One of These Is Not Like the Others:

A Guide to Understanding the Uniqueness of Mucinous Ovarian Cancer

Written for:

Mucinous Ovarian Cancer Coalition/MOCC

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INTRODUCTION

Ovarian cancer (OC) is an all-encompassing term, and sometimes not a very accurate one. Pathologists have known for many years that there are many different types of ovarian cancer, but the rest of us have only recently come to realize this fact.

While mucinous ovarian cancer (MOC) is a rare form, we're learning more about it every day. Because so much of the information out there is about OC and not MOC specifically, it might help to explore some of the different kinds of OC and where they originate in the body. Then we'll look at how MOC is different to other types of OC and pinpoint what that means for treatment.

WHAT ARE THE DIFFERENT OVARIAN CANCER TYPES AND WHERE DO THEY START?

If we divide up OC like a pie, we'd find that nine of the ten pieces of the pie are the "epithelial" type. This means that the cancer cells* started out as a kind of cobblestone-like cell, the sort of cell that lines the outside of the ovary or fallopian tube. It is distantly related to the cells that line our gut and uterus.

The most common – HGSOC

Of those nine pieces, seven are the most common type - high-grade serous ovarian cancer (HGSOC). This is the cancer that most people think of when they hear the term "ovarian cancer". It is the one we know most about, and the one that all the chemotherapies and other treatments were developed for, even if the scientists and doctors who invented them didn't know it at the time.

The current standard of care for OC works best on HGSOC, because that was the type of cancer that most of the women who participated in the early clinical trials had. HGSOC is also the cancer that can be caused by inheriting a faulty BRCA1 or BRCA2 gene.

While it sometimes feels like HGSOC gets all the attention, surprisingly, most if not all of the time it doesn't start in an ovarian cell. Recent studies show that HGSOC frequently begins as a fallopian tube cell.

Because the fallopian tube is so close to the ovary, cancerous cells can invade into the ovary quite early on and grow there very successfully – supported by the rich ovarian environment.

***Glossary #1:**

Cell: The building blocks of all living things; can't be seen without a microscope. Sort of like a fatty balloon filled with proteins, nutrients, DNA, RNA and everything else that's needed for life.

Endometriosis: Painful inflammatory condition where cells from the uterus migrate into the abdomen and settle on the ovary &/or other internal surfaces. Not itself malignant.

Mucin: A thick, gloopy liquid produced by cells, made of proteins and carbohydrates. The lubricant of the living world.

RARE FORMS OF OVARIAN CANCER

So, what about the remaining types of ovarian cancer?

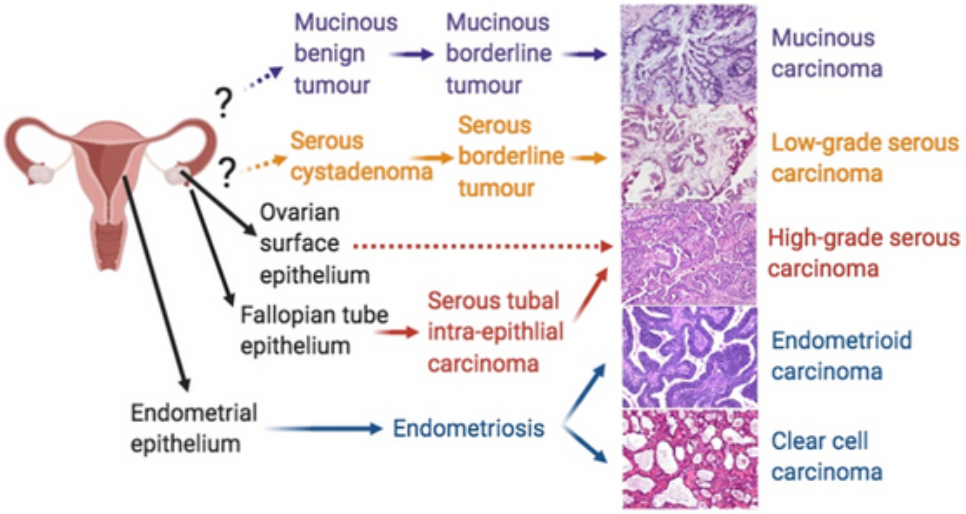
One of the parts in the previous graphic is made of two quite similar types, endometrioid and clear cell. These are, once again, not from ovarian cells, but start from the cells that make up endometriosis*. They are more closely related to cancers of the uterus, but like HGSOC they find that the ovarian environment suits them very well, and so the tumours get detected there most often.

Another piece is made up of several types of rare epithelial subtypes – carcinosarcomas, small cell etc, and bigger chunks of the other two remaining types: low-grade serous ovarian cancer (LGSOC) and mucinous ovarian cancer (MOC).

The origins of these last two are still somewhat mysterious. LGSOC is fairly likely to arise from the ovarian surface epithelium, that layer of cells around the ovary, although it's not 100% certain. We don't know where MOC starts. It could also be the ovarian surface epithelium, but we don't have enough information to say for sure.

The very last part is itself chopped into quite a few different pieces, each made from the different non-epithelial cells found inside the ovary, like the ones that support egg growth. These cancers are true ovarian cancers, and each is rather rare, for example granulosa cell tumours.

The epithelial ovarian cancers: *where they might start and any known intermediate stages. The images to the right are what a pathologist sees when looking down a microscope. They have been treated with a stain that makes the DNA dark purple and proteins pink.*



HOW IS MOC DIFFERENT FROM OTHER OVARIAN CANCER TYPES?

So, what are the main differences between MOC and the other types? I'll stick to comparing it to HGSOC for now, as most of the information about OC is about this most common form.

MOC has different causes
This is kind of a tricky section to write, because we actually don't know what causes MOC, although we do know it is different to HGSOC. Most studies have found that smoking increases the risk of having MOC, although not anywhere nearly as strongly as for lung cancer.

For HGSOC, we know that things like taking oral contraceptives or having children decreases the risk, but these reproductive and hormonal factors don't seem to be as important for MOC. The difficulty for the types of studies that look at cancer risk is that they work best with many thousands of patients, and it is hard to get the numbers for MOC.

MOC looks different
MOC first and foremost, produces mucin* (as you might guess from the name). The mucin is a kind of gloopy soup of proteins and carbohydrates, and is a bit like the stuff that is produced by your gut to help the digested food slide down.

We don't know why MOC makes mucin, perhaps once we know the cell type it starts in, we will better understand. In any case, when mucin-producing cells are seen in an ovarian tumour, that is the basis of the MOC diagnosis.

MOC grows differently
Although we don't know exactly where MOC starts, we do know that it has non-malignant ancestor tumours. There are benign and "borderline" mucinous tumours, and it is very common for MOC to have areas of the tumour that still look like these earlier forms.

Benign and borderline mucinous tumours are much more common than MOC, so not all of them have the potential to become cancer, and almost all can be completely removed without cancer later developing. This progressive development is quite different from HGSOC.

For the more common HGSOC, it often starts with small growths on the fallopian tube (these have been seen in cancer-free women who have had their tubes removed, for example in women who carry a BRCA1 mutation). The change to cancer happens while these growths are still very small, after which even small numbers of cells can spread quite quickly to the ovary or abdomen. This speedy spread is why it is so hard to detect HGSOC early.

MOC grows differently than HGSOC
The cells tend to stay stuck together and grow outwards (so-called "expansile" growth pattern) rather than go off exploring on their own ("infiltrative" growth pattern). This means that the tumours can grow very large on a single ovary without becoming metastatic.

Although having a big tumour is quite scary, it is better than having thousands of tiny tumour cells ranging about causing trouble. It's like having a pan on the stove that overflows slowly (expansile) rather than one that is spitting everywhere vigorously (infiltrative). Because of this large, expansile growth pattern, most MOC is detected at Stage I – confined to the ovary. Having Stage I disease is better than later stages because there is a good chance it can all be removed by surgery and the tumour won't come back.

MOC responds differently to treatment
For those MOC that do develop in an infiltrative way, or are detected with advanced disease, the problem then arises that the chemotherapy that was developed and works quite well on HGSOC doesn't work as well on most MOC.

This is thought to be because MOC doesn't grow as fast, and also has a more stable genome* and intact DNA repair pathways. The mucin might also make it more difficult for the chemotherapy to get to the cells, since mucinous bowel cancer is also more resistant to chemotherapy.

***Glossary #2:**

Genome: All of the genes in the DNA that give instructions on how to make a cell and body. The genome gets copied each time a cell divides to make another cell. Mistakes get made and these are usually repaired really well, but if the repair systems are faulty, as in HGSOC, cancer-causing mutations can occur. However, faulty DNA repair also means that DNA-damaging chemotherapy can work better (e.g., carboplatin).

Mutation: A change in the DNA, like a mistake in a recipe. Imagine your cake recipe said half a pound of cheese instead of cherries – it'd be a very different type of cake!

THE CONFUSION BETWEEN MOC AND METASTATIC TUMOURS FROM OTHER ORGANS

As you may have gathered by now, the ovary can be a cancer-friendly home. There's something about the environment there that supports cancer cell growth. Whether it's the hormones, the support from the surrounding cells or the relatively low levels of immune cells (compared to the gut, say), cancer cells from all over come there to grow.

Because the ovaries hang pretty loosely in the abdomen and are close to a number of potential sources of cancers (gut, pancreas, uterus etc.), many that were first detected at the ovary became known as "mucinous ovarian cancers". Often because they came from organs that produced mucin. In reality, they were metastatic tumours that started life in another organ.

A quick history of why things are better now

Twenty years ago, the slice of pie that was called MOC was much larger than it is now (more than a single piece (11-15%) rather than less than half a piece (3-5%)), because some of these metastases were not recognised for what they really were. With improved methods of diagnosis and imaging, doctors are much better at being able to identify the tumours that are metastases.

Most MOC diagnosed today is pretty confidently considered to be "primary ovarian" (i.e., first growing in the ovary). But we still don't know if it really does start there in the ovarian surface epithelium, or if it comes from the fallopian tube like HGSOC, the uterus like clear cell and endometrioid, or even further afield, like the inside part of the cervix.

We will get the answers one day, and that will help us to understand why MOC is so different to the other types.

WHAT ARE THE GENETIC DIFFERENCES BETWEEN MOC AND HGSOC?

Inherited changes
As mentioned, HGSOC can be caused by faulty copies of genes inherited from a parent (like BRCA1), but this is very rare in MOC. Although there are a few gene variants that slightly increase the risk of getting MOC, their effect isn't strong enough for MOC to occur in families.

Non-inherited changes
All cancers are caused by genetic changes. In MOC almost all of these events are not inherited from a parent but occur by chance as cells divide and grow. Some of the most common events that drive MOC are mutations* in genes called p53, KRAS and CDKN2A. Mutations in p53 are found in almost all HGSOC as well, but the similarity ends there.

HGSOC only rarely has KRAS or CDKN2A mutations but has lots and lots of large-scale increases and decreases in the number of gene copies. Big chunks of the genome with hundreds of genes can go from 2 copies (normal) to 1 or even no copies. Other regions can go from 2 copies to 5, 6, 10 or even dozens of copies.

Losses of genes means the proteins those genes code for are less abundant and might not be able to do their jobs well enough (imagine a cake with half the baking powder, or none at all). Too many of a gene can also be bad (a cake with 20 eggs instead of 2, for example).

In HGSOC as much as half (50%) of the genome can be messed up like this, but in most MOC it is less than 10%. The exception is that up to a quarter of MOC can have many copies of the HER2 (or ERBB2) gene, but this is rare in HGSOC.

WHAT DO THESE GENETIC DIFFERENCES MEAN FOR TREATMENT?

It is likely that the mostly stable genome of MOC means that it won't respond well to carboplatin or cisplatin (HGSOC standard chemotherapies), and also won't respond to new medicines like Olaparib (PARP inhibitors). However, the presence of mutations like KRAS and gene amplifications like HER2/ERBB2 mean that new targeted therapies could be a great option.

Targeted therapies aim to specifically affect the abnormal proteins produced by cancer mutations, with fewer side-effects than chemotherapy. Most MOC will have at least one if not more of these potentially targetable gene events, although we don't yet have evidence to say whether the therapies will definitely work.

This is an area that many scientists like me are working on right now. We hope that we can find therapies that will work for MOC. Follow MOCC on Facebook or join the MOCC mailing list to stay updated on our progress.

MUCINOUS OVARIAN CANCER COALITION

MOCC is a 501(c)(3) organization based in the United States.

You can find us online at Hope4MOC.org

The Mucinous Ovarian Cancer Coalition (MOCC) sends our sincerest thanks to Kylie Gorringe for donating her time and expertise to create this guide. We are confident that it will help women and their families better understand this rare disease.