WORLD OVARIAN CANCER COALITION

Empowering the global ovarian cancer community through collaboration, knowledge and action.

THE WORLD OVARIAN CANCER COALITION ATLAS 2023

GLOBAL TRENDS IN INCIDENCE, MORTALITY, AND SURVIVAL

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GLOBAL OVARIAN CANCER CHARTER
a World Ovarian Cancer Coalition initiative

NO WOMAN LEFT BEHIND

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INTRODUCTION

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 since 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.

The second edition preceded the launch of the World Ovarian Cancer Coalition's next major initiative, the Global Ovarian Cancer Charter which was released in September 2020 at the International Gynaecologic Cancer Society (IGCS) annual meeting. The Charter built on the key recommendations of the Every Woman Study™ (2018) and focused 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 recognised 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

Vision

A world where every woman with ovarian cancer has the best chance of survival, and the best quality of life – wherever she may live.

- **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 certain other cancers 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

INTRODUCTION

This third edition delves further into 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 this paper, the differences between the experiences of women in low-, middle- and high-income countries are also discussed. This remains an ongoing challenge, with most studies emanating from high-income countries, despite the greater burden of disease in low- 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 within 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
- **Social Demographic Index (SDI)** – a summary measure, comprising of average income per capita, educational attainment, and total fertility rate (TFR), that identifies where countries or other geographic areas are situated on the spectrum of development
- **Human Development Index (HDI)** – a summary measure used to evaluate the level of human development in each country. It is defined using three key aspects of human development: health, knowledge, and standard of living

EXECUTIVE SUMMARY

In the four years since the first edition of the World Ovarian Cancer Coalition Atlas there has been an encouraging number of new studies exploring the several aspects of this complex disease around the globe. The findings from these studies strengthen our knowledge and determination about the actions needed to tackle the major challenges facing women who develop ovarian cancer around the world. 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 2020, it was estimated that almost 310,000 women were diagnosed with ovarian cancer worldwide, 200,000 women died from the disease, and there were more than three-quarters of a million women living within five years of their diagnosis. Whilst there have been some improvements in overall survival rates, progress remains stubbornly slow, and research is still a long way from producing a reliable screening method for general populations. Within this context, it is important to remember that although we have seen some positive progress, ovarian cancer still has the highest mortality rate of all the female cancers.

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* which have been described as 'game changing', and more recently new research has involved immunotherapy. However, the majority of women who have ovarian cancer live in low- and 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 gap between those who can access the best possible care and those who cannot will widen without action.

The projected growth in numbers of women developing ovarian cancer (42% increase by 2040, GLOBOCAN 2020) will take place largely but not exclusively in developing countries where access to the best possible care is severely limited through the lack of effective cancer control plans, infrastructure, and strategies that ensure access to necessary cancer medicines without financial ruin.

Without action, the gap between those who can access the best possible care and those who cannot will widen. It is imperative that emerging knowledge about the disease that can drive improvements in outcomes in wealthier countries is also available to inform efforts to close this gap with those in lower resource settings.

* A substance that blocks an enzyme in cells is called PARP. PARP helps repair DNA when it becomes damaged. In cancer treatment, blocking PARP may help keep cancer cells from repairing their damaged DNA, causing them to die. PARP inhibitors are a type of targeted therapy. Also called poly (ADP-ribose) polymerase inhibitor. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/parp-inhibitor

EXECUTIVE SUMMARY

Key findings in this report reveal that:

- There will be a rapid increase in the numbers of women developing ovarian cancer, particularly in low- and middle- income countries
- Acting on familial history and ways of reducing the risk of developing ovarian cancer through hormonal, lifestyle, and surgical intervention, may slow the rising rates and prevent many women from developing the disease in the future
- Across all countries there are wide variations in availability of clinical guidance, and adherence to it in all countries - from assessing symptoms, to surgery and drug management. In particular, guidance in lower-income countries needs to be implementable as well as aspirational for the local setting
- Developing and maintaining trained workforces with adequate infrastructures is relevant in all situations but particularly in lower-income settings
- Understanding differences in survival rates between countries can inform efforts to get the best possible outcomes

Since the outbreak of the COVID-19 pandemic, the challenges for women in terms of getting diagnosed and accessing treatments have been enormously exacerbated, with potentially devastating consequences. There has never been a more pressing need for action For women right around the world, it is imperative that we continue to study this disease, and understand the driving factors behind the poor outcomes, speeding up our efforts wherever possible.

It is important to seize opportunities to prevent ovarian cancer, diagnose it promptly, target treatments more effectively, ensure appropriate workforce and infrastructures, improve access to treatments, and gather data that can inform effective policies relevant to local populations, whether in higher- or lower-income countries.

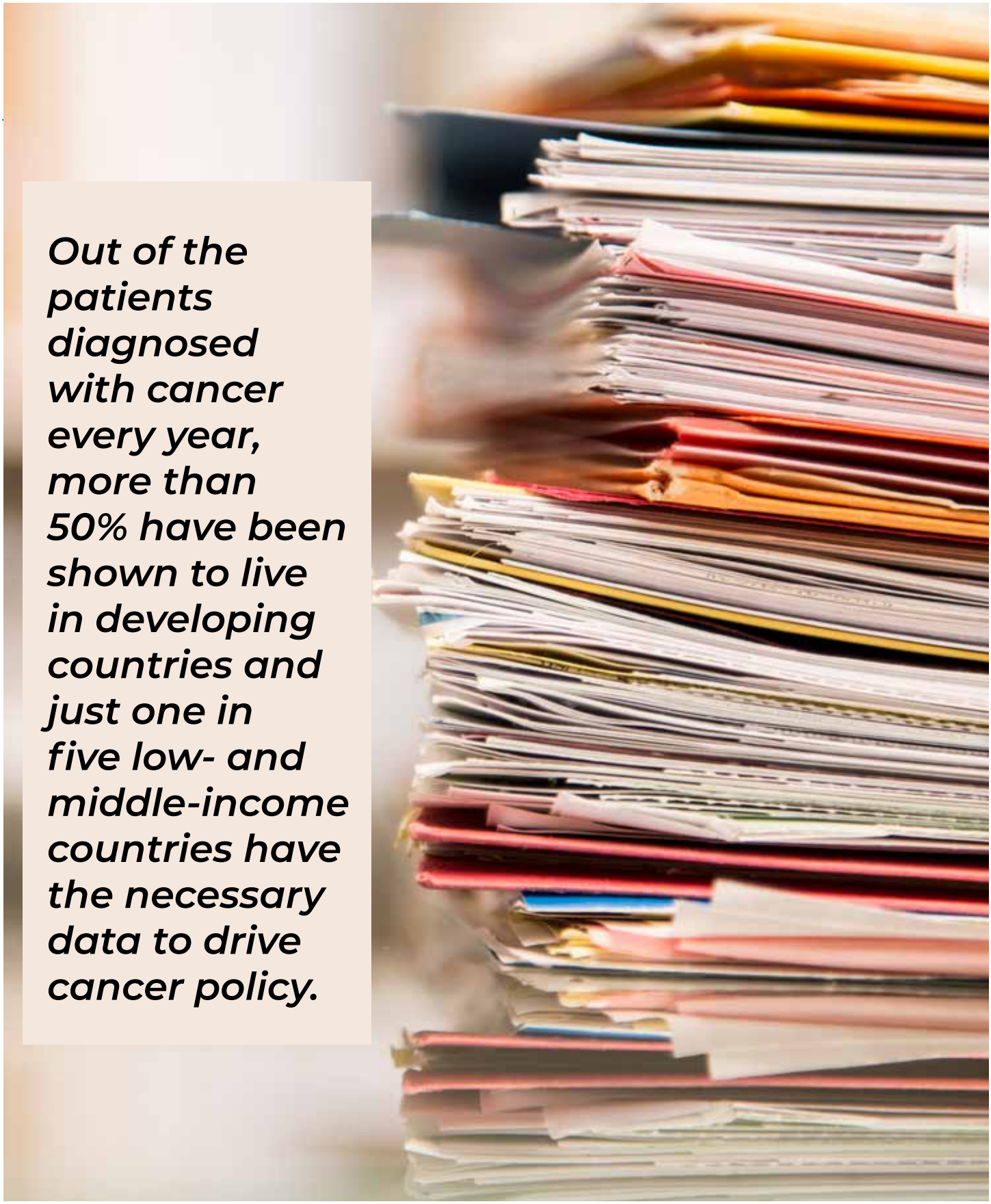
Finally, women themselves must be at the heart of the process - leading the call for action, informing the debate at every step, and sharing their experiences and data where possible.

EXECUTIVE SUMMARY

RECOMMENDATIONS

In order to drive forward progress there is a need for the ovarian and global cancer communities and policy makers 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, type, and spread of the disease
- 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, and implementable in, 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 ensuring 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
- Further 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



Out of the patients diagnosed with cancer every year, more than 50% have been shown to live in developing countries and just one in five low- and middle-income countries have the necessary data to drive cancer policy.

THE GLOBAL CANCER BURDEN

Figures from the World Health Organization (WHO) report that cancer is the second leading cause of death globally with nearly 10 million deaths in 2020[1]. The International Agency for Research on Cancer highlights that in the same year there were 18 million people diagnosed with cancer, and 44 million living within five years of their diagnosis[2]. It is projected that the global cancer burden in terms of deaths will rise to 16.3 million a year by 2040, with incidence reaching 30.2 million[3].

Out of the patients diagnosed with cancer every year, more than 50% have been shown to live in developing countries. 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 options are common. More than 90% of high-income countries reported treatment services being available compared to less than 15% of low-income countries. Shockingly just one in five low- and middle-income countries have the necessary data to drive cancer policy[4].

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[5]. With the associated strain on health systems and economies, timely and accurate statistics are imperative to help develop an evidence base and provide impetus for identifying and developing cancer control strategies at a national level.

The Sociodemographic Index (SDI) is a summary measure that allows for patterns of cancer burden to be analysed across different resource settings. The Sociodemographic Index was developed in 2016 as part of the Global Burden of Disease study. Therefore, it is a recently developed metric comprised of three key aspects of development: income, education, and fertility. The authors argue that since SDI does not include health as part of its equation, it allows researchers to compare countries' health outcomes more robustly[6]. Whilst SDI has begun to make its way into health systems and outcomes research, a comparable and older method called the Human Development Index (HDI) continues to be widely used. HDI was developed by the United Nations to measure countries' levels of social and economic development. It is defined using three key aspects of human development: health, knowledge, and standard of living[7]. We will be highlighting studies that use either metric to discuss cross-national differences in cancer burden.

In their report, the "Global Burden of Disease 2019 Cancer Collaboration" data analysed between 2010-2019 highlights that whilst absolute cancer burden increased across all SDI quintiles, low and low-middle SDI quintiles saw the largest percentage increases[8]. In addition to such heterogeneity in cancer burden increases, Christina Fitzmaurice, and colleagues from the Global Burden of Disease Cancer Collaboration report that the drivers behind increasing cancer incidence also differ substantially by Sociodemographic Index (SDI). In the lowest SDI quintile population growth is the major contributor, in low-middle SDI countries ageing 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[9].

Bray et al, in their summary of "Global Cancer Statistics 2020" based on the data from GLOBOCAN[10] report that, "Cancer transitions are most striking in emerging Human Development Index (HDI) economies, where an increasing magnitude of the disease is paralleled by a changing profile of common cancer types. A lot of the already established risk factors in high-income countries (e.g., smoking, lack of physical

THE GLOBAL CANCER BURDEN

activity, changing diets, and additional body weight) are becoming increasingly prevalent in countries categorised as low and medium HDI. 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"[11], 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 efficiently planning, implementing, and evaluating cancer control initiatives as a means to reduce the widening gap in cancer occurrence and survival worldwide.

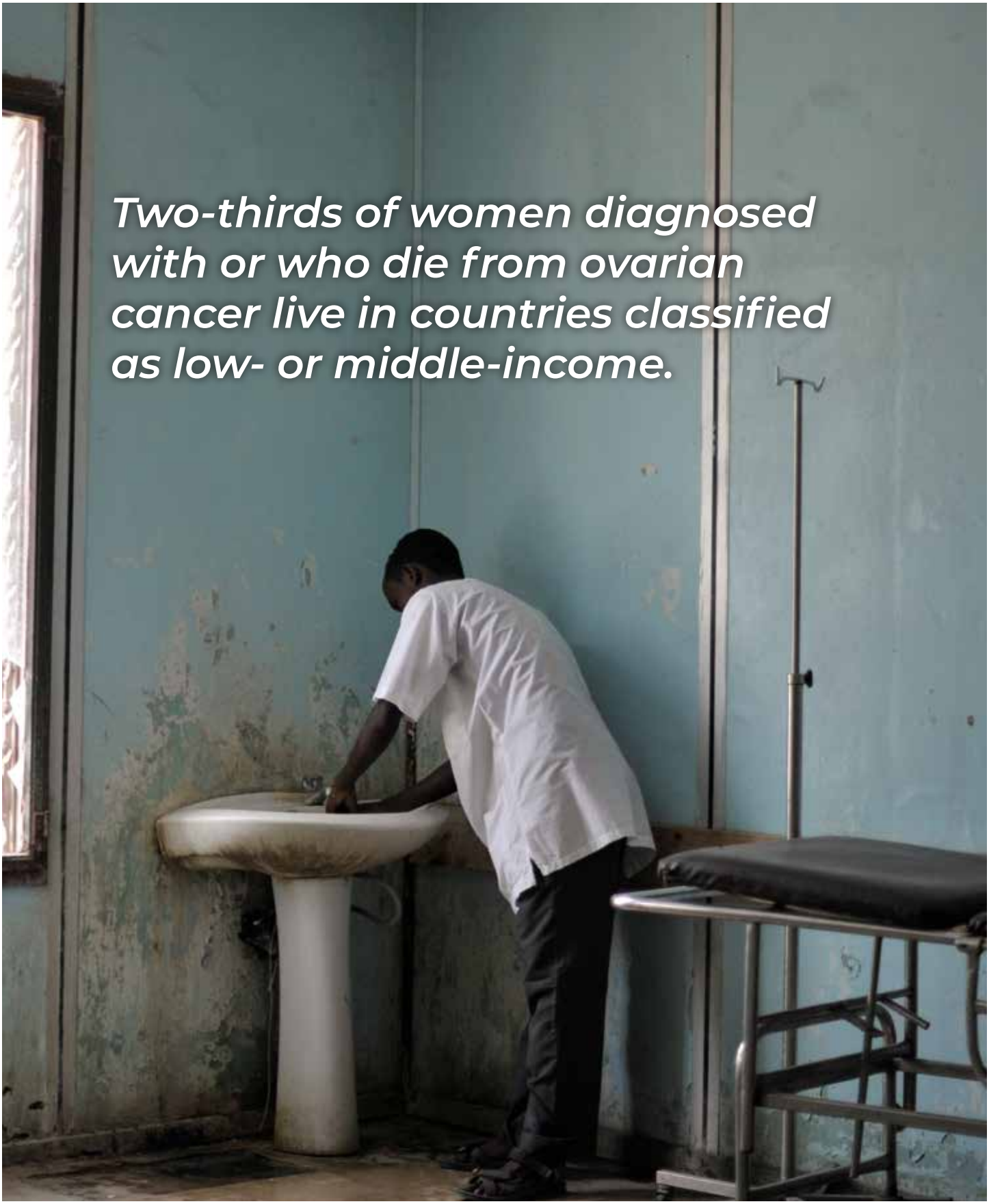
There are major inequities in the availability of high-quality, local data in many countries particularly developing economies, which impact the corresponding robustness of the estimates available. According to a World Health Organization (WHO) report, as of 2019, cancer registries did not exist in more than one out of three countries. Out of those that do have cancer registries, only 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 WHO[12]. A study by Siddiqui and Zafar (2018) on the global availability of cancer registry data found that out of 190 countries, only 52% had PBCRs, whilst 26% did not have any sort of cancer registry at all.[13] 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[14].

Although PBCRs may cover national populations, more often they cover smaller, subnational areas, and particularly in countries experiencing substantial development, only selected urban areas.[15] Out of the 190 countries analysed by Siddiqui and Zafar, only 43% had national coverage.[11] 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.[16] The aim of the project is to provide contemporary estimates of the incidence, mortality, and prevalence of 36 different types of cancer, at a national level in 185 countries.

The latest figures are estimates for 2020. 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 uncertainty intervals, and these estimations were made based on national-level data, timeliness of data, and quality.

Antoni et al[17] 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)[18]. GICRD say that 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, leaving 70% of the cancer burden falling on under-resourced regions least equipped to provide patient care from basic treatment to palliation.


Two-thirds of women diagnosed with or who die from ovarian cancer live in countries classified as low- or middle-income.

OVARIAN CANCER AS A GLOBAL PRIORITY

Figures from GLOBOCAN 2020 show that ovarian cancer is the 7th most common cancer, and 8th most common cause of death from cancer in women across the world[19].

CURRENT AND PROJECTED INCIDENCE AND MORTALITY

It is estimated there were approximately 314,000 cases of ovarian cancer in 2020, almost 207,000 deaths, and more than 823,000 women living within five years of diagnosis (5-year prevalence). On its Cancer Tomorrow website, GLOBOCAN predicts that by the year 2040, incidence will have risen by 42% to a total of just over 446,000, with an even larger increase in the number of deaths each year (up nearly 52% to over 314,000)[20].

Figure 1 shows incidence and mortality In terms of numbers affected and GLOBOCAN future projections by continent.

FIG 1 - INCIDENCE AND MORTALITY BY CONTINENT (GLOBOCAN 2020)

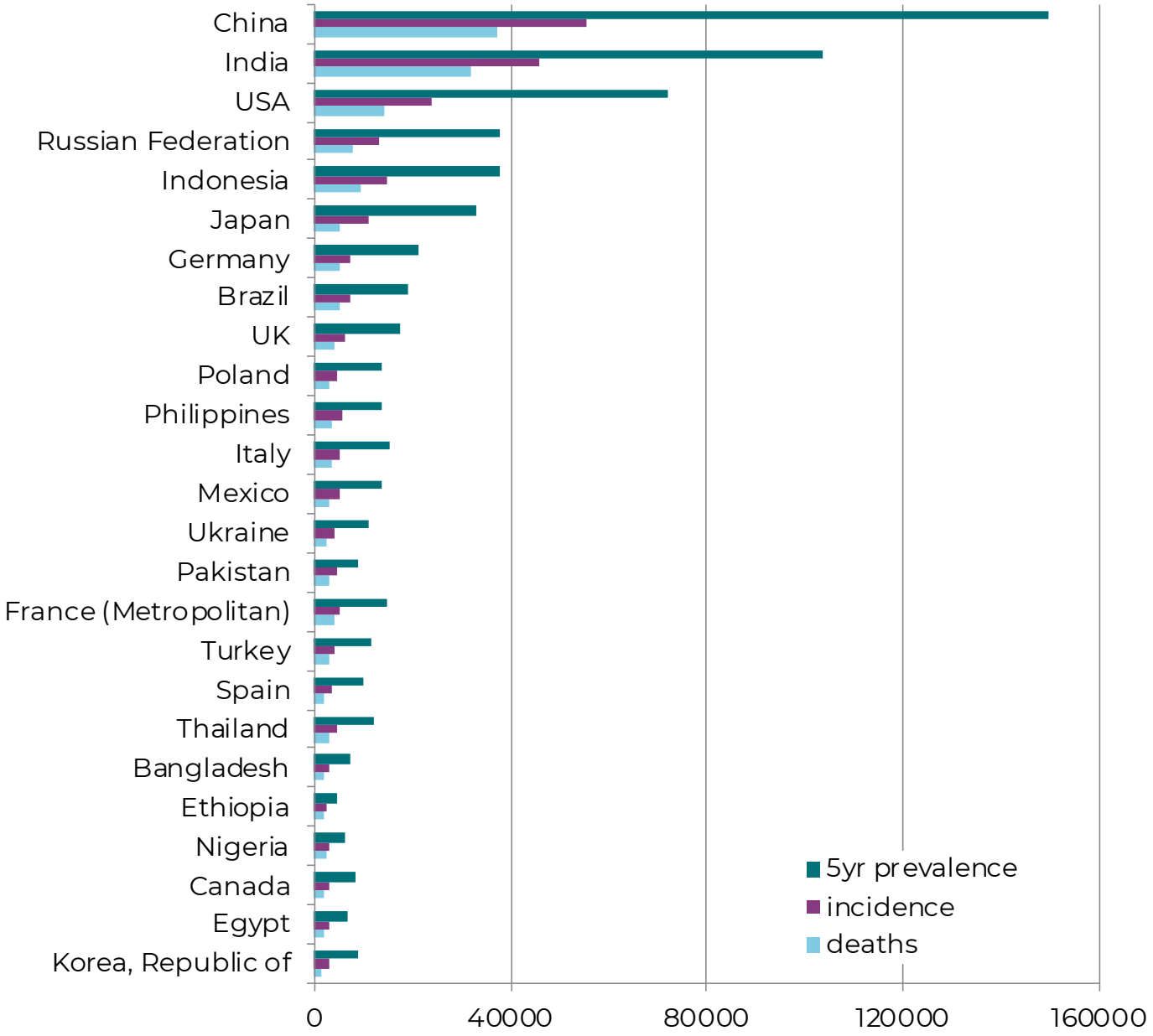
	INCIDENCE			MORTALITY		
	2020	2040*		2020	2040[1]	
Asia	170,759	238,748	**+40%**	112,936	171,676	**+52%**
Europe	66,693	73,124	**+10%**	44,053	51,796	**+18%**
North America	26,630	33,531	**+26%**	16,451	22,528	**+37%**
Latin America/Caribbean	23,513	35,183	**+50%**	15,266	24,755	**+62%**
Africa	24,263	45,332	**+87%**	17,008	32,701	**+92%**
Oceana	2,101	3,048	**+45%**	1,538	2,392	**+56%**
Total	313,959	428,966	**+37%**	207,252	305,848	**+48%**

* 2040 incidence and mortality figures are projections

OVARIAN CANCER AS A GLOBAL PRIORITY

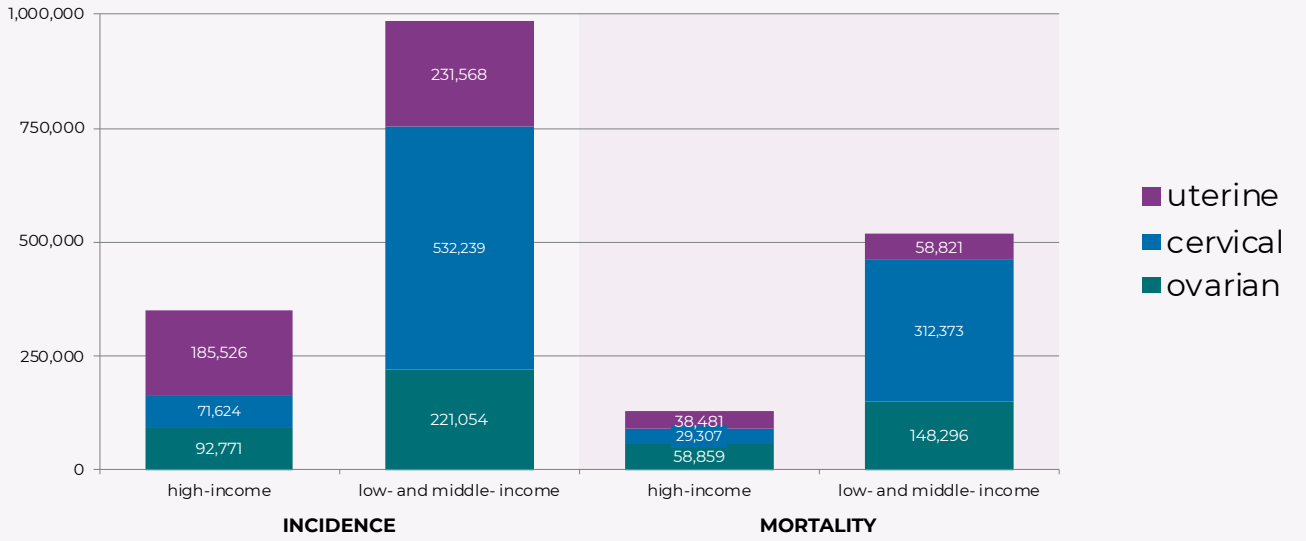
The following chart (Fig. 2) ranks countries by the number of reported cases of ovarian cancer in 2020. It also shows the number of deaths, and five-year prevalence.

FIG 2 - COUNTRIES WITH THE LARGEST NUMBER OF WOMEN WITH OVARIAN CANCER
(source Cancer Today (GLOBOCAN accessed 26th July 2022)



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

FIG 3 - GYNAECOLOGICAL CANCER INCIDENCE AND MORTALITY (GLOBOCAN 2020)



Breast cancer is by far the most common "women's cancer". In 2020, an estimated 2,261,419 new cases, and 684,996 deaths occurred (GLOBOCAN 2020). There were thought to be almost 7.79 million women living within five years of a breast cancer diagnosis.

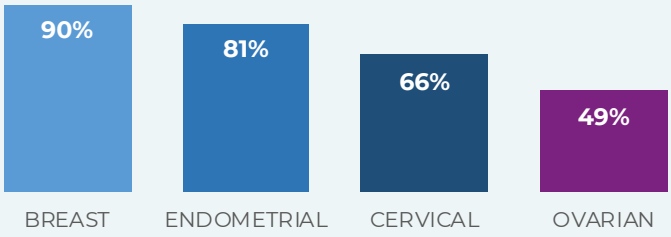
When considering gynaecological malignancies, cervical cancer has been a much more significant issue in less developed areas of the world, largely due to lack of screening, vaccination, and poor sexual health. However, this is beginning to change. Uterine cancer is strongly linked to body mass index (BMI) and has, in recent years, seen a steep rise in incidence in more developed, as well as some developing parts of the world.

Per GLOBOCAN 2020, the risk of ovarian cancer is highest in high-income countries - 8.0 Age Standardised Rate (ASR) per 100,000 versus 5.3 in low-income countries - but is rising more disproportionately in low-income countries as they develop and transition economically[21]. As a result, different countries place gynaecological, and more generally, women's cancer control, at differing priority levels.

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

To compare ovarian cancer five-year survival rates with those of breast, cervical or endometrial cancer, the following statistics in Figure 4 have been extracted from the American Cancer Society's Cancer Facts and Figures (2022) document[22]. It is important to note that ovarian cancer is the most lethal female cancer.

FIG 4 - 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 terms of incidence of the different types, and outlook for women diagnosed with differing forms. This can make it challenging for women to find appropriate information and complicated for researchers to extract type-specific data.

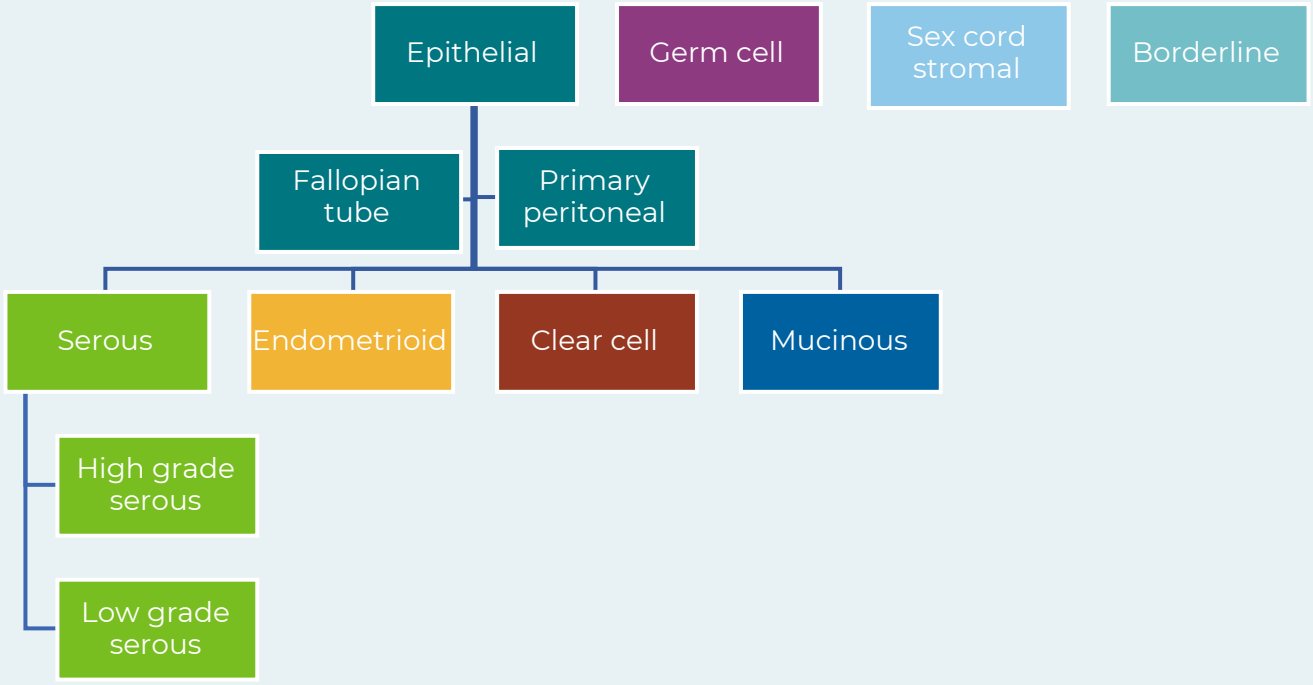
TYPES OF OVARIAN CANCER

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. (Fig. 5)

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[23] 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[24]. He notes that there is either a stepwise mutation from slow growing borderline tumour to well differentiated carcinoma (type I), or there evolves a genetically unstable high-grade serous carcinoma that spreads rapidly (type II). In particular, this type may be very hard to detect at an early point.

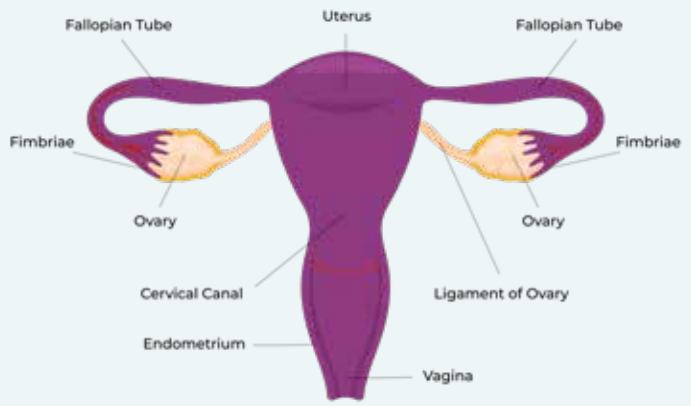
FIG 5 - OVARIAN CANCER TYPES



WHAT IS OVARIAN CANCER?

It is now increasingly thought that these type II tumours begin in the fimbriae 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[25].

FIG 6 - FEMALE REPRODUCTIVE SYSTEM



Lisio et al summarised type I and II tumours for Epithelial Ovarian Cancer as seen in Figure 7 on the following page.[26]

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 females of reproductive age and are often very successfully treated by surgery.

SYMPTOMS

Studies by Goff et al in 2004 and 2007 provided impetus to highlight commonly experienced symptoms associated with ovarian cancer. They found that symptoms such as pelvic/abdominal pain, increased abdominal size/bloating, difficulty eating/feeling full, and urinary urgency/frequency were associated significantly with ovarian cancer[27,28]. Since these studies were published, symptom indices have been developed and modified to aid diagnosis of ovarian cancer. The World Ovarian Cancer Coalition's Every Woman Study™ (2018) also found that more than 90% of women experienced several of the key symptoms regardless of stage or type of ovarian cancer.

DETECTION

There is no universal screening programme for ovarian cancer. The world's largest randomised control screening trial (UKCTOCS) failed to show mortality benefit for screening using CA125 and ultrasound, and instead suggested that it could potentially lead to harm for some women[29]. Despite the setback for screening, further research has highlighted the importance of CA125 as a tool to diagnose symptomatic women, with a heightened understanding of how and when to use it to decide which women might need further investigation[30].

TREATMENTS

Ovarian cancer treatments can be divided into two categories – local treatments and systemic treatments. Local treatments treat tumours without affecting the rest of the body and include surgery or less commonly, radiation therapy. Systemic treatments refer to drugs that are used to treat ovarian cancer. Depending on the type of ovarian cancer diagnosed, different types of systemic drug treatments might be prescribed. Systemic treatments include chemotherapy, hormone therapy, and targeted drug therapy for ovarian cancer. The type and stage of ovarian cancer, overall health status, and fertility plans are important determinants in choosing a treatment route. Most women with ovarian cancer are likely to go through some type of surgery to remove their tumours[31].

WHAT IS OVARIAN CANCER?

FIG 7 - DIFFERENCES BETWEEN TYPE I AND TYPE II OVARIAN TUMOURS
as defined by Lisio et al

	TYPE I	TYPE II
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)


Whilst there is an increased risk of ovarian cancer in more developed countries, and more developed parts of countries, lower socio-economic status confers a higher mortality rate.

RISK FACTORS FOR OVARIAN CANCER

As the following section outlines, 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 too.

FAMILY HISTORY

For generations, it has been clear that ovarian cancer is more prevalent in some families than in the general population. A breakthrough in 1994 determined that faults in the BRCA1 and BRCA2 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 then identify women at risk.

The most predominant hereditary risk factors in the development of ovarian cancer are mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2. With a mutated BRCA1 gene, a woman has a risk of 39%-44% of developing ovarian cancer by the age of 80, and a 11%-17% risk with a mutated BRCA2 gene[32]. 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 mutations, particularly BRCA1 and 2 mutations[33].

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[34].

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)[35]. There are two major categories of mutations – germline and somatic mutations. Germline mutations often occur due to endogenous factors such as errors in cellular replication, changes to DNA, and can be inherited. Somatic mutations are changes acquired due to environmental factors and are not passed on to children. 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[36] in some countries.

RISK FACTORS FOR OVARIAN CANCER

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 BRCA2 genes. For example, in women of Ashkenazi Jewish descent, founder mutations occur mainly in three sites[37], whereas in different populations mutations can occur at many different points. A study by Rebbeck et al (2015) showed that the risks may vary by type and location of BRCA mutation[38].

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[39]. The lifetime risk for individuals with a family history of Lynch syndrome is 6-8%[40].

The most common types of ovarian cancer in these individuals are endometrioid and clear cell. Other cancers associated with Lynch syndrome include womb cancer (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, being highest in older females. However, comparing ages for peak incidence and mortality around the world, it appears to vary by 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[41].

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[42], 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[43]. 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 White women (59.1% vs 47.3% $p<0.001$).

RISK FACTORS FOR OVARIAN CANCER

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 were 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[44].

Matz et al, using data from the CONCORD-2 study, were able to show the average age for the different types of ovarian cancer as seen in Figure 8[45]:

FIG 8 - MEAN AGE BY TYPE OF OVARIAN CANCER (CONCORD-2)

HISTOLOGICAL GROUP	N° OF PATIENTS	%	MEAN AGE*	
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)
Mising morphology	691	0.1	64	(16)

* in years (with standard deviation)
† no information on grade so all endometroid tumours classified as type I
‡ no information on grade available so all serous tumours classified type II

RISK FACTORS FOR OVARIAN CANCER

WHERE WOMEN LIVE

Age standardised incidence rates (ASR) for ovarian cancer vary around the world. Data from GLOBOCAN 2020, as seen in Figure 9, shows that it is highest in more developed regions, with rates in these areas exceeding 8.1 per 100,000, and lowest in Sub-Saharan Africa with rates below 3.8 per 100,000. There is less variation in the mortality rates for ovarian cancer.

Cabasag et al suggest that part of the reason for this reduced variability in mortality is the persistence of poor prognosis and therefore poor survival associated with ovarian cancer in lower HDI (Human Development Index) settings.[46] HDI measures the socio-economic status of people living in different countries. Rates of incidence, 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 as opposed to rural areas[47]. In China, incidence and mortality is rising to the extent that authors have called for it to be recognised as a significant public health problem in Chinese women. 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[48]. This is the main measure of capital spending, including investment in construction projects, machinery, equipment, and real estate development.

An Asia-wide study found a significant positive correlation between the Human Development Index and the standardised incidence rate of ovarian cancer[49]. The paper also points out that a falling birth rate combined with improved life expectancy and older populations will increase the significant burden placed by non-communicable diseases, including cancer, particularly in developing countries. The authors point to genetic and environmental factors, such as socio-economic conditions, and lifestyle affecting risk.

AGE STANDARDISED INCIDENCE RATES (ASR) PER 100,000		
INCOME LEVEL	**INCIDENCE**	**MORTALITY**
High	8.0	4.1
Upper-middle	6.3	3.9
Lower-middle	6.1	4.3
Low	5.3	4.1
World average	6.6	4.2

FIG 9 - ASR BY INCOME LEVEL

Cabasag et al (2022) project that relative to 2020 estimates, projections for 2040 show an expected increase of nearly 96% and 100% in new ovarian cancer cases and deaths respectively in low HDI countries versus 19% and 28% in very high HDI countries. Given that the current burden of ovarian cancer is already being felt disproportionately in low-resource settings, the risk of such an increased burden in the continued presence of such inequities warrants urgent attention.

RISK FACTORS FOR OVARIAN CANCER

FIG 10- ESTIMATED ASR INCIDENCE RATES (WORLD) IN 2020, OVARY, ALL AGES

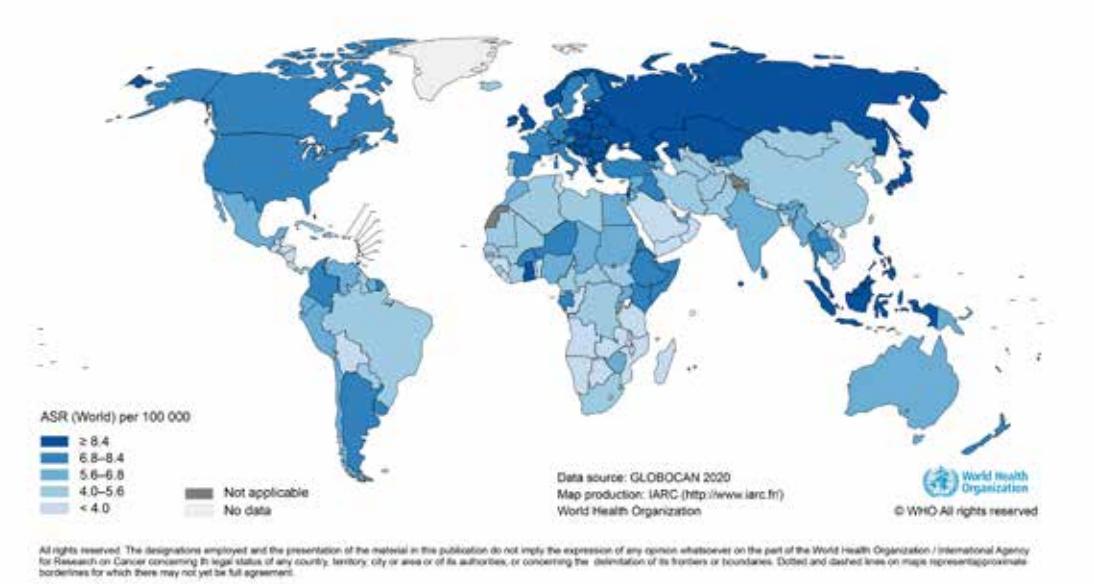
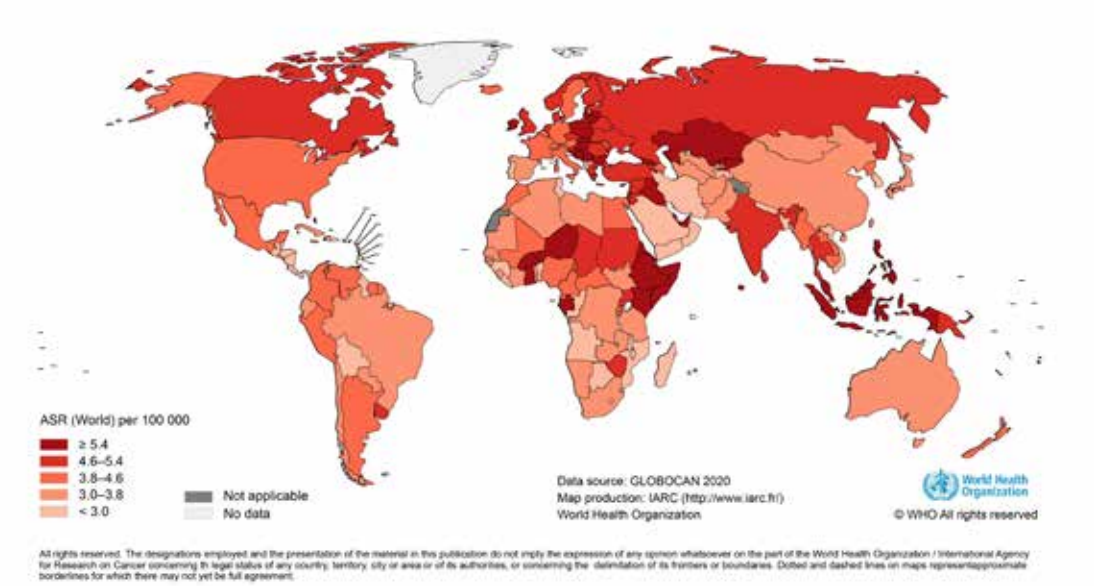


FIG 11- ESTIMATED ASR MORTALITY RATES (WORLD) IN 2020, OVARY, ALL AGES



Figures 10 and 11 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, ASR (age standardised rates), and under cancer sites, select ovary. You can also select mortality and prevalence rates.

RISK FACTORS FOR OVARIAN CANCER

VARIATION BY TYPES OF TUMOURS

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[50]. These tumours are more treatable and occur in younger women.

VARIATION BY RACE

Variations have been described between different races in other studies[51]. Morris et al[52] 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 socio-economic status, and treatment by low volume providers are significant and independent predictors of receiving no surgery, no debulking surgery, no chemotherapy, and non-standard treatment sequences[53]. It is clear that optimum cancer diagnosis and care are not equitably accessible to all.

This theme is also explored in a more recent paper by Momenimovahed et al that looked at the epidemiology and risk factors for ovarian cancer around the world. The authors conclude that whilst 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), this is due to differences in access to diagnostic and therapeutic services, but mortality has a different pattern, with the highest mortality rate being seen in African populations[54].

According to the NIH, between 1975 and 2016, the 5-year relative survival rates for ovarian cancer saw an increase from 33% to 48% among non-Hispanic White women, compared to a decrease from 44% to 41% in African American women[55]. In a 2022 study, Bruce et al highlighted how such pre-existing disparities were exacerbated due to the COVID-19 pandemic.[56] In another study by Schmidt et al, Black and Hispanic patients diagnosed with cancer were more likely to be susceptible to COVID-19, and that they faced higher chances of experiencing care delays compared to non-Hispanic White patients[57].

The opportunities offered by developments in genomics have been identified as a way to drive improvements for people with cancer in different population groups. One study in particular for women with cancer in India 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[58].

It is important to acknowledge that up until recently, the inclusion of diverse populations in ovarian cancer research has been limited. As a result, there have been a paucity of studies and data on the ovarian cancer risk factors and experiences in diverse populations. Even with

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the limited range of research involving these diverse populations, the focus has often involved taking a cells approach to identify genetic markers and establish treatment pathways. However, change is afoot. The US National Institutes of Health (NIH) announced recently that it aims to carry out a range of studies that adopt a "cells-to-society" approach that focuses not only on the biological underpinnings of ovarian cancer, but also on the socio-economic, behavioural, and clinical factors that might lead to the racial disparities of disease[59]. They believe that such efforts are crucial in obtaining a more comprehensive view of the inequities experienced by African American and Hispanic women diagnosed with ovarian cancer.

REPRODUCTIVE/HORMONAL AND LIFESTYLE FACTORS

A paper by Malvezzi et al[60] in 2016 examines the trends in mortality rates. Their findings showed persisting and substantial difference in ovarian cancer patterns and trends:

- In the 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 falls in these countries may be due to the fact that they had the highest ovarian cancer rates in the past.

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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 these areas over the last decades, and multiple parity (childbirths) 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. However, 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[61]. 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 factors:

- Women who have ever 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
- Every 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 a child have a 30% reduction in risk compared to women with no children

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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)[62].

Hanley et al, in a retrospective population based cohort study in Canada (2022) found that women who had undergone opportunistic salpingectomy (removal of the fallopian tubes whilst having other surgery) had significantly fewer serous ovarian cancers than expected, suggesting that opportunistic salpingectomy is associated with reduced ovarian cancer risk.[63]

Some studies have also explored the impact of common drugs, taken for other conditions, on ovarian cancer risk. A very recent pooled analysis of 8 case control studies shows frequent use of aspirin conferred a 13% reduction in risk of non-mucinous ovarian cancers, and suggested that for women at high-risk of the disease, there should be further research to explore its use as a preventative strategy[64]. There has also been 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[65].

Global dietary patterns continue to be dominated by an increasing number of relatively cheap, ready-to-eat ultra-processed foods (UPFs). In 2023, Chang et al examined the associations between the consumption of UPFs and risk of cancer and associated mortality for several site-specific cancers[66]. This study involved a large cohort of British adults, more than 50% of whom were women. The authors found statistically significant associations between consumption of UPFs and incidence of ovarian cancer specifically. Furthermore, they say that an incremental increase in the consumption of UPFs was also associated with an increased risk of mortality for cancer overall, and specifically for ovarian and breast cancers. While this study adds to the growing base of evidence that consumption of UPFs is likely to be associated with an increased risk of cancer, further research is needed to confirm these findings and understand the underlying mechanisms.

RISK FACTORS FOR OVARIAN CANCER

SUMMARY

In summary, Figure 12 details the complex factors have been shown to be, or potentially, linked to a woman's risk of developing ovarian cancer and the chance of her dying from the disease.

FIG 12 - 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	Location within a country, and economic development of a country can both impact on risk
Race / Ethnicity	Risk varies according to race/ ethnicity	Affects age profile, and types of tumours. Duration of breast feeding, and opportunistic removal of fallopian tube have been shown to reduce risk
Family History	Increases risk, including known BRCA mutations and Lynch syndrome	
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/societal 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	

New treatments are much less commonly available in low- and middle-income countries and women in these countries appear to self-fund for more than half of the available drugs (old or new), versus the state paying in 75% of high-income countries.

VARIATION IN GUIDELINES FOR OVARIAN CANCER DIAGNOSIS AND TREATMENT

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

VARIATIONS IN DIAGNOSIS GUIDELINES

Funston et al's research in 2019 highlights 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[67]. All of the guidelines 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/transvaginal ultrasound and serum marker CA125 were most mentioned, there were variations in guidance as to when and how these tests should be conducted.

Pathology is an important aspect of diagnosis, identifying the type of epithelial ovarian cancer and guiding subsequent care management in women with the disease. The 2021 assessment of guidelines for ovarian cancer diagnosis and treatment by the ASCO Expert Panel highlighted that whilst pathology is critical in determining the next course of action for disease management, there is variability in the financing and availability of pathological services around the world. In certain resource-limited settings, clinicians may have to resort to other avenues apart from pathology to make a diagnosis[59]. As such, differences in resource availability can be a significant contributing factor in causing international variations in diagnosis.

VARIATIONS IN TREATMENTS

The type and quality of treatments that patients receive are influenced by factors such as the availability of resources needed for surgery, sufficient intensive care beds, funding and affordability of anti-cancer drugs, and the development and use of national-level research and analysis to bring about change and improve health outcomes[68].

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[69]. In particular, the authors say that centralising care to higher volume centres and surgeons, and the growth of gynaecological oncology

VARIATION IN GUIDELINES FOR OVARIAN CANCER DIAGNOSIS AND TREATMENT

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 2020 study by Norell et al that examines several high-income countries suggests that international variations in ovarian cancer treatment are in fact quite prevalent. Despite guidelines being consistent across the countries, reported surgical practices differed internationally. It was found that whilst guidelines recommend either primary or interval debulking for advanced-stage patients, clinicians from countries with greater survival (e.g., Norway and Australia) reported higher rates of primary debulking. In addition, even though guidelines do not explicitly suggest extensive or ultra-radical surgeries, countries who performed better were more likely to agree with "ultra-radical" surgeries than lower-performing countries. Ultra-radical or extensive surgery is an extension of standard (radical) surgical procedures. Its aim is to remove all visible disease, with the intention of improving survival compared with standard (radical) surgery[70]. Depending on the country, perceived barriers such as lack of supportive care and medical co-morbidities seem to contribute to variations in approaches to achieving optimal cytoreduction[71]. They reinforce the need for further research to examine whether there is a relationship between international guidelines and health outcomes, particularly survival. Crude comparisons did not point towards a statistically significant association.

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 Cancer Network (90%), but that implementation is hindered because local facilities are inadequate, guidelines are not applicable to the local setting, and the information in them is too complex[72].

As shown, different regions around the world have variable access to diagnosistic tools and treatments of ovarian cancer. In the presence of such disparities, the ASCO Resource-Stratified Guidelines Advisory Group collaborates with clinicians working in low- and middle-income countries to consider the wide variability of resource levels in hospitals and adopt a stratified approach to developing guidelines for ovarian cancer diagnosis and treatment. By doing so in resource-constrained settings, they are attempting to ensure that no matter where a woman lives, she receives the best possible care either locally, or can be referred to higher-resource settings[73].

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 receive multidisciplinary team care[74].

However, progress towards centralisation and specialisation of care was slow. A study published in 2015 showed that by 2009 many women were still not receiving specialist surgery, and that the majority were not being operated on by General Medical Council accredited gynaecologic oncologists, and moreover there was considerable regional variation[75]. Anecdotal evidence in the UK

VARIATION IN GUIDELINES FOR OVARIAN CANCER DIAGNOSIS AND TREATMENT

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, whilst high-volume care was associated with increased likelihood of cytoreduction, shorter length of stay, and lower hospital-related costs of care[76].

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[77].

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)[78].

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[79], 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[80].

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[81], 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". Pramesh et al argue that the limited availability of quality context-specific evidence, and ability to establish "treatment decisions,

VARIATION IN GUIDELINES FOR OVARIAN CANCER DIAGNOSIS AND TREATMENT

clinical guidelines, and resource allocation" is a consequence of the paucity of clinical trials in low- and middle-income countries with the highest global burden of cancer [82].

AVAILABILITY OF TREATMENTS

The mainstays of global ovarian cancer drug treatment continue to be platinum and taxane treatments, such as Carboplatin and Paclitaxel, which have been around for decades. These are included on the World Health Organization's Essential Medicines List (21st edition, 2019), along with Bleomycin, Cisplatin, and Gemcitabine[83]. Alexandru Eniu et al examined which drugs were available and issues that may impact availability within the Asia Pacific region (Fig 13). In particular, they showed the challenges relating to low- and middle-income countries[84].

Eniu at al also say 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.

FIG 13 - AVAILABILITY OF WHO ESSENTIAL MEDICINES FOR OVARIAN CANCER IN ASIA AND ASIA PACIFIC as studied by Eniu et al.

	WHO ESSENTIAL MEDICINES LIST FOR:	ISSUES IN RELATION TO PATIENT ACCESSIBILITY IN ASIA & 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-income countries – China, Kazakhstan, Malaysia, Thailand, and at up to 25% cost in Iran Patients pay full cost in lower middle-income countries (Bangladesh, India , 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	
Cisplatin	Ovarian germ cell tumour	As above, however it is free in Myanmar
Gemcitabine	Epithelial ovarian cancer	Information not available
Paclitaxel	Epithelial ovarian cancer & germ cell tumours	As for Bleomycin & Carboplatin except data missing for China

VARIATION IN GUIDELINES FOR OVARIAN CANCER DIAGNOSIS AND TREATMENT

The UN 2030 Sustainable Development Goal 3.8 on Universal Health Coverage[85] requires that everyone, everywhere can access needed healthcare without experiencing financial toxicity and ruin. 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 universal health coverage 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 "availability" of cancer medicines including:

- Shortening the time for approval and registration of cancer medicines in low- and middle-income countries
- Improving the 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 the "affordability" by price negotiation (government), including value-based pricing, availability of quality assured generics, patient assistance programmes from pharmaceutical companies or non-profits, and compulsory licensing

The World Ovarian Cancer Coalition undertook its own research in 2021, examining availability of 15 new and older drugs used in ovarian cancer treatment, across 13 countries and all income groups. This included desk research, and consultation with a leading clinician in each country, and industry representatives. The research highlighted that there was wide variation in approvals, as well as access to approved treatments between and within countries. The new treatments were much less commonly available in low- and middle-income countries. Women in these countries appear to self-fund for more than half of the available drugs (old or new), versus the state paying in 75% of high-income countries - further exacerbating the devastating financial impact on women and their families.

In addition to the key points Eniu makes, there are other factors that can also impact on availability of ovarian cancer medicines in low- and middle-income countries, as discussed at a World Ovarian Cancer Coalition RoundTable event with leading global advocates and experts (April 2022) and included in the Coalition's report: The Journey Towards More Equitable Ovarian Cancer Care. Inequities between high- and low-resource settings mean the treatment pathway for ovarian cancer in low-resource settings is often patchy and needs to make the most of the limited number of resources available. Barriers to progress include:

- The current inability to articulate the value of cancer care, particularly the value of older, cheaper chemotherapies from the EML list. A needs analysis is needed to build the case for economic and social investment in the basic ovarian cancer drugs
- The narrative of 'more drugs faster' is not appropriate, rather, securing core diagnostics and treatments (surgery and drugs) that can be implemented and sustained
- A discord between available guidelines and local resource, limiting the ability to implement successfully

One- and five-year survival rates for ovarian cancer are very much determined by the stage at which it is diagnosed.

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 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[86].

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 were unable to receive any form of treatment, primarily because they were too unwell[87].

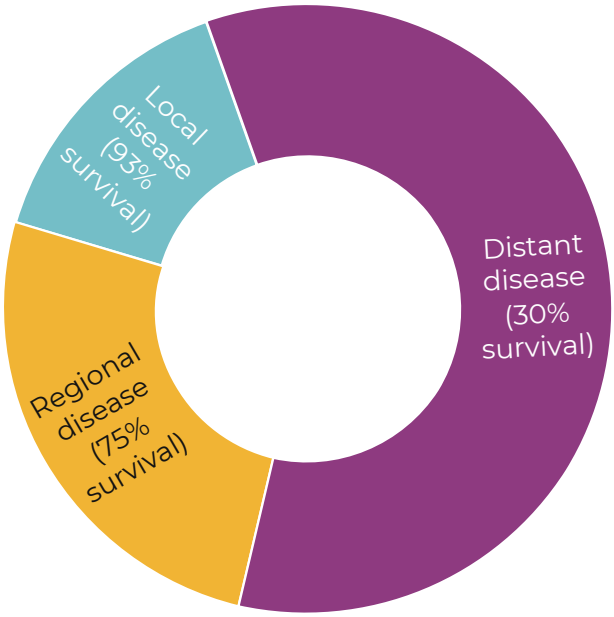
A study in the US concluded for a sample of over 9,000 women with either stage III or IV disease that 43% died within the first year, 26% of the cohort within the first 90 days. Older age, increased co-morbidity, stage IV disease, lack of a visit to a gynaecologic oncologist, and lack of surgery were all associated with an increase in 90-day mortality[88]. 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[89]. More recently another paper from the study shows that lower income status and singlehood are associated with a higher

SURVIVAL RATES FOR OVARIAN CANCER

risk of early death[90]. Whilst the study was not able to look at patient or primary care delay, it did show that several admissions to hospital for symptoms relating to ovarian cancer in the six months prior to diagnosis were also linked to higher short-term mortality, and that early death was probably due to physical deterioration in the ineffective waiting time. It concluded that there were opportunities, within the hospital setting, by considering parallel investigation programmes, to ensure more rapid diagnosis.

This supports the view that there is a very significant proportion of women with ovarian cancer for whom their diagnosis comes too late, where their status is such they cannot receive treatment, or that emergency presentation means an increased risk of non-assessment by a multi-disciplinary team and surgery by a non-specialist where surgery is required as a matter of urgency.

FIG 14 - SPREAD OF OVARIAN CANCER ON DIAGNOSIS WITH ASSOCIATED SURVIVAL (AMERICAN CANCER SOCIETY 2020)



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 numbers in Figure 14 show the following proportions together with their associated five-year survival rates. They cite the overall five-year survival rate as 49%.

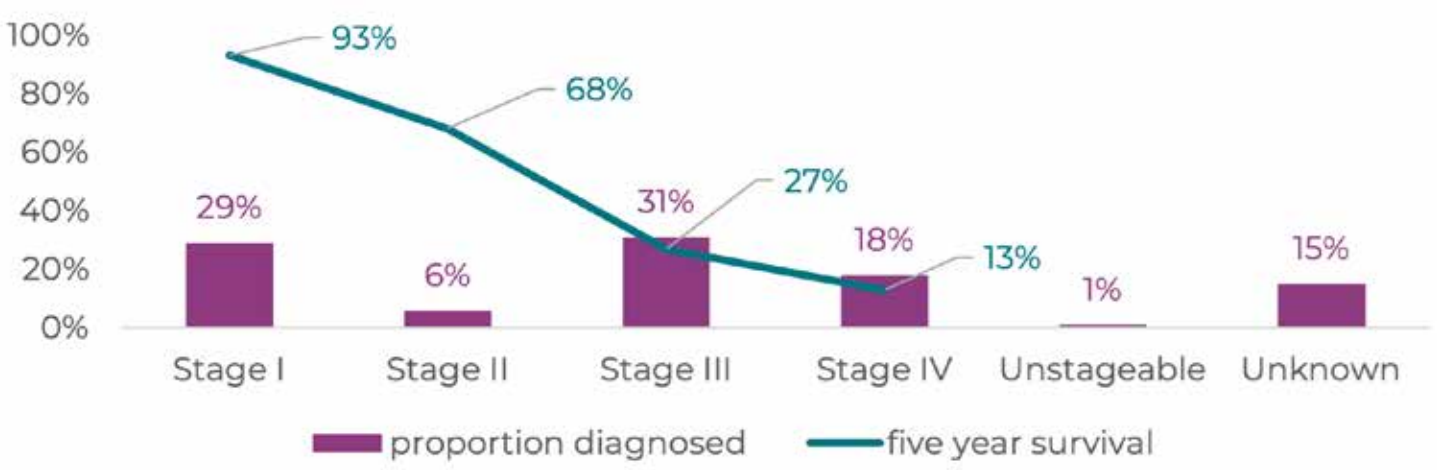
Data from England is shown in Figure 15 on the next page, and shows survival by FIGO stage for women diagnosed between 2013 and 2017, followed up to 2018[91].

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 Gynaecology 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[92].

Given that ovarian cancer diagnosis at an earlier stage is associated with improved survival[93], it is important to quantify and analyse the impact of the COVID-19 pandemic on later-stage diagnoses. In a 2022 paper, Bruce et al highlight that since access to cancer care was limited due to the pandemic, women with ovarian cancer experienced significant delays in receiving a diagnosis. Urgent referrals were believed to have been reduced in number as ovarian cancer symptoms are often non-specific and cancer screening was limited during the pandemic.

SURVIVAL RATES FOR OVARIAN CANCER

FIG 15 - 5 YEAR SURVIVAL BY FIGO STAGE – WOMEN IN ENGLAND DIAGNOSED 2013-2017



They also show that asymptomatic surveillance visits were also reduced and delayed, increasing the chances of a later-stage diagnosis[94].

A 2020 Lancet article highlights that ovarian cancer care, as in other cancer care, should be viewed as a continuum. A delay in one part of the patient pathway will impact subsequent avenues as well. If diagnosis is late, treatment is also likely to get delayed[95.] They were able to quantify that because of the COVID-19 lockdown in UK, referrals through the 2-week-wait urgent pathway reduced by up to 84%. In addition, based on the modelling that they ran using UK data, they suggested there is a clinically significant impact on lives and life-years lost if the delays to the 2-week-wait pathway are extensive and prolonged.

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[96]. 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 as well. An assessment of the economic burden of epithelial ovarian cancer (EOC) in Spain, as part of the OvarCost study, resulted in estimates that indicate that the global average cost per patient per year in Spain varied significantly depending on the stage of ovarian cancer. Whilst the average cost per patient with stage I EOC was €8,641, the average cost per patient with stage IV EOC was €42,547, highlighting that the need for more healthcare resources and home care during late-stage disease translates into higher economic costs[97].

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

SURVIVAL RATES FOR OVARIAN CANCER

per annum could potentially be saved, and 1,400 patients would benefit[98]. To put this figure into context, the National Cancer Research Institute partners (UK) spent a total of £8.5m on ovarian cancer research in 2015-16[99]. 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[100]. 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. Even when this is taken into account, variations occur between countries.

Their work showed that type I 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 II 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 II 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 in Figure 16[101].

They go on to break it down by stage and race. 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[102]

FIG 16 - 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%

SURVIVAL RATES FOR OVARIAN CANCER

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 methodology and 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[103]. 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[104].

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 2010-14, 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 40–49% in 24 countries: 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 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 remained 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.

SURVIVAL RATES FOR OVARIAN CANCER

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 to improve cancer survival.

Sweden did not take part 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 survived the first year were the second highest. Norway and Canada had the best results overall for this period (Fig. 17).

For ovarian cancer, different stages of diagnosis accounted for some, but not all, the variability[105]. 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.

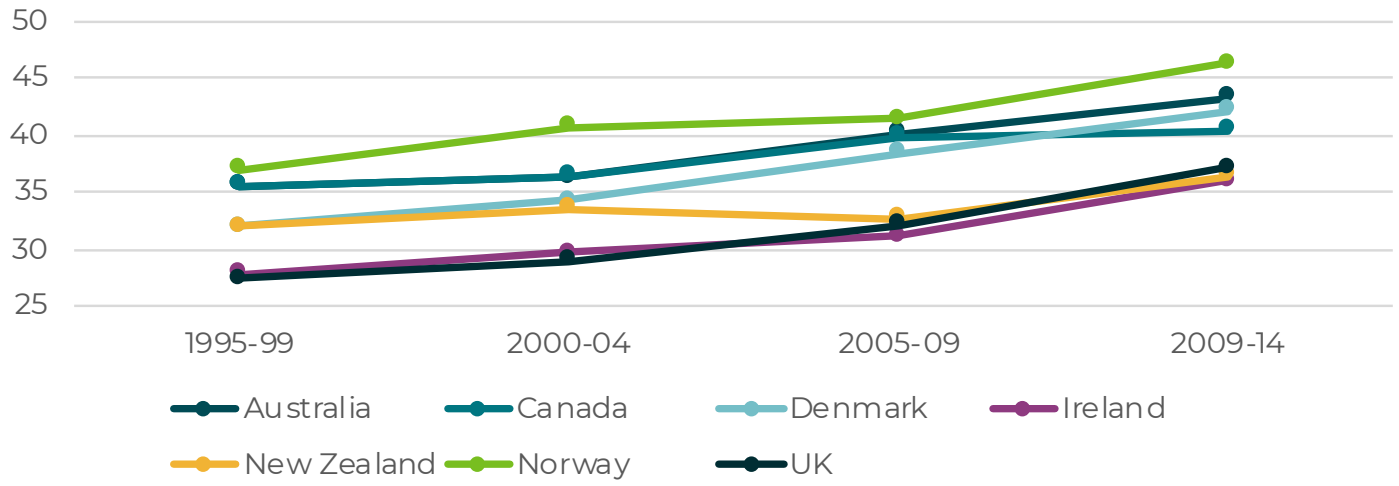
More recent data (Fig. 18 on page 42) from the study shows some progress over the last 25 years in five-year age-standardised survival, with Denmark, UK and Norway improving the most, and Canada and New Zealand, the least. The improvements were even greater when women over the age of 75 were excluded from the data[106].

FIG 17 - OVARIAN CANCER SURVIVAL RATES (%) IN HIGH-INCOME COUNTRIES (DIAGNOSED 2005-2007)

SURVIVAL	AUSTRALIA	CANADA	DENMARK	NORWAY	UK
1-YR survival	73.5	75.6	70.6	75.2	65.0
5-YR	37.5	41.9	36.1	39.7	36.4
5-YR survival if survived 1st year	48.7	54.4	48.8	50.9	53.8

SURVIVAL RATES FOR OVARIAN CANCER

FIG 18 - AGE-STANDARDISED 5-YEAR NET SURVIVAL BY COUNTRY AND PERIOD OF DIAGNOSIS (ICBP – SURVMARK2)



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[107].

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[108].
The ICBP Study has also shown a correlation between primary care physicians' willingness to act and cancer survival in that jurisdiction.

Whilst 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[109].

Though, the ICBP study is on-going, 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 north west and south west London. The NHS hopes to continue to roll out these types of centres so approximately 9 million additional tests and checks per year can be performed by 2025[110].

SURVIVAL RATES FOR OVARIAN CANCER

Using the current data for one-, five-, and five-year conditional survival for the countries in the ICBP study[111], together with the estimated incidence rates from GLOBOCAN 2020, the World Ovarian Cancer Coalition has estimated the increased numbers of women who could survive one and five years, by applying the best one- and five-year survival rates (green) to each country. The lowest figures are in blue (Fig. 19).

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[112].

SURVIVAL IN LOWER INCOME COUNTRIES

As yet there is little data detailing survival differences for ovarian cancer in lower income countries, but there is research underway by the SurvCan team (see following page). 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.

FIG 19 - ESTIMATES OF INCREASED NUMBERS OF WOMEN SURVIVING 1 & 5 YEARS

COUNTRY	INCIDENCE *GLOBOCAN 2020 estimate*	5-YEAR SURVIVAL % *ICBP*	1-YEAR SURVIVAL % *ICBP*	5-YEAR CONDITIONAL SURVIVAL ON 1-YEAR % *ICBP*	# EXTRA WOMEN SURVIVE 1-YEAR IF HAD BEST 1-YEAR SURVIVAL	# EXTRA WOMEN SURVIVE 5-YEAR IF HAD BEST 5-YEAR SURVIVAL
New Zealand	320	36.3	71.5	50.7	20	27
United Kingdom	6056	37.1	70.3	52.8	531	577
Canada	2802	41	72.8	55.6	157	138
Denmark	456	42	77.4	54.5	5	17
Australia	1397	43.7	78.6	55.7	0	36
Norway	433	46.1	77.5	59.6	4	0

SURVIVAL RATES FOR OVARIAN CANCER

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[113]. Despite the fact that 65% of deaths from cancer occur in low-resource countries, only 5% of resources for cancer control are directed to these settings. Together, these point towards a future where such lower income countries will be increasingly challenged coping with the cancer burden. Indeed, current GLOBOCAN estimates reveal the following increases by 2040[114] (numbers shown in Fig. 20 are based solely on population increases)..

FIG 20 - OVARIAN CANCER BURDEN INCREASE BY HDI (GLOBOCAN 2020)

HDI	2020	2040	INCREASE
Very high	116,505	138,403	19.0%
High	116,347	154,367	32.5%
Medium	65,594	105,046	60.1%
Low	15,379	30,143	96.0%

SURVCAN

Sankaranarayan et al evaluated 300,000 cancer deaths in Africa, Asia, and Central America between 1990 and 2001 in Lancet Oncology[115]. The project called SurvCan 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[116], highlighted particular issues[117]:

- 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 fewer than one pathologist for every million people

- Access to healthcare - cancer is often seen as a disease caused by spiritual curses, and as such cancer cases are often referred to healers or shamans for traditional or spiritual treatment. Health care providers in rural areas lack training on cancer, often misdiagnosing cancer as other illnesses. 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 resources 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 to more attractive settings with better salaries, working conditions, career paths and support

In a more recent paper by Verna Vanderpuye et 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[118].

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[119].

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[120].

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[121] he pointed out that whilst the economic burden of each cancer case 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 that cancer outcome correlated significantly with economic indicators and the amount of health expenditure per capita (HEpc) escalated exponentially[122]. The median actual total HEpc ranged from US$44 to US$4643. The authors propose a new standardised 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.

SURVIVAL RATES FOR OVARIAN CANCER

SUMMARY

In summary, the reasons for variations in survival rates between countries are complex, and still to some extent, 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 Fig. 21 below indicates.

FIG 21- 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 excessively
Ability to retrain 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 on

SURVIVAL RATES FOR OVARIAN CANCER

FIG 21- POTENTIAL FACTORS FOR VARIATION IN SURVIVAL RATES (CONT'D)

KNOWN OR POTENTIAL FACTORS FOR VARIATION IN SURVIVAL RATES	OUTLINE	NOTES
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

Very little academic research has focused on women's experience of being diagnosed and living with ovarian cancer.

DATA ON OVARIAN CANCER PATIENT EXPERIENCE

Whilst 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[123]. They call for screening of women for psychological distress. A systematic review of studies focusing on quality of life for women with ovarian cancer in 2016 concluded that there was a wide range of conditions because 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 also lacking[124].

More recent studies are attempting to shed even further light on the ways in which ovarian cancer diagnosis and treatments can impair health-related quality of life (HRQOL). HRQOL is a multidimensional construct that includes subjective understanding of the positive and negative impacts of the physical, emotional, and social symptoms experienced by cancer patients, as well as side effects of treatment[125]. In a 2021 study, Boban et al highlighted that over the past 20 years or so, patients have had the opportunity to provide more information and participate in clinical decisions for managing their cancer. The development of patient-reported outcome measures (PROMs) is one of the consequences of this increased patient-clinician communication. Currently, four validated ovarian cancer PROMs have been developed to measure HRQOL of patients. However, PROMs often focus on physical symptoms rather than help highlight the more complex psychosocial impacts of living with ovarian cancer. Therefore, Boban et al carried out a qualitative study as an initial attempt at defining the development of a more comprehensive PROM. The Australian study found that several factors including financial toxicity, poorer sexual well-being, and deteriorating emotional well-being because of infertility and lack of intimacy, negatively impacted HRQOL[126]. At the same time, they acknowledged that HRQOL does not cover all aspects of a cancer patient's experiences and that there is a need for higher quality data on ovarian cancer patient experience.

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, to provide information to drive local quality improvements, and inform the work of various charities and stakeholder groups supporting cancer patients[127].

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)[128] is the largest such study in ovarian cancer to date. Published in the International Journal of Gynaecologic Cancer, it has been heralded as a "new era 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 however, 95% of respondents came from high-income countries.

DATA ON OVARIAN CANCER PATIENT EXPERIENCE

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 received 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 fewer 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 formed the

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basis of the Global Ovarian Cancer Charter that was launched in September 2020. The Study also showed that women's mental wellbeing was as important as physical wellbeing in terms of quality of life, how information and support needs varied over time, and were often not met, and what women felt to be the areas requiring urgent progress.

A pan-European survey amongst women with gynaecological cancers by ESGO-ENGAGe explored some other aspects of care, revealing variations between European countries[129]. 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 about 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 the Every Woman Study: Canadian Edition (2020)[130], developed with support from the World Ovarian Cancer Coalition.

LOOKING TOWARDS THE FUTURE

Recognising that it is critical to address the needs of all women with ovarian cancer, no matter where they live, the World Ovarian Cancer Coalition has committed to undertaking two major pieces of work.

Working with its strategic advocacy partner, the International Gynecologic Cancer Society, the Coalition has developed a low- and middle-income edition of the Every Woman Study™, currently being undertaken in up to 24 countries, each with up to 10 hospitals taking part. With over 2,000 women expected to particpate, it is hoped that the Study will provide significant data at a global, regional, and national level to help advocate for change. This is important in the face of rapid increases of cases, so that opportunities to improve women's quality of life and survival are not missed.

It is clear that there are already wide gaps based on location between care and support offered to women with ovarian cancer, and between higher and lower income countries. These gaps will only widen going forward unless urgent action is taken.

As part of its mission to inspire, inform, and enable, the Coalition has also begun work on mapping out potential directions of travel for ovarian cancer care in the future. In the hope of making a solid case for impactful change, the Coalition will evidence the currrent and future costs to society of not taking action, quantifying the impact that positive changes could make and identifying priorities for a global plan of action. Combined with the patient experience evidence of the Every Woman Study™ (2018) and Every Woman Study™: Low- and Middle-Income Edition, a global report and action plan endorsed by the international community will contribute to laying out a comprehensive map for the future of ovarian cancer care.

CONCLUSION

The heightened risk of ovarian cancer in developed countries, and the increasingly disproportionate burden of ovarian cancer in developing countries provide compelling reasons to address globally low survival rates. Ovarian cancer is by far the most lethal female cancer.

Sankaranarayanan and Ferlay provide a useful summary in their chapter on gynaecological cancers in The Handbook of Disease Burdens and Quality of Life Measures [131]: 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 as 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 remain unobtainable.

If the gap between countries is not to widen, we must all be prepared to act to support women right across the world, to give them a better chance of surviving and living well with this disease, no matter where they live.

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 effectively
- Use a consistent framework for reporting the stage or spread of the disease
- Incorporate the types 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 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 improving access to lower income countries
- Consider how to develop centres of expertise for women with ovarian cancer, even in low resource settings

CONCLUSION

- 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 further 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 I

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+).

APPENDIX II

REGISTRATION AREA (CASES RECORDED 2000-2014)	SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2005-2009		SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2010-2014	
	ESTIMATE	95% PROBABILITY INTERVAL*	ESTIMATE	95% PROBABILITY INTERVAL*
Africa (1010 cases analysed)				
Algerian registries (423)	54.3	44.7-63.8 †	66.5	53.5-79.5
Mauritius (244)	79.7	69.6-89.8	-	-
Nigeria (225)	59.4 † ‡	24.9-93.9	49.1 † ‡	33.8-64.4
South Africa (Eastern Cape) (118)	81.0 † ‡	58.8-100	67.8 † ‡	47.4-88.2
America (Central and South) (16,023)				
Argentinian registries (1,688)	43.2	38.6-47.9	38.6	34.3-42.9
Brazilian registries (1,201)	34.1	29.4-38.9	34.9	29.5-40.3
Chilean registries (698)	29.0	23.3-34.7	28.05	21.3-34.7
Colombian regstries (1,759)	35.4	30.3-40.6	33.3 †	28.2-38.4
Costa Rica (1,408)	47.1	40.5-53.7	56.9	49.1-64.7
Cuba (4,560)	38.4	33.1-44.5	37.9	32.1-43.7
Ecuadorian registries (1,732)	38.8	33.4-44.5	37.9	32.1-43.7
Guadeloupe (110)	24.2 † ‡	8.9-39.5	29.5 † ‡	13.8-45.2
Martinique (191)	34.0	24.6-43.4	35.7 †	23.4-48
Puerto Rico (1,728)	37.2	33.4-41.1	37.3	32.0-42.6
Uruguay (948)	37.4	31.9-42.8	37.4 †	31.4-43.4
America (North) (312,954)				
Canada (31,395)	41.0	40.0-42.0	40.9	39.9-41.8
US registries (281,559)	42.0	41.7-42.4	43.4	43.1-43.8
Asia (109,998)				
Chinese registries (10,517)	40.6	38.8-42.5	41.8	39.8-43.7
Cyprus (553)	46.2 †	39.9-52.4	46.4 †	40.0-52.7

* These figures represent the interval in which the probability of the result is 95% i.e. there is a 95% chance of the actual rate lying within this range. The narrower the interval, the more likely the estimate is to be correct or nearly correct.
† data that is considered unreliable
‡ data that is not age standardised

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REGISTRATION AREA (CASES RECORDED 2000-2014)	SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2005-2009		SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2010-2014	
	ESTIMATE	95% PROBABILITY INTERVAL*	ESTIMATE	95% PROBABILITY INTERVAL*
Indian registries - 2 (172)	13.2	7.7-18.7	15.6	10.2-21.1
Israel (5,663)	43.5	41.4-45.9	45.0	42.3-47.7
Japanese registries (31,244)	43.9	42.8-45.1	46.3	44.9-47.7
Korea (28,076)	44.1	42.7-45.5	47.5	46.2-48.9
Kuwait (221)	35.4	25.2-45.6	35.1	25.6-44.7
Malaysia (Penang) (805)	36.4 †	27.3-45.6	46.8 †	34.5-59.0
Qatar (214)	62.6 † ‡	47.5-77.6	39.2 †	26.3-52.1
Singapore (3,514)	46.8	42.8-50.7	43.9	40.7-47.0
Taiwan (16,872)	47.5	45.5-49.5	48.8	46.9-50.8
Thai registries (5,469)	35.8	32.3-39.3	37.2	34.0-40.5
Turkish registries (6,678)	40.0	37.4-42.6	39.7	37.3-42.0
Europe (399,675)				
Austria (11,567)	41.2	39.6-42.7	41.0	39.4-42.7
Belgium (10,447)	42.8	41.3-44.3	43.1	41.6-44.6
Bulgaria (12,206)	33.9	32.2-35.5	37.3	35.4-39.1
Croatia (7,138)	33.4	31.3-35.5	36.0	33.9-38.2
Czech Republic (18,875)	35.2	34.0-36.5	36.5	35.2-37.8
Denmark (9,024)	37.4	35.7-39.2	39.7	37.8-41.6
Estonia (2,122)	37.2	33.8-40.7	42.3	37.4-47.1
Finland (8,101)	44.2	42.2-46.2	41.1	39.2-43.0
French registries (8,658)	42.1	40.4-43.7	43.5	40.0-46.9
German registries (38,064)	40.6	39.6-41.6	41.2	40.2-42.2
Iceland (276)	40.9	31.3-50.5	40.3	31.2-49.4
Ireland (4,952)	31.2	28.9-33.4	32.8	30.3-35.3
Italian registries (31,025)	39.3	38.5-40.1	39.4	38.3-40.5
Latvia (3,842)	39.8	38.5-40.1	45.5	38.3-40.5

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REGISTRATION AREA (CASES RECORDED 2000-2014)	SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2005-2009		SURVIVAL ESTIMATE FOR THOSE DIAGNOSED 2010-2014	
	ESTIMATE	95% PROBABILITY INTERVAL*	ESTIMATE	95% PROBABILITY INTERVAL*
Lithuania (5,452)	31.6	29.5-33.8	35.0	32.0-37.9
Malta (547)	27.5	22.0-33.0	28.0	21.4-34.6
Netherlands (19,252)	37.2	36.0-38.5	37.5	36.2-38.7
Norway (7,207)	42.8	40.7-45.0	45.5	43.3-47.7
Poland (53,462)	35.4	34.6-36.2	37.5	36.7-38.3
Portugal (6,532)	31.8	39.7-44.0	43.6	38.7-48.4
Romania (Cluj) (460)	28.9 †	22.3-35.6	37.2 †	29.7-44.6
Russian registries (10,628)	33.2	31.3-35.0	34.8	32.8-36.8
Slovakia (5,207)	34.5	31.7-37.3	33.4	28.6-38.2
Slovenia (2,750)	35.4	32.3-38.4	37.0	33.4-40.5
Spanish registries (7,710)	37.9	36.1-39.6	39.8	36.9-42.7
Sweden (12,132)	42.9	41.2-44.6	46.5	44.8-48.2
Swiss registries (4,964)	42.0	39.5-44.4	44.1	41.3-46.8
United Kingdom (97,061)	33.2	32.6-33.7	36.2	35.7-36.8
Oceania (25,841)				
Australian registries (21,124)	41.0	39.8-42.2	42.0	40.8-43.2
New Zealand (4,717)	33.4	31.0-35.9	36.7	34.1-39.3

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