advanced disease

In a situation where there is very advanced disease, all of which cannot be excised by surgery, many surgeons perform 'debulking' surgery, endeavouring to leave behind as little tumour as possible. This is thought to improve the efficacy of adjuvant chemotherapy, but the evidence to support this is questionable. Two ongoing studies are addressing this important question, EORTC 55971, and CHORUS.^{116,117}

Adjuvant chemotherapy in advanced ovarian cancer

In more advanced disease, some studies have reported improved survival when paclitaxel is combined with a platinum agent.^{118,119} However, the largest study, ICON3, suggested that there was no difference in outcome with

combination therapy.¹²⁰ Debate continues with regard to these findings, and the National Institute for Clinical Effectiveness (NICE) recommends that women requiring chemotherapy should have a platinum agent administered, and the possible addition of paclitaxel should be discussed on an individual basis.¹²¹

Treatment of disease relapse: surgery

The role of routine surgery in relapsed disease is another area of controversy.¹²² Surgery can sometimes be helpful in the alleviation of symptoms, but whether its routine use is useful needs addressing through clinical trials. From retrospective studies, it appears that optimum debulking surgery at relapse results in lengthened survival.¹²³

Treatment of relapsed disease: chemotherapy

In relapsed disease, the main determinant of continued survival and, indeed, response to further chemotherapy is the time interval from completion of the last therapy. Disease which develops within six months from the end of treatment is deemed resistant to that therapy, and further therapy will be individualised. Outside this time period, further responses to platinum can be anticipated, or to paclitaxel if it was not used previously. ICON4, an RCT, revealed that in relapsed disease (occurring six months or more after cessation of treatment), the combination of carboplatin and paclitaxel afforded a better survival when compared to single agent carboplatin.¹²⁴ This finding contradicts those of ICON3 but, of course, the disease processes at relapse may be different. A phase I trial of olaparib, a PARP inhibitor^h, found that it was well-tolerated and had a high response rate in BRCA1 or BRCA2 mutation carriers who were either platinum-sensitive or platinum-resistant.¹²⁵

The future – possibilities of screening

Ovarian cancer fulfils some of the criteria necessary for the introduction of population screening: it is an important health problem, being the fourth most common cause of female cancer death in the UK, and early detection is associated with improved outcomes.¹²⁶ Potential screening tests for ovarian cancer have not yet been shown to reduce mortality, although both ultrasound and

tumour markers can detect a significant proportion of ovarian cancers pre-clinically and when used as sequential screening tools have been shown to extend median survival.¹²⁷ Currently there is no national screening programme for ovarian cancer and evidence is pending from ongoing RCTs.

Population screening

A very large RCT is currently being conducted in the UK which aims to recruit 200,000 post-menopausal women. The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) will assess the cost, acceptability and mortality benefit of population screening. Final results are expected in 2015. Women have been randomly assigned to three groups: no treatment (control group); annual multimodal screening (MMS; CA125 followed by transvaginal ultrasound as a second-line test); or annual ultrasound (UUS). Preliminary results from the prevalence screen of 100,000 women have recently been published.¹²⁸ The results show that large scale population screening is feasible and does detect ovarian cancer in symptomless women. Both MMS and UUS detected ovarian cancers, half of which were at an early stage compared to around 28% in most clinical series. While sensitivity was similar between both screening arms, specificity was much higher in the MMS resulting in fewer false positives. As women enter the trial, blood samples are taken - this biobank of information will help in understanding the natural history of ovarian cancer and aid the search for better biomarkers for early detection.¹²⁹ Algorithms are being developed which help to assess a woman's risk of ovarian cancer using information in addition to the screening test results.

Screening for women with a family history of ovarian cancer

Five thousand women aged over 35 with a significant family history of ovarian cancer are participating in the UK Familial Ovarian Cancer Screening Study (UKFOCSS), which assesses the utility of annual screening with CA125 measurement and ultrasound. In addition, blood samples are being collected every four months for retrospective analysis of existing and novel tumour markers.¹³⁰

^h Most chemotherapy drugs work by causing breaks in DNA, and their effectiveness can depend on how well a cell can repair this damage. PARP – otherwise known as poly (ADP-ribose) polymerase – is an enzyme that signals the presence of DNA damage and helps in its repair. PARP inhibitors work by blocking the repair process, hence disrupting chemotherapy resistance in cancer cells.

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Further information

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

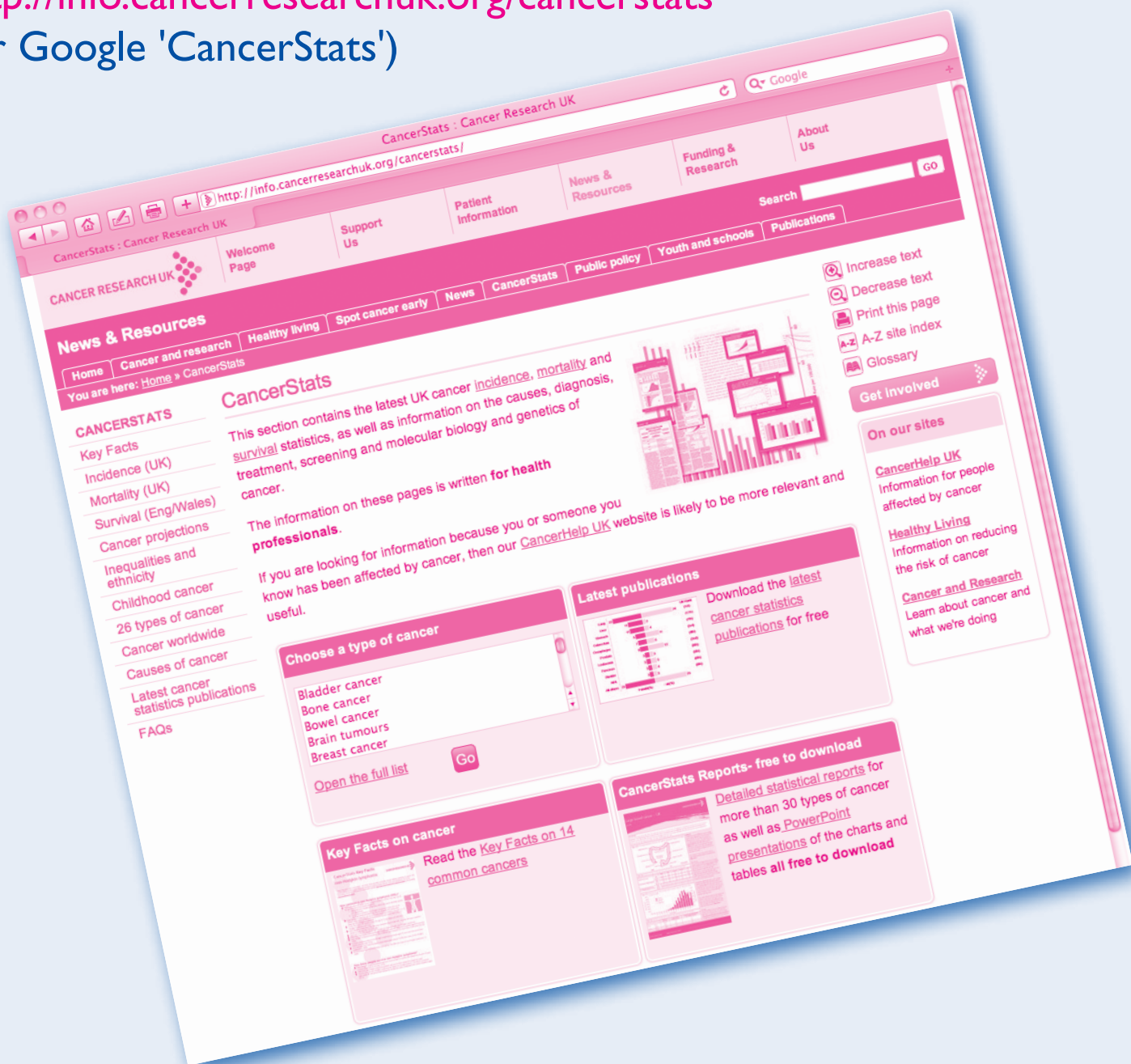
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