WORLD OVARIAN CANCER COALITION ATLAS 2020

Global trends in incidence, mortality, and survival.

WORLD
OVARIAN
CANCER
COALITION

WORLD OVARIAN CANCER COALITION ATLAS 2020

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INTRODUCTION

The vision of the World Ovarian Cancer Coalition is a world where every woman with ovarian cancer has the best chance of survival, and the best quality of life, wherever she may live. Our Mission is to empower the global ovarian cancer community through knowledge, collaboration, and action.

The first edition of the World Ovarian Cancer Coalition Atlas was produced in 2018 to inform the development of the Coalition's Every Woman Study. It has been such a useful resource that the Coalition has undertaken to update the Atlas at regular intervals to inform our own advocacy efforts and support those of our partner organisations.

This second edition follows the launch of the World Ovarian Cancer Coalition's next major initiative, the Global Ovarian Cancer Charter Launched in September 2020 at the International Gynaecologic Cancer Society (IGCS) annual meeting, the Charter builds on the key recommendations of the Every Woman Study™ and focuses on six Global Goals:

- **Global Priority**: Ovarian cancer must become a global priority, so that the increasing burden and challenges of successfully treating women with ovarian cancer are recognized and planned for at local, regional, and national levels;
- **Rapid Diagnosis:** Women must have access to diagnosis without delay. Symptom awareness must be improved so women seek and access appropriate help quickly. Doctors also need support so they know who should undergo testing and that they have access to tests without delay so more women can start and tolerate treatment quickly;
- **Best Possible Care**: Women must have access to surgery, treatments, and clinical trials that optimize their chances of survival and quality of life, no matter where they live. Lack of finance should not be a barrier to best possible care, nor should the gap between highest and lowest resource countries widen any further;
- **Family History:** Women and doctors must have access to appropriate and timely genetic testing and counselling. For women with a family history of ovarian and other cancers1 it is important to determine if they or others in their family are also at risk;
- **Data Improvement:** The quality and quantity of data fluctuates around the world, hindering abilities to quantify the burden of ovarian cancer or develop evidence-based strategies. Data used to develop cancer control plans and treatments must reflect the diversity of local populations to ensure the best possible outcomes;
- **Information and Support:** Women must have access to good, quality information and support in their own language that helps them to live well with the disease. Mental and physical well-being should be addressed and considered in equal measure.

This paper explores ovarian cancer in the context of the global cancer burden. The most recent estimates of incidence, mortality, and the numbers of women living with the disease are given together with projections for the year 2040. Developments in the

understanding of the disease are discussed, as are the various factors affecting a woman's chance of developing the disease. Evidence relating to variation of care is explored before more specific evaluation of variations in survival rates.

Throughout the Atlas, the differences between the experiences of women in low-, middle- and high-income countries are also discussed. This remains an ongoing challenge, with the majority of studies emanating from high-income countries, in contrast to the greater burden of disease in lower- and middle-income countries.

The following terms are used frequently:

- **Incidence** - the number of cases of the disease;
- **Incidence rate** - the percentage of the population who will develop the disease within given boundaries, for example 7 women per 100,000 female population might develop the disease each year;
- **Mortality** - the number of deaths from the disease;
- **Mortality rate** - the percentage of the population who will die from the disease within given boundaries, for example 3 per 100,000 female population might die from the disease each year;
- **5-year prevalence** - the number of people living with 5 years of a diagnosis;
- **Survival rates** – the percentage of those affected by the disease who are alive at a certain time point beyond diagnosis, for example, 5-year survival rate is the percentage of women alive 5 years after their diagnosis;
- **5-year conditional survival** - the proportion of those alive who survived the first year, and subsequently went on to survive five years;
- **Population-based cancer registries (PBCRs)** - a core component of cancer control strategy. A PBCR systematically collects information from multiple sources on all reportable cancers occurring in a geographically defined population. The purpose of a PBCR is to provide information on cancer burden and to assess possible causes of cancer in the community, as well as to carry out studies on prevention, early detection and screening, and cancer care.

EXECUTIVE SUMMARY

In the two years since the first edition of the World Ovarian Cancer Coalition Atlas there has been an encouraging number of new studies around the world exploring the nuances of this complex disease. Findings from these studies strengthen our knowledge about actions needed to tackle the major challenges facing women around the world who develop ovarian cancer. As you will read, these challenges are compounded by a rise in risk factors for the disease particularly as countries develop, and populations grow and age.

In 2018 it was estimated that almost 300,000 women were diagnosed with ovarian cancer worldwide, approximately 185,000 women died from the disease, and more than three-quarters of a million women were living within five years of their diagnosis. Whilst there have been some improvements in overall survival rates, progress remains stubbornly slow, and we are a considerable way away from a reliable screening tool for the general population. Although we have seen some positive progress, ovarian cancer still has the highest mortality rate of all female cancers in higher income countries.

New and emerging treatments have the potential to transform the outlook for those women who can access them and for whom they are effective. These include PARP inhibitors[1] which have been described as "game changing", and, more recently, promising new research in immunotherapeutics. However, the majority of women who have ovarian cancer live in low and lower middle-income countries where access to such innovative treatments is extremely limited. Even access to the mainstay drug treatments of the last 30 years, or expert surgery, can be impossible or financially crippling for many women and their families.

The projected 47% increase of women developing ovarian cancer by 2040[2] will largely, but not exclusively, occur in developing countries where the access to best possible care is severely limited. Many lack effective cancer control plans, critical infrastructure, and afforable access to necessary cancer treatments. For many, the individual financial burden of care is just too great.

Without question, the gap between those who can access the best possible care and those who cannot is widening and will continue to do so without concrete action. Emerging knowledge about the disease that can improve outcomes in wealthier countries must also inform efforts in lower resource settings to close this gap.

Key findings in this report reveal that:

- There will be a rapid increase in the numbers of women developing ovarian cancer, particularly in lower- and middle- income countries;
- Responding to possible familial (genetic) risks, prevention, and ways to reduce risk factors through hormonal and lifestyle factors may help decelerate rising incidence rates;
- In all countries, there are wide variations in the availability of, and adherence to, clinical guidance - from assessing symptoms, to surgery, and drug management. In particular, guidance in lower-income countries needs to be locally feasible as well as aspirational;
- Developing and maintaining trained workforces with adequate infrastructures is relevant in all situations but particularly vital in low-income settings;
- Understanding differences in survival rates between countries can inform efforts to get the best possible outcomes;
- There has never been a more compelling need for progress. For women right around the world, it is imperative that we continue to study this disease and understand the driving factors behind poor outcomes;

- Regardless of setting, it is crucial to seize opportunities to prevent, quickly diagnose, and treat ovarian cancer, and to ensure development of appropriate workforce and infrastructures, while gathering a diversity of data that can inform effective policies relevant to local populations;
- Women themselves must be at the heart of this process - leading the call for action, informing the debate at every step, and sharing their experiences and data where possible.

RECOMMENDATIONS

In order to drive forward progress there is a need to:

- Recognise ovarian cancer as a global priority;
- Improve the quality of national cancer data and population-based cancer registries to inform cancer control plans;
- Use a consistent framework for reporting the stage or spread of the disease;
- Incorporate the type of ovarian cancer in all data collection;
- Improve the knowledge of women and doctors in relation to ovarian cancer to reduce delays in diagnosis;
- Reduce variation in guidelines for diagnosis and treatment, at the same time making them relevant to local populations;
- Support the United Nations and the Union for International Cancer Control action on universal health coverage to make drugs included in treatment guidelines available to all, without causing financial hardship on women and their families;
- Monitor the availability of new targeted therapies and associated genetic testing around the world, and find ways of opening up access to lower-income countries;
- Consider how to develop centres of treatment expertise for women with ovarian cancer, even in low resource settings;
- Invest in the cancer workforce, ensuring imaging, pathology and other key services better support rather than impede diagnosis, and provide incentives for trained staff to continue to provide experienced care;
- Explore how the role of cancer nurses in low-and middle-income countries could be developed;
- Examine the differences in survival between countries, with a view to developing interventions to improve cancer care;
- Ensure that quality of life of those diagnosed with ovarian cancer is not ignored or forgotten.

THE GLOBAL CANCER BURDEN

Figures from the World Health Organisation (WHO) report that cancer is the second leading cause of death globally with an estimated 9.6 million deaths in 2018[3]. The International Agency for Research on Cancer highlights that in the same year there were 18 million people diagnosed with cancer, and 43.8 million living within five years of their diagnosis[4]. It is projected that the global cancer burden in terms of deaths will rise to 16.4 million a year by 2040, with incidence reaching 29.5 million[5].

The WHO also reports that approximately 70% of cancer deaths occur in low- and middle-income countries, and that late-stage presentation and inaccessible diagnosis and treatment are common. More than 90% of high-income countries reported treatment services being available compared to less than 30% of low-income countries. Shockingly just one in five low- and middle-income countries have the necessary data to drive cancer policy[6].

In an article in the Lancet, Professor Michel Coleman describes the three engines of escalating cancer burden as being on the move: rapid population growth, ageing populations, and an increase in cancer risk (lifestyle/environment) at each age[7]. With the associated strain on economies, timely and accurate statistics are imperative to provide evidence and impetus for identifying and developing cancer control strategies at a national level.

Dr. Christina Fitzmaurice and colleagues from the Global Burden of Disease Cancer Collaboration report that the drivers behind increasing cancer incidence differ substantially by socio-demographic index (SDI). In the lowest SDI quintile population growth is the major contributor, in low-middle SDI countries aging and changes in incidence rates contribute equally (each 12%), and in high-middle and high SDI countries increased incidence is mainly driven by population ageing.[8]

Bray et al, in their summary of 'Global cancer statistics 2018' (based on the data from GLOBOCAN[9]) report that, 'cancer transitions are most striking in emerging economies, where an increasing magnitude of the disease is paralleled by a changing profile of common cancer types. A recurring observation is the ongoing displacement of infection-related and poverty-related cancers by those cancers that already are highly frequent in the most developed countries (e.g., in Europe, North America, and high-income countries in Asia and Oceania).

Various authors in another report, 'The global cancer burden and human development: A Review'[10], also demonstrate that the future cancer burden will disproportionately affect less developed regions according to national Human Development Index scores. They call on international efforts to aid countries in social and economic transition in order to efficiently plan, implement and evaluate cancer control initiatives as a means to reduce the widening gap in cancer occurrence and survival worldwide.

There are major inequalities in the availability of high-quality, local data in many countries, particularly developing economies, which impact on the corresponding robustness of the estimates available. Just one in three population-based cancer registries (PBCRs) report high-quality cancer data to the International Agency on Cancer Research, and only one in five countries report equivalent mortality data to the World Health Organisation[11]. In some countries, such as

Norway, cancer reporting is a legal requirement, and data is then linked with the cause of death registry. For 2001-2005 data, Norway's cancer data was 98.8% complete, with 93.8% verified by biopsy samples under a microscope[12].

Although PBCRs may cover national populations, more often they cover smaller, subnational areas, and particularly in countries experiencing substantial development, only selected urban areas. In these instances where there is a paucity of cancer data, national incidence and mortality data is often estimated from datasets of regional registries, or even neighbouring countries.

For the purposes of this report, figures are largely drawn from those produced by the GLOBOCAN project.[13] The aim of the project is to provide contemporary estimates of the incidence, mortality and prevalence for 36 types of cancer, at a national level in 185 countries.

The latest figures are the estimates for 2018. Because methodology has been adapted between different publications of GLOBOCAN it is not possible to highlight trends between different years. For the latest figures, they have introduced 95% uncertainty intervals, and these take into account estimations based on sub-regional rather than national data, timeliness of data, and quality.

Antoni et al[14] stress that efforts should be made on an on-going basis to develop and improve the methods used, and they call for support to be given to the Global Initiative for Cancer Registry Development (GICRD)[15]. Per the GICRD, only one in five low- and middle-income countries currently have the necessary data to drive policy and reduce the burden and suffering due to cancer. This effectively leaves 70% of the cancer burden falling on those regions least equipped to provide patient care from basic treatment to palliation.

OVARIAN CANCER AS A GLOBAL PRIORITY

Figures from GLOBOCAN 2018 show that ovarian cancer is the 8th most common cancer, and the 8th most common cause of death from cancer in women in the world[16].

CURRENT AND PROJECTED INCIDENCE AND MORTALITY

It is estimated there were over 295,000 cases of ovarian cancer in 2018, almost 185,000 deaths, and more than 750,000 women living within five years of diagnosis (5-year prevalence). On its Cancer Tomorrow website, GLOBOCAN predicts that by the year 2040, incidence will rise by 47% to a total of just over 434,000, with an even larger increase in the number of deaths each year (up nearly 59% to over 293,000)[17].

Figure 1 shows the numbers affected and GLOBOCAN future projections by continent.

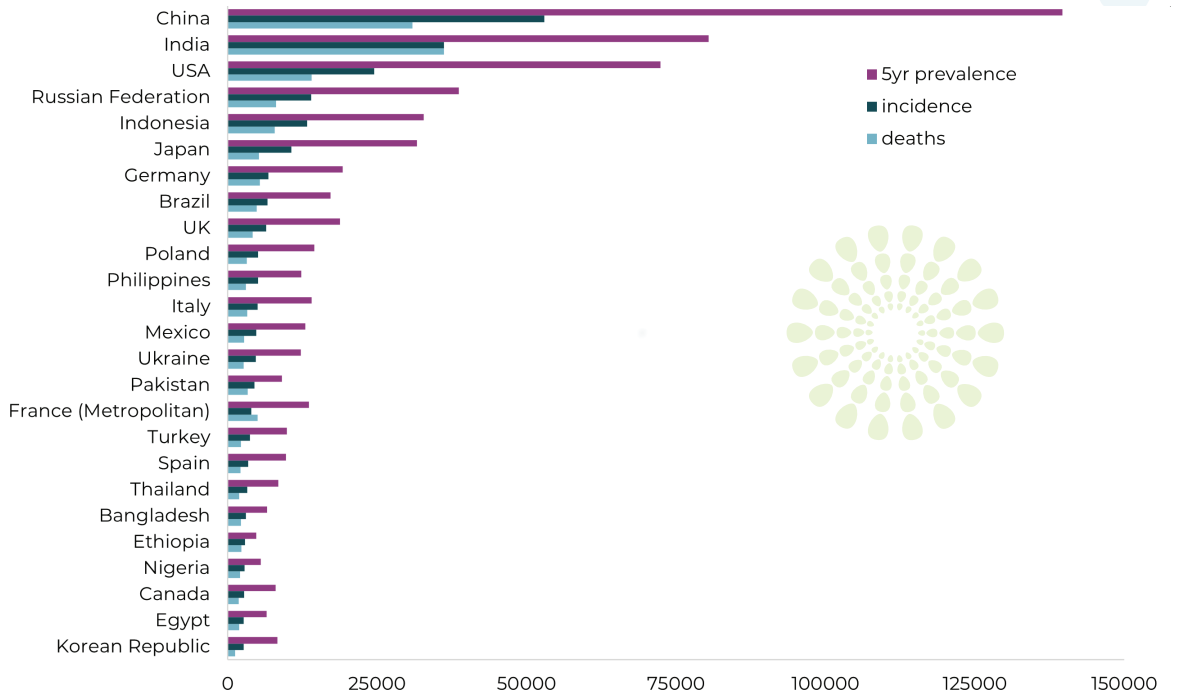
Fig 1

	Incidence		Mortality	
	2018	2040‡	2018	2040‡
Asia	153,076	218,758	92,527	146,536
Europe	67,771	74,635	44,576	53,461
North America	27,194	35,723	15,862	22,878
Latin America and Caribbean	23,285	36,868	13,668	23,926
Africa	21,925	43,462	16,702	34,145
Oceania	2,163	3,265	1,464	2,368
World	295,414	434,184	184,799	293,039

‡ projected

Figure 2 ranks countries by the number of reported cases of ovarian cancer in 2018 and also shows the number of deaths, and five-year prevalence.

Fig 2 COUNTRIES WITH THE LARGEST NUMBER OF WOMEN WITH OVARIAN CANCER

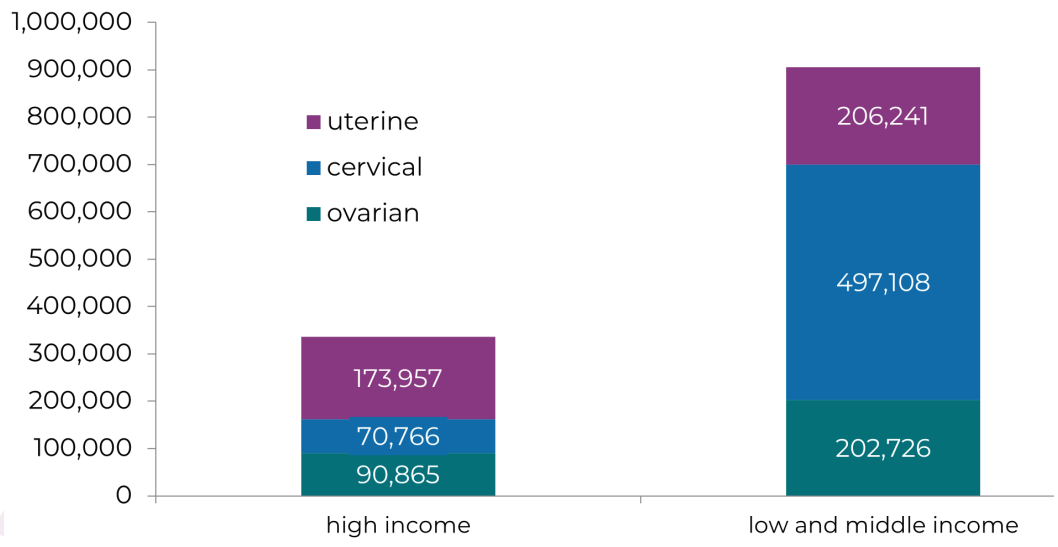


source Cancer Today *(GLOBOCAN accessed 17th January 2020)*

OVARIAN CANCER AS A PRIORITY IN TERMS OF WOMEN'S CANCER

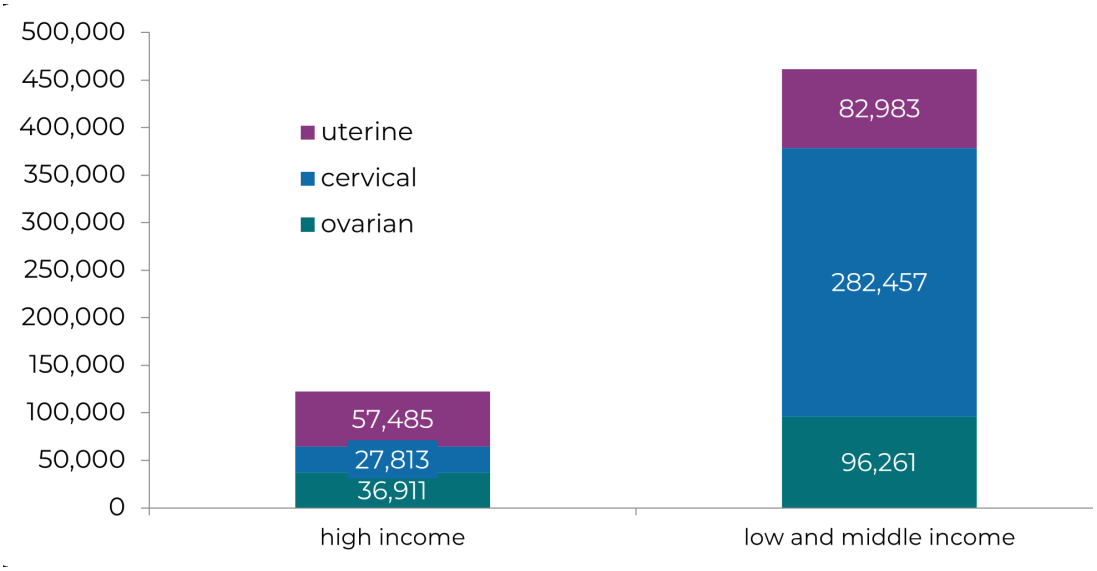
Breast cancer is by far the most common cancer for women. In 2018, there were estimated to be 2,088,849 cases, and 626,679 deaths (GLOBOCAN 2018). There were thought to be almost 6.9 million women living within five years of a diagnosis.

Fig 3 GYNECOLOGICAL CANCER INCIDENCE (GLOBOCAN 2018)



In terms of gynecological malignancies, cervical cancer has been a much greater issue in less developed parts of the world, largely due to lack of screening, vaccination, and poor sexual health,

Fig 4 GYNECOLOGICAL CANCER MORTALITY (GLOBOCAN 2018)



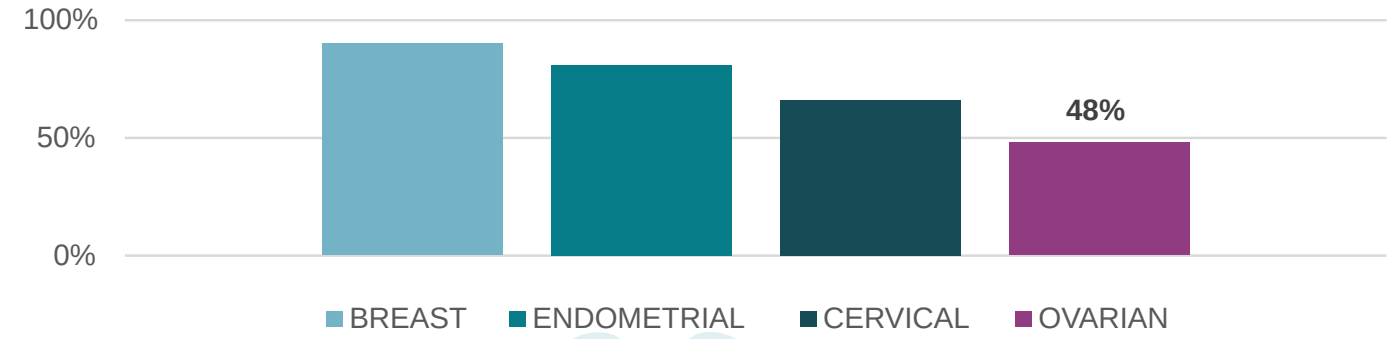
but that is beginning to change. Uterine cancer is strongly linked to body mass index and has seen a steep rise in incidence in more developed and developing parts of the world in recent years.

The risk of ovarian cancer is highest in high-income countries (8.2 ASR per 100,000 versus 4.7 in low-income countries. GLOBOCAN 2018), but is rising in lower-income countries as they develop economically[18]. As a result, different countries prioritize gynecological and women's cancer in general much differently.

As can be seen from Figures 3 and 4 however, two-thirds of women diagnosed with or who die from ovarian cancer live in countries classified as low- or middle-income.

For the purpose of comparing ovarian cancer survival statistics with those of breast, cervical or endometrial cancer, the following figures have been extracted from the American Cancer Society's Cancer Facts and Figures (2020) document[19]. It is important to note that ovarian cancer is the most lethal female cancer.

Fig 5 FIVE YEAR SURVIVAL RATE



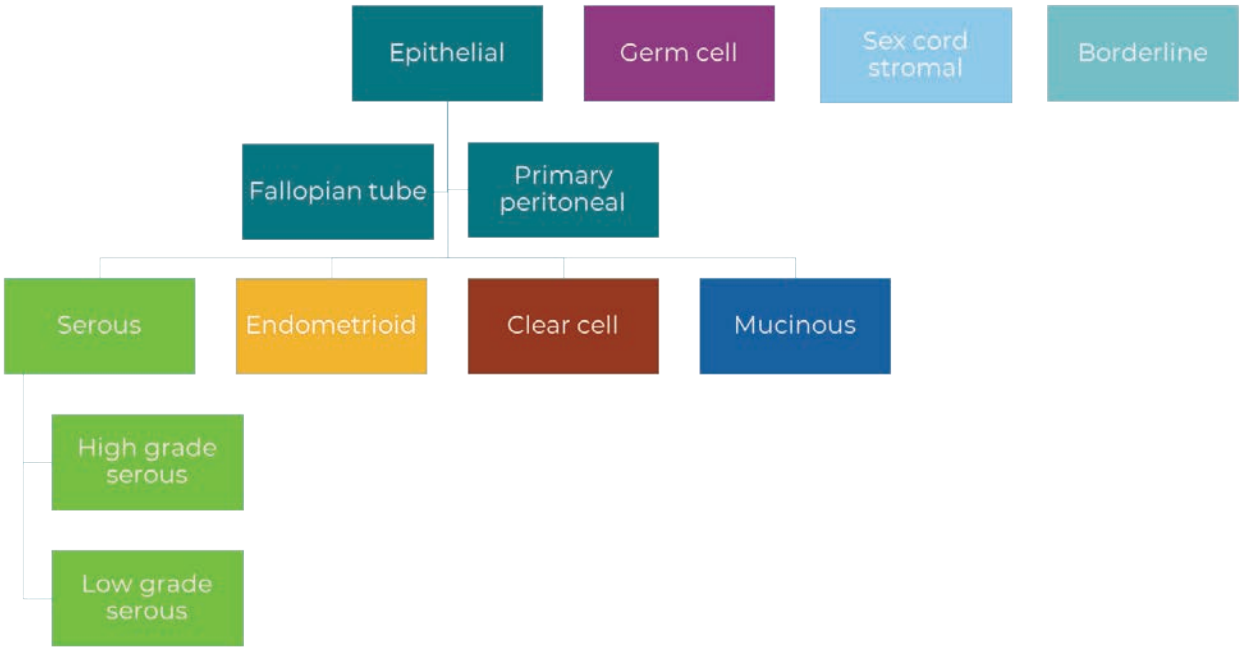
WHAT IS OVARIAN CANCER?

'Ovarian cancer' is not a singular diagnosis, rather it is an umbrella term for a multitude of different types of cancer that affect the ovaries, fallopian tubes, and the primary peritoneal cavity. It is estimated that there are more than 30 different types of ovarian cancer, and there is a very wide variation in incidence and outlook in terms of the different types. This can make it challenging for women to find appropriate information and complicated for researchers to extract type specific data.

TYPES OF OVARIAN CANCER

The most common form of the disease is high grade serous ovarian cancer which is a type of epithelial ovarian cancer. Primary peritoneal cancer and fallopian tube cancer are treated as epithelial ovarian cancer. (Figure 5)

Fig 5 OVARIAN CANCER TYPES



TUMOUR DEVELOPMENT

With ovarian cancer it is becoming apparent that there can be fundamental differences between early and later stage tumours, with suggestions that there may not always be a linear and predictable connection (i.e. starting at FIGO stage I and progressing through II, III, IV). Lengyel in 2010 described ovarian tumours as developing in any of 3 potential sites (the surface of the ovary, the fallopian tube, or the mesothelium-lined peritoneal cavity)[20]. He notes that there is either a stepwise mutation from slow growing borderline tumour to well differentiated carcinoma (type 1), or there evolves a genetically unstable high-grade serous carcinoma that spreads rapidly (type 2). In particular, this type may be very hard to detect at an early point.

It is now increasingly thought that these type 2 tumours begin in the fimbria region of the fallopian tubes, which are located very close to the ovaries, and subject to the same environmental stressors. Fimbriae are rich in blood vessels that facilitate metastasis to the ovaries through the blood stream[21].

Lisio et al's summay of type 1 and 2 tumours for Epithelial Ovarian Cancer is seen in Figure 6:[22]

Fig 6 DIFFERENCES BETWEEN TYPE 1 AND TYPE 2 OVARIAN TUMOURS AS DEFINED BY LISIO ET AL

	Type 1	Type 2
Genomic profile	Frequent oncogenic alterations in RAS-MAPK and PI3K, P53 wild type but otherwise genomically stable	P53 mutations, genomic instability due to defects in pathways contributing to DNA repair
Presentation characteristics	Stepwise progression from pre-malignancy, to borderline, to large unilateral cystic presentation. Often diagnosed early stage	Rapid development often widely disseminated at diagnosis
Prognosis	When diagnosed at an early stage confined to the ovary prognosis is excellent	Poor overall prognosis, but potential for role of PARP inhibitors
Types of ovarian cancer	Low grade endometrioid, Low grade serous, Clear cell, mucinous	High grade serous High grade endometrioid ovarian cancer (a rare form)

Much rarer, germ cell and sex cord stromal tumours are other types of ovarian cancer, each with several different subtypes, some of which are benign (non-cancerous). Germ cell tumours tend to occur in girls and women of reproductive age and are often very successfully treated by surgery.

RISK FACTORS FOR OVARIAN CANCER

There are certain factors that increase or decrease a woman's risk of developing ovarian cancer:

- Family history;
- Age;
- Where she lives in the world;
- Hormonal and reproductive factors;
- Lifestyle factors.

The type of ovarian cancer and the age at which it is diagnosed can also be affected by some of the above factors.

FAMILY HISTORY

For generations it has been clear that ovarian cancer is more prevalent in some families than in the general population. A major breakthrough in 1994 determined that faults in the BRCA1 and 2 genes could increase a woman's risk of developing breast or ovarian cancer. Following this discovery, tests were then developed to identify germline mutations (i.e. those passed on from generation to generation) that could identify women at risk.

With a mutated BRCA1 gene, a woman has a 44% risk of developing ovarian cancer by the age of 80, and a 17% risk with a mutated BRCA2 gene[23]. Mutations in other genes such as TP53 and RAD51c can also play a role in raising the risk of ovarian cancer, but their impact is nowhere near as significant as the BRCA genes. 18% of epithelial ovarian cancer cases, particularly high grade

serous carcinomas, are thought to be related to inherited genetic faults, particularly BRCA1 and 2 mutations[24].

It has become apparent that a proportion of sporadic ovarian cancers also share some of the traits of BRCA mutation, but in the absence of those germline (inherited) mutations. This has been called 'BRCAness'– homologous recombination deficiency (HRD). It was a term first used by the team at the Institute of Cancer Research in London but is now being redefined as understanding increases [25].

Women with ovarian cancer who have homologous recombination deficiency (HRD) exhibit specific clinical behaviours including an improved response to treatments such as platinum-based therapies and poly adenosine diphosphate ribose polymerase inhibitors (PARPi; Olaparib [Lynparza]; Niraparib; Rucaparib)[26]. Germline mutations in the BRCA 1 or 2 genes are the most well-known mechanisms of HRD. However, other mechanisms, such as germline and somatic (acquired) mutations in other homologous recombination genes and epigenetic modifications, have also been implicated in homologous recombination deficiency.

Up until relatively recently, guidelines, where they existed, said that genetic tests should only be carried out on women who had several close blood relations affected by ovarian and/or breast cancer. However, this new insight about acquired mutations and a greater understanding of genetic risk in families where there may not be many or any recent cases, has led to reconsideration of referral criteria for ovarian cancer patients for genetic testing and counselling[27].

The potential to test more women with ovarian cancer will help in two important areas:

- To determine the most appropriate individualised treatments;
- To find more women at increased risk. If managed correctly with appropriate support and counselling for those undergoing testing, the prospect of increased primary prevention is a significant one, potentially reducing the impact of this deadly disease in future years.

There is still much more work to be done, in different populations, to identify where mutations occur within the BRCA1 and 2 genes. For example, in women of Ashkenazi Jewish descent, founder mutations occur mainly in three sites[28], whereas in different populations mutations can occur at many different points. A recent study by Rebbeck et al has shown that the risks may vary by type and location of BRCA mutation[29].

Lynch syndrome is an autosomal dominant cancer predisposition syndrome that is responsible for 1-3% of all colorectal cancers, and 10-15% of all inherited ovarian cancer cases[30]. The lifetime risk for individuals with a family history of Lynch syndrome is 6-8%[31].

The most common types of ovarian cancer in these individuals are endometrioid and clear cell. Other cancers associated with Lynch syndrome include endometrial, stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin cancer. Mutations occur in one of the four mismatch repair genes MHL1, MSH2, MSH6 and PMS2. Women who develop ovarian cancer because of these mutations are most likely to be diagnosed at stage I or II.

AGE

It is commonly reported that the risk of ovarian cancer is strongly related to age, highest in older females. However, comparing ages for peak incidence and mortality around the world, it appears to vary according to country. Possible explanations might include co-morbidities, variations in tumour type, and/or exposure to risk factors. Momenimovahed et al reviewed studies relating to age at diagnosis, and they found a range of median ages from 50 to 79 in different populations[32].

Nationally produced statistics show a wide variation. For example, in the United Kingdom, according to figures from Cancer Research UK, over half (53%) of cases are diagnosed in women aged 65 and over. Age specific incidence rates peak in the UK for women aged 75-79, then drop sharply.

In contrast, however, one study on gynaecological cancers in a Ghanaian teaching hospital[33], showed the mean age seen for women with ovarian cancer was 46 years old, but there was little or no commentary or comparative data. In the Jiangsu province of China, age specific incidence rates appear to peak aged 60-64, with age specific mortality highest in the 65-69 age group.

A study in the US showed that the median age for diagnosis for Asian women was 56, compared with 64 for white women[34]. Asian women were more likely to undergo primary surgery, have an earlier stage of disease, have a diagnosis of a non-serous histology and have lower grade tumours. Five-year disease specific survival was higher compared to whites (59.1% vs 47.3% $p<0.001$).

There were also differences within the group of Asian women studied. Between those who were born in the US and those who were immigrants, the immigrants presented at a younger age, and had better survival rates. A subset analysis of the different ethnicities showed differences in survival: for example, 5-year disease specific survival rates for Vietnamese 62.1%, Filipino 61.5%, Chinese 61.0%, Korean 59%, Japanese 54.6% and Asian Indian/Pakistani 48.2% $p<0.015$.

In further work by Katherine Fuh, published in 2019, she and other colleagues were able to show that Asian women enrolled into phase III ovarian cancer clinical trials were younger, with better performance status, earlier-stage disease and with a greater number of clear cell and mucinous tumours. After adjusting for these prognostic factors, Asian women have better survival when compared to Caucasians in the USA[35].

Matz et al, using data from the CONCORD-2 study, were able to show the average age for the different types of ovarian cancer (Figure 7)[36]:

Fig 7 MEAN AGE, BY TYPE OF OVARIAN CANCER (CONCORD-2)

Histological group	Number of patients	%	Mean age in years (with standard deviation)
Type I epithelial*	152,970	22	58 (14)
Type II epithelial**	488,634	70.2	64 (14)
Germ cell	13,306	1.9	36 (18)
Sex cord stromal	11,430	1.6	54 (16)
Other specific non-epithelial	17,619	2.5	61 (15)
Non-specific tumours	11,282	1.6	66 (17)
Missing morphology	691	0.1	64 (16)

*No information on grade available so all endometrioid tumours classified as type I

** No information on grade available so all serous tumours classified as type II

WHERE WOMEN LIVE

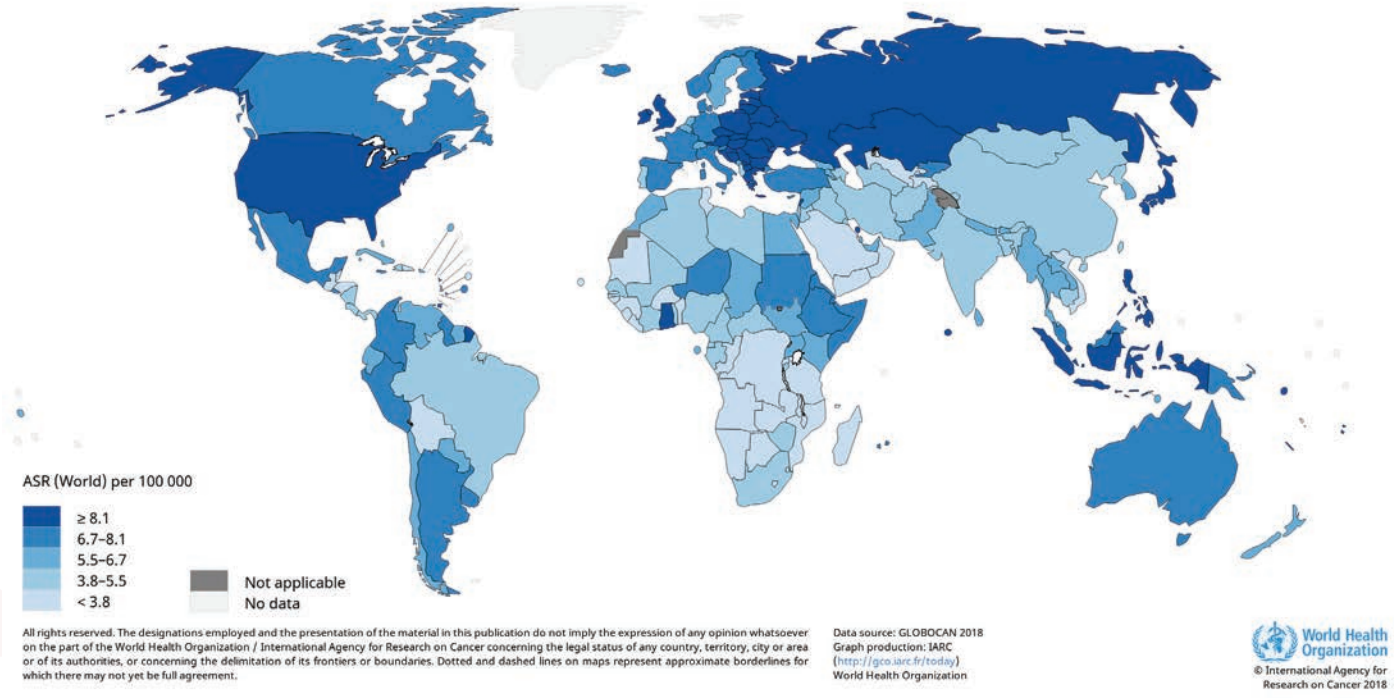
Age standardised incidence rates (ASR) for ovarian cancer vary around the world (see Figure 8). GLOBOCAN 2018 data shows they are highest in more developed regions, with rates in these areas exceeding 8.2 per 100,000, and lowest in Sub-Saharan Africa with rates below 3.8 per 100,000. For explanations of the terminology see Appendix 1. There is less variation in the mortality rates.

Fig 8 ASR BY INCOME LEVEL

	(ASR) per 100,000	
	Incidence	**Mortality**
High income	8.2	4.2
Upper middle income	6.1	3.3
Lower middle income	6.0	4.1
Low income	4.7	3.9
World average	6.6	3.9

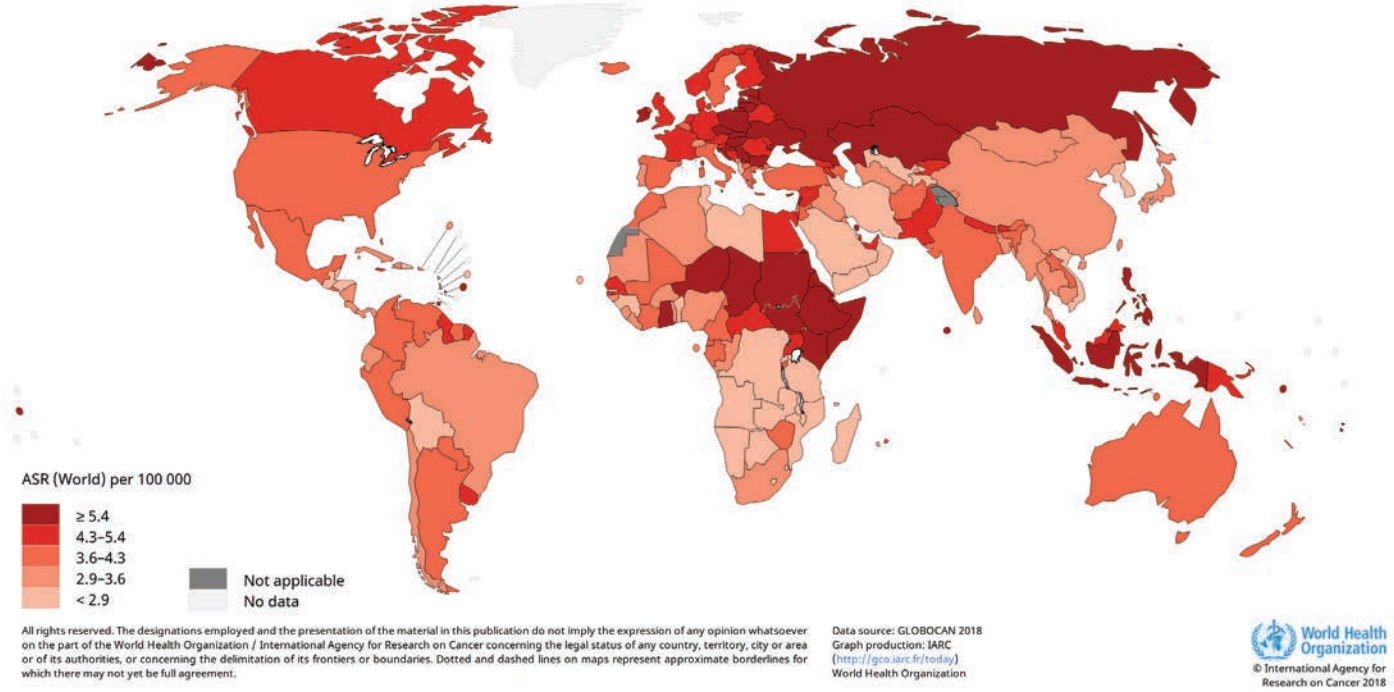
Figures 9 and 10 are from the CANCER TODAY website, based on the latest GLOBOCAN data. To access these maps and other data visit https://gco.iarc.fr/today/home, select maps, then heatmap, incidence, females, global, age standardised rates, and under cancer sites, select ovary. You can also select mortality and prevalence rates.

Fig 9 ESTIMATED AGE-STANDARDISED INCIDENCE RATES (WORLD) IN 2018, OVARY, ALL AGES



Rates of incidence and mortality, as already shown, are higher in more developed countries. As countries undergo development, ovarian cancer rates appear to rise, particularly in urban areas. This has been demonstrated in studies in China and Egypt, where incidence rates are almost twice as high in urban areas as opposed to rural areas[37]. In China, incidence and mortality is

Fig 10 ESTIMATED AGE-STANDARDISED MORTALITY RATES (WORLD) IN 2018, OVARY, ALL AGES



rising to the extent that authors have called for it to be recognised as a significant national public health problem. Yang et al explored a range of urbanisation level evaluating indicators and female health outcomes. In particular, they link fuel oil consumption and urban fixed asset investment to increasing mortality rates for ovarian cancer[38]. This is the main measure of capital spending, including investment in construction projects, machinery, equipment, and real estate development.

An Asian-wide study found a significant positive correlation between the Human Development Index (which measures the socio-economic status of people living in different countries) and the standardised incidence rate of ovarian cancer[39]. The paper also points out the impact of a falling birth rate and better life expectancy resulting in increasingly older populations will mean that non-communicable diseases such as cancer will increasingly place a significant burden in the future, particularly in developing countries. The authors point to genetic and environmental factors, such as socio-economic conditions, and lifestyle affecting risk.

VARIATION BY TYPES OF TUMOUR

Limited evidence suggests that there is a difference in the balance of types of ovarian cancer, depending on the level of development in a country. In developed countries, 90% of ovarian cancer cases are epithelial in origin, with germ cell tumours accounting for 2-3% of cases, and sex cord stromal tumours accounting for 5-6%. However, in Africa and Asia, it appears that germ cell tumours account for between 10 and 15% of cases[40]. These tumours are more treatable and occur in younger women.

VARIATION BY RACE

Variations have been described between different races in other studies[41]. Morris et al[42] reported that ovarian cancer incidence was higher for White women (12.8/100,000) than Black women (9.8/100,000). Yet, when compared with White women, African-American women were more likely to have higher mortality which the authors suggest is potentially due to the lack of sufficient diagnostics and sophisticated treatments, meaning women presented with later stage disease and had shorter disease-free survival.

Moreover, a study in California over 10 years showed that among patients with advanced-stage ovarian cancer, African-American race, low social economic status, and treatment by low volume providers are significant and independent predictors of receiving no surgery, no optimal debulking surgery, no chemotherapy and non-standard treatment sequences[43]. It is clear that optimum cancer diagnosis and care is not accessible to all.

This theme is also explored in a more recent paper by Momenimovahed et al that looked at risk factors and epidemiology for ovarian cancer around the world. The authors conclude that while the highest prevalence of ovarian cancer is seen in non-Hispanic white women (12.0 per 100,000), followed by Hispanic women (10.3 per 100,000), non-Hispanic black women (9.4 per 100,000) and Asian/Pacific Islander women (9.2 per 100,000) due to differences in access to diagnostic and therapeutic services, mortality has a different pattern, with the highest mortality rate being seen in African populations[44].

The opportunities offered by developments in genomics have been identified as a way to drive improvements for people with cancer in different population groups, and by one study in particular for women with cancer in India. It calls for much more widespread collection of data to enable development and use of type appropriate treatments for populations that are more diverse than previously studied [45].

REPRODUCTIVE/HORMONAL AND LIFESTYLE FACTORS

A paper by Malvezzi et al[46] in 2016 examines the trends in mortality rates. Their findings showed persisting and substantial difference in ovarian cancer patterns and trends:

In the European Union (EU), age-adjusted ovarian cancer mortality rates decreased 10% between 2002 and 2012, to 5.2 per 100,000. The decline was 16% in the USA, to 4.9 per 100,000 in 2012. Latin American countries also had lower rates, and declines were observed in Argentina and Chile. Likewise, modest declines (2.1%) were observed in Japan, whose rate remained low (3.2 per 100,000 in 2012). Australia had a rate of 4.3 per 100,000 in 2012, and a 12% decline.

The falls were larger in young women, rather than in middle or old age. Recent rates at age 20–49 were higher in Japan than in the EU and the USA. Predictions to 2020 indicated a further 15% decline in the USA and 10% in the EU and Japan.

The authors attribute some of the progress to the long-term protective effect of the Oral Contraceptive Pill (OCP) (decreasing risk), particularly in countries of Northern Europe and the USA where uptake of the OCP was early and more widespread.

These authors say a recent decrease in menopause hormone use may also partly explain the fall in rates for middle aged and elderly women in countries like Germany, the UK or the USA, where the use of menopausal hormones was more common. Part of the decrease in these countries may be due to the fact that they had the highest ovarian cancer rates in the past.

They also argue that delays in the adoption of recent advancements in diagnosis and management may have unfavourably affected mortality in central and eastern European countries in ovarian and other cancers. They acknowledge that improvements in ovarian cancer

management in general are, in any case, limited. The authors say it is difficult to explain the persisting high rates in central and Eastern Europe. They suggest fertility has been relatively low in that area over the last decades, and multiple parity and breastfeeding reduce ovarian cancer risk. However, they say the substantial differences are unlikely to be explainable by differences in fertility alone. Other environmental factors, including obesity and diet, have been related to ovarian cancer risk. The quantification of their effect on national mortality rates remains undefined.

Finally, the authors say it is also difficult to explain the low rates in Japan and Korea. Diet and leanness in the past may partly account for them, but parity and oral contraception pill use have been relatively low in those countries. Thus, hormonal and reproductive features cannot account for their low rates. Recent trends in these countries have not been declining appreciably, suggesting a future global levelling of ovarian cancer mortality, as confirmed by the recent higher rates in young Japanese women compared with western countries.

In another paper, Zhang et al also examine risk factors amongst birth cohorts in regions, tracking many different factors across different age groups and locations over time[47]. They say that individuals born in the same time period tend to adopt similar lifestyles that may influence their carcinogenic risks both positively and negatively. These trends also change over time in different locations.

They explore the following patterns:

- Women who have smoked have a 6% higher risk of ovarian cancer than those who never smoked;
- A healthy dietary pattern was associated with a 14% reduction in risk, and a western-style dietary pattern including high intake of red meat and processed meat was associated with a 19% increase in risk;
- Diet in early life is important;
- Overweight women have a 7% increase in risk, and obese women a 28% higher risk;
- Each five years of oral contraceptive pill use equates to a 20% reduction in risk;
- Each birth reduces the risk of ovarian cancer, and women who have given birth have a 30% reduction in risk compared to those who did not.

Momenimovahed et al, in addition to some of the themes mentioned above, also explore age at childbirth (older age reduces risk), endometriosis (increased risk), and tubal ligation (decreased risk)[48].

There is also some preliminary research showing that women who have taken statins to lower their cholesterol have a lower risk of developing ovarian cancer, but further work needs to be done to clarify if the drug could be used to lower risk[49].

SUMMARY

In summary, the complex factors seen in Figure 11 have been shown to be linked, or potentially linked to, the risk for an individual woman of developing ovarian cancer and her chance of dying from the disease.

Fig 11 FACTORS LINKED TO THE DEVELOPMENT OF OVARIAN CANCER

Risk Factor	Outline	Notes
Age	In general, increased age increases risk of developing ovarian cancer	Different populations have differing age profiles
Geographic Location Socio-Economic Status	Increased risk in more developed countries, and more developed parts of countries Lower socio-economic status confers a higher mortality rate	Risk can be altered by moving location and by economic development within a country
Race/Ethnicity	Risk varies according to race/ethnicity	Affects age profile, and types of tumour
Family History	Increases risk, including known BRCA mutations and Lynch syndrome	Affects age profile and types of tumour
Hormonal Or Reproductive Factors	Use of oral contraceptive pill, number of pregnancies, later age of pregnancy, and duration of breastfeeding affect risk (positively) Use of hormone replacement therapy may increase the risk	Applies around the world, but cultural factors determine effect
Lifestyle Factors	Nutrition, diet, obesity, lack of physical activity, alcohol, and smoking have been linked in some but not all studies to increased incidence	

VARIATIONS IN DIAGNOSIS AND TREATMENT

VARIATION IN GUIDELINES

Several recent studies have highlighted the wide variation in guideline adherence and clinical practice across low-, middle- and high-income countries relating to diagnosis and treatment.

These variations begin right at the start of the patient journey, with Funston et al highlighting the considerable differences in international guidance documents for assessment of symptomatic women. The authors suggest that this could impact on ovarian cancer detection and outcomes, with the authors pointing out that further research is important[50]. The recommendations in the study provided guidance on 'symptoms' but these ranged from four to 14 symptoms, with only bloating/abdominal distension/increased abdominal size appearing in all 18 documents that were included in their research. They also showed there were five different testing strategies, and whilst transabdominal and transvaginal ultrasound, and serum marker CA125 were most commonly mentioned, there were variations in guidance as to when and how these tests should be conducted.

In 2019, White et al reviewed guideline adherence and clinical variation in relation to ovarian cancer care. This novel study which reviewed papers from the US, Europe, Canada and South Korea, concluded that there is evidence of deviation from effective care in ovarian cancer, demonstrated through deviation from best practice guidelines, and that this can lead to unwarranted clinical variation[51]. In particular, the authors say that centralising care to higher volume centres and surgeons, and the growth of gynaecological oncology as a speciality appear to be associated with enhanced guideline adherence, reduced variation and better outcomes as a result. They also point to the development, implementation and reporting of quality performance programmes leading to reduced unwarranted variation and improved outcomes.

A wider study on oncology guidelines and their usage in low- and middle-income countries showed that, for example, clinicians in Nigeria are aware of cancer treatment guidelines, particularly those produced by the National Comprehensive Network (90%). However, implementation is hindered because local facilities are inadequate, the guidelines are not applicable to the local setting, and the information in them is too complex[52].

LOCAL AND NATIONAL VARIATIONS IN SPECIALIST SURGERY

Following the Calman-Hine report in the UK (1995), national guidance was introduced on commissioning cancer services. "Improving outcomes in gynaecological cancers – The Manual 1999" provided a focus for the creation of specialist cancer centres, where women would be treated by subspecialty trained surgeons and received multidisciplinary team care[53].

However, progress towards centralisation and specialistion of care was slow. A study published in 2015 showed that by 2009 many women were still not receiving specialist surgery, the majority were not being operated on by General Medical Council accredited gynaecologic oncologists, and, moreover, there was considerable regional variation[54]. Anecdotal evidence in the UK more recently suggests that the situation has improved, but it is included here to demonstrate that shifting towards surgery in specialist centres is not necessarily straightforward or timely.

The focus on specialist surgery has been of interest around the world. In 2009 Bristow et al showed that after controlling for other factors, ovarian cancer surgery performed by a high-volume surgeon was associated with a 69% reduction in the risk of in-hospital death, while high-volume care was associated with increased likelihood of cytoreduction, shorter length of stay and lower hospital related costs of care[55].

Another study in California in 2014 led by Bristow, showed that among patients with advanced stage ovarian cancer, the provider combination of high-volume hospital and high-volume physician is an independent predictor of improved disease specific survival. However, it highlighted how access to high-volume ovarian cancer providers is limited, and that barriers are more pronounced for patients with low socio-economic status, Medicaid insurance, and those from racial minorities[56].

A single institution observation study in Tokyo, Japan, led by Shinichi Tate and Makio Shozu tracked the implementation of an aggressive surgery protocol for 5 years. They studied 106 consecutive patients. The surgeons underwent training for 9 months prior to beginning the service. Their study confirmed that implementing such a regime did not cause a significant increase in mortality, and they saw increases in median progression free survival (from 14.6 to 25 months), and overall survival (38 months to 68 months)[57].

The centralisation of healthcare services for the management of ovarian cancer is seen as an increasingly important step. The introduction of a national cancer patient pathway in Denmark, which had had lower ovarian cancer survival than countries with comparable health systems,

as studied in the International Cancer Benchmarking Partnership Study[58], has had a profound effect on reducing delays in diagnosis and treatment, and the authors note that the most marked improvements in recent net survival in the study took place in Denmark. The centralisation of services led to an increase in radical surgery, and the greatest improvements were seen in relation to women over the age of 75, those with stage III or IV cancer, and those without co-morbidities[59].

There is clear benefit in developing systems for specialists to treat women in high-volume centres, but there can be many barriers in setting up such surgery, such as a lack of associated disciplines (e.g. pathology, imaging), a lack of funding, and a lack of political will. There also may be geographical factors and the issue of a lack of training in gynaecological oncology as evidenced in many regions around the world.

In a paper by Johnston et al[60], even within established training programmes, there are differences in what is taught: some programmes do not include intestinal or urological surgery (Asia), and in Europe chemotherapy is not normally administered by gynaecologic oncologists. The authors also highlight the need for basic oncology and pathology resources, and that the key to success for any program providing training assistance in low- and middle-income countries is to be flexible and responsive enough to adapt to 'the broad spectrum of needs in each country, and to deliver expertise in a context-specific, culturally sensitive and politically expedient manner'.

AVAILABILITY OF TREATMENTS

The mainstays of global ovarian cancer drug treatment continue to be platinum and taxane treatments such as Carboplatin and Paclitaxel. These are included on the World Health Organisation's Essential Medicines List (21st edition, 2019), along with Bleomycin, Cisplatin and Gemcitabine[61]. Alexandru Eniu et al examined which drugs were available and issues that may impact availability within the Asia Pacific region (Figure 12). In particular, they showed the challenges relating to low- and middle-income countries[62].

Fig 12 AVAILABILITY OF WHO ESSENTIAL MEDICINES FOR OVARIAN CANCER IN ASIA & ASIA PACIFIC *as studied by Eniu et al.*

	WHO Essential Medicines list for:	Patient Accessibility Issues in Asia and Asia Pacific
Bleomycin	Ovarian Germ Cell Tumour	Available in high income countries for up to 50% of cost for patients (Japan, South Korea, Singapore). Free in upper middle countries – China, Kazakhstan, Malaysia, Thailand, and at up to 25% cost in Iran. Patients pay full cost in lower middle-income countries (Bangladesh, India[63], Myanmar, Pakistan), free in Indonesia and Vietnam, and discounted rates in the Philippines. In low income countries (Afghanistan, Cambodia, Nepal), patients pay the full cost.
Carboplatin	Epithelial ovarian cancer	As for Bleomycin
Cisplatin	Ovarian germ cell tumour	As for Bleomycin except that it is free in Myanmar
Gemcitabine	Epithelial ovarian cancer	Information not available
Paclitaxel	Epithelial ovarian cancer and germ cell tumours	As for Bleomycin except data was missing for China

Eniu at al also say that there are issues with reliability or lack of suppliers, lack of commercial motive, and budget capitation in relation to the above drugs in certain countries including: Kazakhstan, India, Myanmar, Philippines, Pakistan, Afghanistan, Nepal and Iran.

Whilst there have been developments in targeted therapies for ovarian cancer, these are by no means widely available across the world. Anecdotal evidence shows that for low- and lower middle- income countries, access is severely limited if it indeed exists at all. There is a need to quantify access to such drugs and to find ways of making them available where they are not, and to make genetic testing more widely available around the world.

The UN 2030 Sustainable Development Goal 3.8 on Universal Health Coverage(UHC)[64] requires that everyone, everywhere can access needed healthcare without experiencing financial ruin as a result of care. Eniu et al note that the current literature from low- and middle-income settings paints a bleak picture of the financial hardships associated with accessing cancer care, even where UHC exists, meaning many are at risk of financial catastrophe as a result of cancer care.

He and his colleagues go on to suggest strategies to improve the accessibility of cancer medicines including:

- Shortening the time for approval and registration of cancer medicines in low- and middle-income countries;
- Improving availability of medicines if they are on the national list of essential medicines, and included in national clinical practice guidelines;
- Increasing the budget allocation for effective anti-cancer medicines for specific indications;
- Improve affordability by price negotiation (government), including value-based pricing, availability of quality assured generics, and patient assistance programmes from pharmaceutical companies or non-profits, and compulsory licensing.

SURVIVAL RATES FOR OVARIAN CANCER

In this section we explore the factors that might affect a woman's chance of survival, and look at the key findings of some major international studies.

Comparing survival rates between countries, and between cancer types is not a straightforward task, as they are measured in many different ways, using different criteria, and including or excluding certain data. The figures contained in this section should only be used within the context that they are cited and not taken as applicable in other situations. Usually they are cited in terms of one- or five-year survival and indicate the proportion of women diagnosed with ovarian cancer who are likely to be alive at one year, and five years post diagnosis. Of course, for an individual woman it is impossible to estimate this likelihood with any certainty. However, many women (but certainly not all) would like to know what the possibilities are.

SHORT-TERM MORTALITY AND EMERGENCY PRESENTATION

A report by the National Cancer Registration and Analysis Service (NCRAS) in England highlighted short-term ovarian cancer mortality as a particular issue, with 15% of women with ovarian cancer dying within 2 months of their diagnosis[65].

Three risk factors were identified for death within a year of diagnosis:

- Emergency presentation (56% died in first year);
- Advanced age - 43% of those aged 70-79 died in first year, and 70% of over 80s;
- Tumour morphology – those who had 'unclassified epithelial ovarian cancer' or 'miscellaneous or unspecified 'morphology.

Women who had more than one of these risk factors had an even higher chance of dying quickly. Further analysis of their data in 2018 showed that 20% of women are unable to receive any form of treatment, primarily because they are too unwell[66].

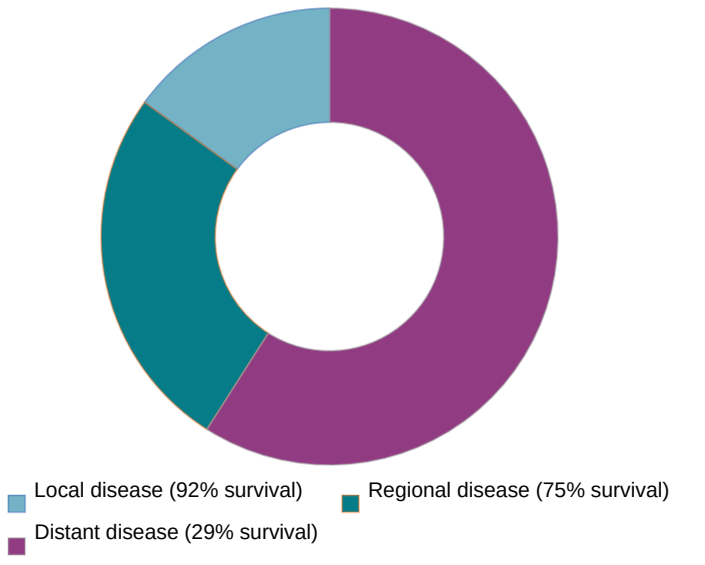
A study in the US concluded for a sample of over 9,000 women with either stage III or IV disease that 43% died within the first year, 26% of the cohort within the first 90 days. Older age increased co-morbidity, stage IV disease, lack of a visit to a gynaecologic oncologist and lack of surgery were all associated with an increase in 90-day mortality[67]. A study in Denmark showed that suboptimal debulking, and being older than 64 at the time of diagnosis led to an increased likelihood of death within 180 days of diagnosis[68].

It is evident that, for a significant number of women, their diagnosis comes too late for them to tolerate treatment. Additionally, their emergency presentation increases the risk of non-assessment by a multi-disciplinary team, and of urgent surgery conducted by non-specialists.

STAGE OF DIAGNOSIS

It is accepted that both one- and five-year survival rates for ovarian cancer are very much determined by the stage at which it is diagnosed, i.e. the extent to which it has spread. The American Cancer Society figures show the following proportions together with their associated five-year survival rates. They cite the overall five-year survival rate as 48%:

Fig 13 SPREAD OF OVARIAN CANCER ON DIAGNOSIS WITH ASSOCIATED SURVIVAL

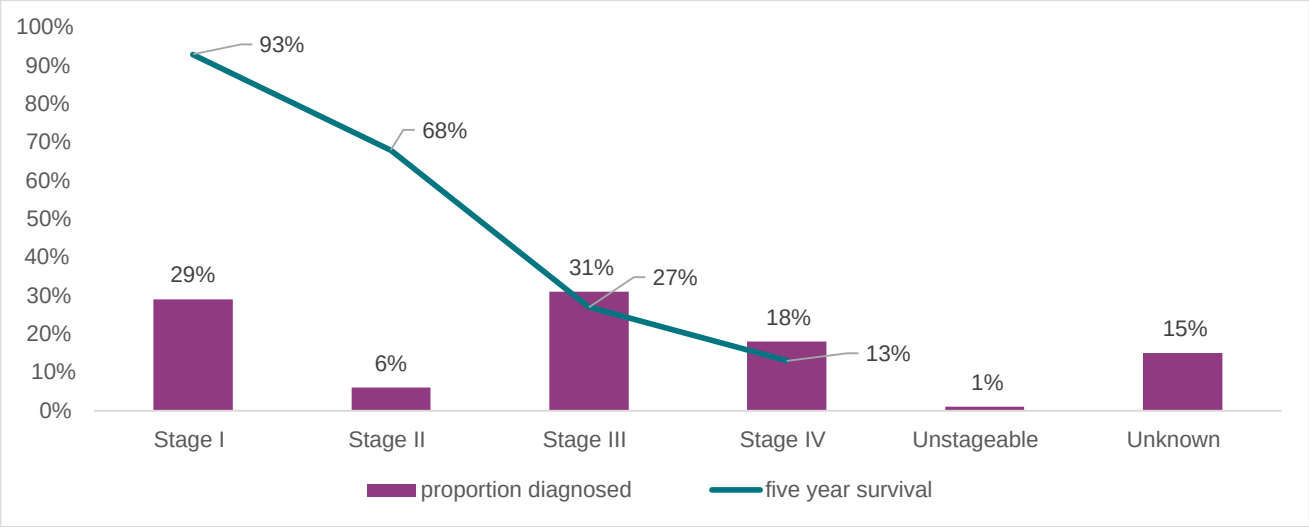


(figures from the American Cancer Society, 2020)

Data (Fig 14) from England shows survival by FIGO stage for women diagnosed between 2013 and 2017 followed up to 2018[69]:

As can be seen, there are differences in terminology used to describe the spread of ovarian cancer between different countries, with the SEER (Surveillance, Epidemiology and End Result) and FIGO (Federation of International Gynecology and Obstetrics) systems being displayed here. Clinicians can also give 'TNM' data in relation to the extent of the tumour (T), nodal involvement (N) and metastasis (M). This can hamper efforts to perform accurate cancer survival comparisons between countries, and the researchers in the International Cancer Benchmarking Partnership are calling for a common international staging system[70].

Fig 14 5 YEAR SURVIVAL BY FIGO STAGE - WOMEN IN ENGLAND DIAGNOSED 2013-2017



LOCAL VARIATIONS – DIAGNOSIS

Data produced by the Ovarian Cancer Audit Feasibility Pilot in England shows, that despite differences in completeness of reporting data, there are differences in the proportions of patients diagnosed at early and late stages within the country, and that assessment of geographic variations in survival rates may help to identify areas of best practice which could be used to drive improvements[71]. Data from 195 Clinical Commissioning Groups (CCGs) in England showed that the proportion of women diagnosed with stage I disease varied from 10% to 47.9% depending on location.

The imperative is not just moral, but financial too. Analysis of costs in England showed potential for significant savings, if all CCGs who organise health services in a particular area were able to achieve the levels of early diagnosis of the best performing CCGs for ovarian cancer, then £16m per annum could potentially be saved, and 1,400 patients would benefit[72]. To put this figure into context, the National Cancer Research Institute partners (UK) spent a total of £8.5m on ovarian cancer research in 2015-6[73]. On those figures, if the money saved was diverted, the ovarian cancer research spend in the UK could be almost trebled.

TYPE OF OVARIAN CANCER

Matz et al have examined ovarian cancer survival by stage and type and show there are very wide variations[74]. Their findings lead them to call for histology to be included in all future international comparisons of ovarian cancer survival, as varying proportions of different types may well affect overall results.

Their work showed that type 1 ovarian cancers had a 5-year survival rate that generally fell between 50 and 60% but ranged from 82.9% in Hong Kong, (72.4% to 93.4%), to 30.8% in Argentina (16.3% to 45.2%). Five-year survival rates for type 2 ovarian cancers including high grade serous were in the region of 20% to 45%, ranging from 61.5% in Hong Kong (54.8%-68.2%), to 18.1% in Chile (6.3% to 29.9%). Survival rates for germ cell tumours were higher than type 2 ovarian cancers but varied widely by country, and the survival rate for sex cord stromal tumours was the highest.

Torre et al in their paper for the American Cancer Society 'Ovarian Cancer Statistics 2018' show the differing five-year survival for the different types of ovarian cancer as seen in Figure 15[75]:

Fig 15 5 YEAR SURVIVAL FOR DIFFERENT TYPES OF OVARIAN CANCER

Epithelial ovarian cancer						
All epithelial	**Serous**	**Endometrioid**	**Mucinous**	**Clear Cell**	**Sex cord stromal**	**Germ cell tumour**
47%	43%	82%	71%	66%	88%	94%

They go on to break it down by stage and race too. Women from non-Hispanic black origin tend to fare worse than those from Hispanic, Asian/Pacific Islanders, or non-Hispanic white origins, which the authors put down to lower adherence to treatment protocols.

SURVIVAL RATES BETWEEN COUNTRIES – KEY FINDINGS

It is often hard to provide direct comparisons between survival rates in different countries. Reasons include:

- Time lag in collection of data from around the world means comparative data is often older than that currently being used in a specific country;
- Differences may occur in which morphology codes are or are not included;
- Researchers construct life tables to estimate background mortality in a given country or region. Variations in the type of data used to construct these tables will result in variations in the resulting survival rates[76].

As such, it is inadvisable to draw conclusions of survival statistics where these are drawn from several different studies. Care should be taken when making comparisons that only one study source is used, where they can verify consistency in approach. A number of studies have done this.

The CONCORD Studies

The CONCORD-2 study published in 2015 aimed to initiate a worldwide surveillance of cancer survival as a measure of the effectiveness of health systems[77]. Previous studies (ICBP, Eurocare, and SurvCan) all adopted different methods, and so results cannot be brought together. Their most recent study (CONCORD-3) which was published in 2018 is discussed below[78].

CONCORD-3 includes analysis of data from 71 countries in 18 cancer types and revealed very wide differences in survival that are likely to be attributable to differences in access to early diagnosis and optimum treatment. Results for ovarian cancer were based on data from over 865,000 women in 61 countries diagnosed in 2010-2014, and overall was of a higher quality (i.e. more complete) than CONCORD-2 which the authors note may be driving any improvements or worsening of figures. The data was collected for ovarian cancer and included fallopian tube, uterine ligaments and adnexa, as well as the peritoneum and retroperitoneum where high grade serous carcinomas are often detected.

For women diagnosed during 2010–14, 5-year survival was in the range of 40–49% in 24 countries: in Canada and the USA; seven countries in Asia (Singapore [south Asia]; China, Korea, Japan, and Taiwan [east Asia]; and Israel and Turkey [west Asia]); 14 European countries (Denmark, Estonia, Finland, Iceland, Latvia, Norway, and Sweden [northern Europe]; Portugal and Spain [southern Europe]; and Austria, Belgium, France, Germany, and Switzerland [western Europe]); and Australia.

Survival was in the range of 30–39% in 19 countries: four in Central and South America (Argentina, Brazil, Ecuador, and Puerto Rico); Kuwait and Thailand; 12 European countries (Ireland, Lithuania, and the UK [northern Europe]; Croatia, Italy, and Slovenia [southern Europe]; Bulgaria, the Czech Republic, Poland, Russia, and Slovakia [eastern Europe]; and the Netherlands [western Europe]); and New Zealand.

Survival was less than 30% in Malta and less than 20% in India.

Survival trends between 1995–99 and 2010–14 were fairly flat in most countries. However, 5-year survival rose by 5–10% in the USA; Israel, Korea, and Taiwan; 11 European countries (Denmark, Iceland, Ireland, Norway, and Sweden [northern Europe]; Portugal and Spain [southern Europe]; Bulgaria and Poland [eastern Europe]; and France and Switzerland [western Europe]); and Australia. Survival increased by more than 10% in Estonia and Latvia, and by 20% in Japan.

International Cancer Benchmarking Partnership Study

The International Cancer Benchmarking Partnership Study (ICBP) has been working to track and analyse survival rates for breast, bowel, lung and ovarian cancers in high-income countries (or states within) including Canada (Alberta, British Columbia, Manitoba, Ontario), Australia (New South Wales, Victoria), New Zealand, the United Kingdom (England, Scotland, Wales, Northern Ireland), Norway, and Denmark. They have been considered suitable for comparison due to their level of cancer registration and spend on healthcare. There are five modules looking at:

- Cancer survival;
- Population awareness and beliefs about cancer;
- Attitudes, behaviours, and systems in primary care;
- Delays in diagnosis and treatment and the causes thereof;
- Treatments, co-morbidities, and other factors.

Results to date have shown that variation is quite wide, and they are beginning to inform cancer policy in order to improve cancer survival. Sweden did not participate in the ovarian cancer part of the study.

In terms of ovarian cancer in Denmark and the UK, for women diagnosed up to 2007, it was apparent that poor one-year survival rates drove the overall survival rates, pointing to issues with diagnosis and initial treatment. This was particularly so for the UK, where five-year survival rates for women, if they survive the first year, were the second highest. Norway and Canada had the best results overall for this period. (Figure 16)

Fig 16 OVARIAN CANCER SURVIVAL RATES (%) IN HIGH INCOME COUNTRIES (DIAGNOSED 2005-2007)

Survival	Australia	Canada	Denmark	Norway	UK
1 year	73.5	75.6	70.6	75.2	65.0
5 year	37.5	41.9	36.1	39.7	36.4
5 year - (if survived 1ST year)	48.7	54.4	48.8	50.9	53.8

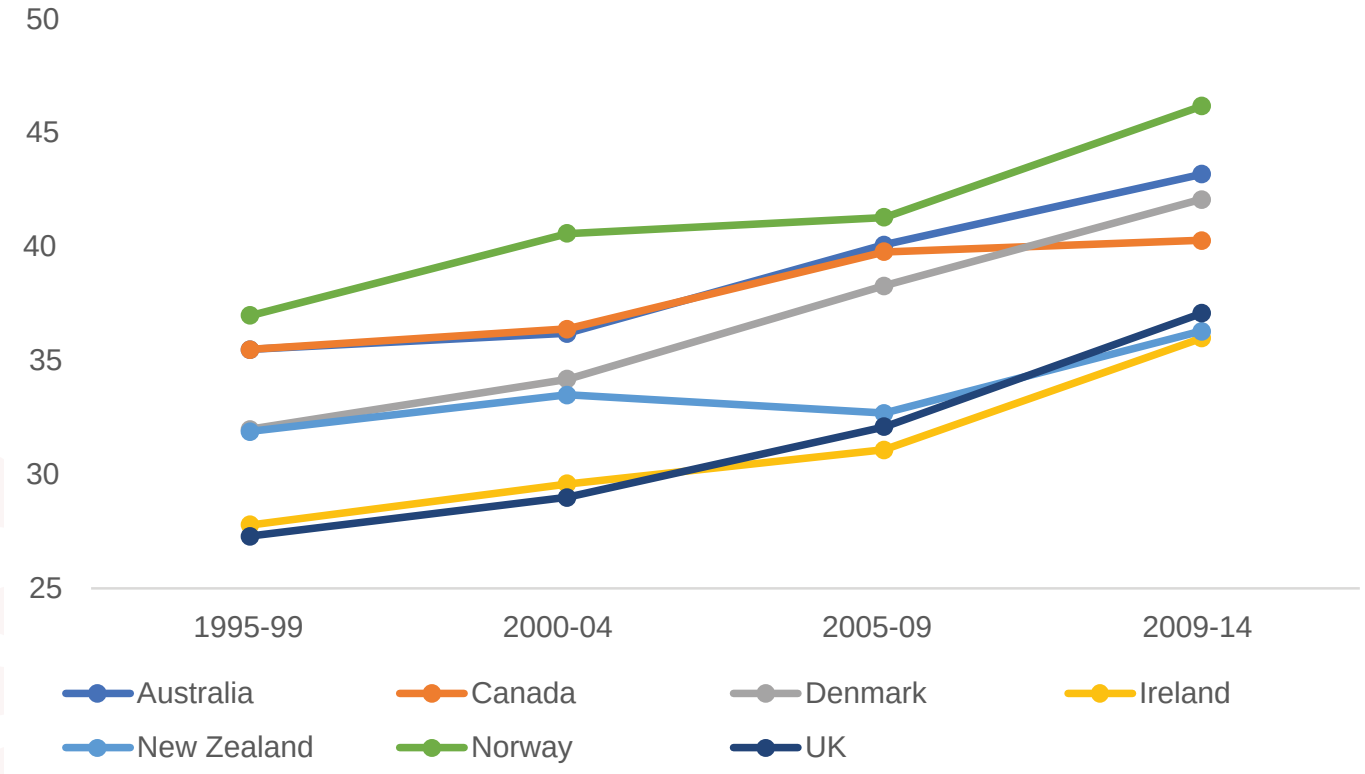
For ovarian cancer, different stages of diagnosis accounted for some but not all the variability[79]. The UK and Denmark had the lowest one-year survival. Denmark had the lowest proportion of diagnoses at an early stage, but overall, the UK had a similar proportion to the other countries. However, the UK was worst in terms of recording stage at diagnosis, with 30% of data missing, compared to 10% in Norway. Survival was worse for those whose stage was not recorded.

More recent data from the study shows some progress over the last 25 years in five-year age-standardised survival, with Denmark, UK and Norway improving the most, and Canada and New Zealand, the least. The improvements were even greater when women over the age of 75 were excluded from the data[80].

Another recent paper from the study showed the international differences in ovarian cancer survival were more marked in older women, and in those where the disease was diagnosed at an advanced stage. It also showed intra-jurisdictional differences. The authors suggest differences in access to and quality of care, adherence to national and international guidelines, differences in surgical philosophy and treatment approaches, and the organisation of healthcare services were factors warranting further exploration[81].

Beliefs about ovarian cancer and awareness of ovarian cancer symptoms have been examined. In the UK, perceived barriers to symptom presentation were highest with 34% of people believing they would be wasting the doctor's time, and people had less knowledge of age and other risk factors. This compared to 9% in Sweden. Knowledge of the symptoms of ovarian cancer (in particular persistent bloating) was consistently low across all participating countries[82].

Fig 17 AGE-STANDARDISED 5 YEAR NET SURVIVAL BY COUNTRY AND PERIOD of DIAGNOSIS (ICBP-SURVMARK2)



The ICBP Study has also shown a correlation between primary care physicians' willingness to act and cancer survival in that jurisdiction. While there were differences in access to advice on whether or not to refer to secondary care and access to diagnostic tests, no consistent reasons for this variation in willingness have yet been found for the cancers studied as a whole, and further work is being carried out. However, the authors of the study concluded that some jurisdictions might consider lowering the thresholds for primary care physicians to investigate cancer either directly, or by specialist referral to improve outcomes[83].

The ICBP study is on-going but, in the UK and in Denmark, results are already helping focus efforts to improve cancer survival at a national level. This includes moves to improve access to diagnostic tests, improve family doctors' knowledge, improve awareness of symptoms, and improve cancer registration. It also includes the creation of multi-disciplinary diagnostic centres for patients with vague symptoms - "one-stop shops"- successfully rolled out in Denmark and currently being piloted in the UK[84].

Using the current data for one-, five-, and five-year conditional survival for the countries in the ICBP study[85], together with the estimated incidence rates from GLOBOCAN 2018, the following estimates (as seen in Figure 17) of increased numbers of women surviving one and five years were made by the World Ovarian Cancer Coalition by applying the best one- and five-year survival rates (green) in each instance. The lowest figures are in orange.

Fig 18 ESTIMATES OF INCREASED NUMBERS OF WOMEN SURVIVING 1 & 5 YEARS

Country	Incidence[§]	5-year survival % (ICBP)	1-year survival % (ICBP)	5-year conditional on 1 year % (ICBP)	No. extra women survive 1 year if had best 1-year survival	No. extra women survive 5 years if had best 5-year survival
New Zealand	280	36.3	71.5	50.7	20	27
United Kingdom	6407	37.1	70.3	52.8	531	577
Canada	2716	41	72.8	55.6	157	138
Denmark	433	42	77.4	54.5	5	17
Australia	1496	43.7	78.6	55.7	0	36
Norway	329	46.1	77.5	59.6	4	0

[§] Taken from GLOBOCAN 2018 estimate

Eurocare

The Eurocare 5 study (2015) which looked at cancer survival across Europe for people diagnosed between 2000 and 2007 concluded that despite increases over time, survival for women's cancers remained poor in Eastern Europe, likely due to advanced stages of diagnosis, and or suboptimum access to adequate care. Low survival for women living in the UK/Ireland and Denmark, it suggested, was possibly due to late detection and delays in referral.

Overall the study highlighted poor survival for ovarian cancer across the continent and over time and suggested the need for major research effort to improve the prognosis for this common cancer[86].

SURVIVAL IN LOWER-INCOME COUNTRIES

As yet little data exists detailing survival differences for ovarian cancer in lower-income countries, but there is research underway by the SurvCan team (see below). The lack of high-quality data has been an issue but it is clear for cancer outcomes as a whole that the challenges can be greater than those experienced in higher-income countries. Developing countries are still coping with huge burdens of communicable disease, poor infrastructure and very limited health budgets.

Prof. Michel Coleman, however, describes the three engines of escalating cancer burden as being on the move: rapid population growth, an ageing population and increase in cancer risk at each age[87]. Consequently, lower-income countries will be increasingly challenged to cope with the cancer burden.

Sankaranarayanan et al evaluated 300,000 cancer deaths in Africa, Asia and Central America between 1990 and 2001 in Lancet Oncology[88]. Their SurvCan project showed that just 22% of cancer patients in Gambia survived 5 years, and in Uganda (excluding breast cancer patients) the figure was even lower at 13%. They commented on the huge stigma facing those with a cancer diagnosis in some of these settings.

The authors highlighted how variations in survival correlated with early detection initiatives and level of development in health services. They also concluded that wide variation in cancer survival between regions emphasises the need for urgent investments in improving awareness, population-based cancer registration, early detection programmes, health-services infrastructure, and human resources.

A position paper produced by the African Organisation for Research and Training in Cancer in 2016, highlighted particular issues[89]:

- Lack of early and accurate diagnosis is a challenge to appropriate care. More than 80% of patients in Africa are diagnosed at advanced stages of cancer. Inadequate pathology leads to wrong diagnosis and patients may receive inappropriate treatment. Scarcity of care providers and researchers is a problem in pathology training, and many countries have less than one pathologist for every million people;
- Access to healthcare - cancer is often seen as a disease caused by spiritual curses, and, as such, cases are often referred to healers or shamans for traditional or spiritual treatment. Health care providers in rural areas lack cancer training, often misdiagnosing it as other illness. Lack of data on cancer prevalence and trends in Africa and historical focus on communicable diseases impede government efforts on cancer research and treatment;

- Availability of treatment modalities - high quality treatment is difficult due to limited healthcare sources and low affordability. The current number of physicians practising in Africa (145,000) represents 5% of the European total (2,877,000). Treatment access is also limited: approximately 22% of the 54 African countries have no access to anti-cancer therapies. Barriers to treatment include significant out-of-pocket expenses. Out-of-pocket health expenditure is estimated to push many people globally into dire poverty when treatment costs are substantially higher than income;

- Finally, there is a constant threat to the clinician pool due to 'brain drain'. More than half of 168 medical schools surveyed reported losing between 6 to 18% of teaching staff to emigration in the last 5 years. It will be critical to entice African health care personnel with better salaries, working conditions, career paths and support.

In a more recent paper by Verna Vanderpuye at al 'Cancer care workforce in Africa: perspectives from a global survey', the authors highlight that African oncologists within the AORTIC network have a substantially higher clinical workload and lower job satisfaction than oncologists elsewhere in the world and that there is an urgent need to address these issues[90].

In 2013 a report in Lancet Oncology entitled 'Status of radiotherapy resources in Africa' showed a huge variation in accessibility to machines, with South Africa and Egypt having over 60% of the equipment[91].

The potential for nurses to address the growing cancer burden in low- and middle-income countries through primary prevention and early detection, in addition to treatment and supportive roles, has been raised by groups involved in the International Society of Nurses in Cancer Care. Published papers however highlight how this requires a scaling up of oncology nursing in such countries, to build sustainable programmes that reach deep into communities[92].

At the American Society for Clinical Oncology annual meeting in 2015, Dr Gilberto Lopes MD, MBA, FAMS explored reducing the global economic burden of cancer. Having examined data from the Union for International Cancer Control[93] he pointed out that while the economic burden of each cancer cases in the US, UK, and Japan ranged from $183 - $460 per patient every year, in South America, India and China it ranged from a paltry $0.54 to $7.92 per patient. Overall, high-income regions spent more than 5-10 times more on cancer control on a per capita basis, than low- or middle-income countries.

In a study comparing cancer outcomes and correlation with healthcare expenditure, the researchers showed cancer outcome correlated significantly with economic indicators and the amount of health expenditure per capita (HEpc) escalated exponentially[94]. The median actual total HEpc ranged from US$44 to US$4643. The authors propose a new standardized method for global comparison considering the variations in incidence of different cancers between countries, and their chances of cure.

However, for many women and their families in low- and lower-middle income countries, the cost burden of cancer care falls to them, with often devastating impacts, and acts as a deterrent to seeking help.

SUMMARY

In summary, the reasons for variations in survival rates between countries are complex and still not fully understood. Whilst the balance of tumour types in any country may differ, and may impact on survival rates, there are many other known and suspected reasons for variation as Figure 19 indicates.

Fig 19 POTENTIAL FACTORS FOR VARIATION IN SURVIVAL RATES

Known Or Potential Factors For Variation In Survival Rates	Outline	Notes
Delays In Diagnosis	Low awareness Delays in women seeking help Stigma surrounding cancer preventing women seeking help	Health systems, attitudes and financial burden may play a part. Cancer nurses in low-income countries may be able to help
Delays In Initial Investigations	Doctors not realising symptoms may indicate ovarian cancer Access to tests Willingness of doctor to investigate Lack of referral to specialist care	Diagnosis following an emergency presentation is a key driver for early deaths
Lack Of Doctors (General)	Some low-income countries have few doctors	
Differences In Stage At Diagnosis	Varies between different countries Some influence of balance of tumour types but also may indicate prolonged/ delayed diagnosis	In particular, looking at 1 and 5-year survival rates can provide an indicator of whether there are issues with treatment or diagnosis
Lack Of Specialist Staff	Trained in gynaecologic oncology	Particularly in low-income countries but not exclusively
Ability To Retain Specialist Staff	Issue in lower-income countries in particular	
Access To Specialist Services	High-volume centres and surgery performed by high-volume surgeons are important	Networks of such centres are rare in low- and middle- income countries and problematical even when they do exist in terms of referring women in
Access To Pathology/ Specialist Pathology	Getting the diagnosis right can drive accessing the right treatments	In some very low-income settings, even diagnosing as cancer would be progress. Finding out the tumour type will drive more accurate treatments for individuals
Access To Existing And New Drugs	Mainstay treatments for ovarian cancer are still not universally available for women Access to targeted therapies such as Bevacizumab or PARP inhibitors is very varied, and non-existent in many lower-income countries Women often cannot afford to pay for diagnosis and/or treatments in certain countries	Federal or regional health structures can impede access despite national guidance

DATA ON OVARIAN CANCER PATIENT EXPERIENCE

While there has been much academic discussion about incidence, mortality and survival around the globe, very little academic research has focused on women's experience of being diagnosed and living with ovarian cancer.

Some studies exist highlighting the psychological impact of such a devastating diagnosis and being subjected to aggressive surgical and medical protocols. They call for screening of women for psychological distress.[95] A systematic review of global studies focusing on quality of life for women with ovarian cancer in 2016 concluded that there was a wide range of conditions as a result of treatment that may persist for a long time and impact negatively on a woman's quality of life. The review noted that studies proposing interventions and treatments were lacking.[96]

In terms of policy development, the National Health Service in England introduced the National Cancer Patient Experience Survey comparing experiences of people with different cancers and in different locations within England. Results have been used to monitor national progress on cancer care, and to provide information to drive local quality improvements, and inform the work of various charities and stakeholder groups supporting cancer patients.[97]

In terms of looking at the overall experience of women, from the time when they were or were not aware of symptoms, through treatment and living with the disease, it has been the charitable sector and, to some extent, pharmaceutical companies who have made efforts to gather this information.

The World Ovarian Cancer Coalition's Every Woman Study™ (2018)[98] is the largest such study in ovarian cancer to date. Launched at the ESMO conference in 2018, results have been presented at scientific meetings including SGO and BGCS (oral presentations), and ESGO (poster), and a paper has been published in the International Journal of Gynecologic Cancer[99]. It has been heralded as a 'new area in patient advocacy', providing a wealth of data relating to all aspects of women's experiences of the disease. 1531 women from 44 countries took part.

The Study found significant variations in women's experiences between countries in a wide range of measures. No one country was without challenges, and whilst one country may have expertise and good practice in a particular area, it may struggle in other aspects. For example, women in the United Kingdom were most likely to visit a doctor about symptoms, but then had the longest time period from visiting that doctor to diagnosis. However, almost all women receive specialist care.

In Germany fewer women visited a doctor about symptoms. Those who did went very quickly, yet only around 60% of women received care in specialist centres despite national guidance.

Women in Japan had the quickest time to diagnosis after visiting a doctor but less than one in ten received genetic testing as opposed to over 80% in the US. The variations provide an opportunity for countries to drive improvements in the short and medium term. Recommendations from the study form the basis of the Global Ovarian Cancer Charter which was launched in September 2020.

A pan-European survey amongst women with gynaecological cancers by ESGO-ENGAGe explored some other aspects of care, revealing variations between European countries[100]. Delays of more than two months in starting treatment were highest in countries such as Hungary and Poland (21.1%, 25.5%) and lowest in Denmark (4.2%). The availability of psychological support services was highest in Spain (68.7%) and lowest in Hungary (26.3%).

The authors were particularly concerned at the overall lack of other interventions that could support quality of life, such as dietary and nutritional support only available to 26.3% of all participants, and just 5.1% of women being offered counselling to help regain sexual function.

Country specific examples include the Target Ovarian Cancer Pathfinder Study (2009, 2012, 2016) in the United Kingdom, Ovarian Cancer Australia surveys in 2014 and 2015, and 'Our Way Forward' by pharmaceutical company Tesaro, in the USA in 2017.

CONCLUSION

The heightened risk of ovarian cancer in developed countries, and the increasing burden of ovarian cancer in developing countries provide compelling reasons to address globally low survival rates.

Sankaranarayanan and Ferlay provide a useful summary in their chapter on gynaecological cancers in The Handbook of Disease Burdens and Quality of Life Measures[101]: the differences in the outcomes of cancer treatment across the world are due to vast disparities in health service infrastructures, human resources, service delivery, and accessibility of services.

They conclude that a significant proportion of patients are unable to access preventive, diagnostic, and therapy services in many countries due to inadequate health care services and financing. Formulation and translation of appropriate cancer control policies and investments in raising awareness, human resources development, and healthcare infrastructure are vital to reduce the current burden of gynaecological cancer in low- and medium-resource countries. On the other hand, attention should be focused on emerging cost-effective options to sustain and further improve current control prospects in the developed world.

It is an exciting time for those involved in the care of women with ovarian cancer. New research is producing the first major breakthroughs in several generations, and it is encouraging to see an increasing focus on the disease and understanding why variations in incidence, mortality and survival occur. However, given the enormous challenges facing those in lower-income countries, for many the new treatments are unobtainable.

If the gap between countries is not to widen, we must all be prepared to act to support women around the world so they have a better chance of surviving and living well with this disease, no matter where they are located.

In particular there is a need to:

- Recognise ovarian cancer as a global priority;
- Improve the quality of national cancer data or population-based cancer registries to inform cancer control plans;
- Use a consistent framework for reporting the stage or spread of the disease;

- Incorporate the type of ovarian cancer in all data collection;
- Improve the knowledge of women and doctors in relation to ovarian cancer to reduce delays in diagnosis;
- Reduce variation in guidelines for diagnosis and treatment, but make them relevant to local populations;
- Support the United Nations and the Union for International Cancer Control action on Universal Health Coverage (UHC) to make drugs included in treatment guidelines available to all, without causing financial hardship on women and their families;
- Monitor the availability of new targeted therapies and associated genetic testing around the world, and find ways of opening up access to lower-income countries;
- Consider how to develop centres of expertise for women with ovarian cancer, even in low-resource settings;
- Invest in the cancer workforce, ensuring imaging, pathology and other key services better support rather than impede diagnosis, and provide incentives for trained staff to continue to provide experienced care;
- Explore how the role of cancer nurses in low-and middle-income countries could be developed;
- Examine the differences in survival between countries, with a view to developing interventions to improve cancer care;
- Ensure women's quality of life is not ignored or forgotten.

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APPENDIX 1

GLOSSARY OF TERMS - AS DEFINED IN THE GLOBOCAN 2012 ESTIMATES

Incidence

Incidence is the number of new cases arising in a given period in a specified population. This information is collected routinely by cancer registries. It can be expressed as an absolute number of cases per year or as a rate per 100,000 persons per year (see Crude rate and ASR below). The rate provides an approximation of the average risk of developing a cancer.

Mortality

Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year.

Prevalence

The prevalence of a particular cancer can be defined as the number of persons in a defined population who have been diagnosed with that type of cancer, and who are still alive at the end of a given year, the survivors. Complete prevalence represents the number of persons alive at certain point in time who previously had a diagnosis of the disease, regardless of how long ago the diagnosis was, or if the patient is still under treatment or is considered cured. Partial prevalence , which limits the number of patients to those diagnosed during a fixed time in the past, is a particularly useful measure of cancer burden.

Prevalence of cancers based on cases diagnosed within one, three and five are presented as they are likely to be of relevance to the different stages of cancer therapy, namely, initial treatment (one year), clinical follow-up (three years) and not yet cured (five years). Patients who are still alive five years after diagnosis are usually considered cured since the death rates of such patients are similar to those in the general population. They would be included in complete prevalence figures. There are exceptions, particularly breast cancer.

Prevalence is presented for the adult population only (ages 15 and over), and is available both as numbers and as proportions per 100,000 persons.

Crude rate

Data on incidence or mortality are often presented as rates. For a specific tumour and population, a crude rate is calculated simply by dividing the number of new cancers or cancer deaths observed during a given time period by the corresponding number of person years in the population at risk. For cancer, the result is usually expressed as an annual rate per 100,000 persons at risk.

ASR (age-standardised rate)

An age-standardised rate (ASR) is a summary measure of the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer. The ASR is a weighted mean of the age-specific rates; the weights are taken from population distribution of the standard population. The most frequently used standard population is the World Standard Population. The calculated incidence or mortality rate is then called age-standardised incidence or mortality rate (world). It is also expressed per 100,000. The world standard population used in GLOBOCAN is as proposed by Segi and modified by Doll. The age-standardised rate is calculated using 10 age-groups (0-14;15-39;40-44;45-49;50-54;55-59;60-64;65-69;70-74;75+).

NOTES:

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