Causes of lymphoma

There is no known cause in most cases of lymphoma. This page describes some of the possible factors that could contribute to the development of lymphoma.

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What causes lymphoma to develop?

Lymphoma can develop when lymphocytes (white blood cells that fight infection) grow out of control. This is caused by genetic changes in the cells
that mean they no longer ‘listen’ to signals that control their growth and death. Researchers are finding out more about the genetic changes in lymphoma, and this is leading to new treatments. In most cases it is not known what actually causes these changes. Most genetic changes probably happen by chance. Several genetic changes are usually needed before lymphoma develops. This is known as the ‘multi-hit theory’.

There are some risk factors that make you more likely to develop lymphoma. There are many different types of lymphoma and risk factors can differ for each type. Most people who develop lymphoma have none of these risk factors and the cause is unknown.

The main risk factors for lymphoma are problems with your immune system. This is unlike many other forms of cancer, where lifestyle factors often play a larger role in their development.

What are ‘risk factors’?

Anything that increases your risk of a certain condition is called a ‘risk factor’. Having one or more risk factors for lymphoma does not mean you will develop it. It means you are more likely to develop lymphoma than someone with no risk factors. For an average person, the risk of developing lymphoma is small. Even with risk factors that increase your likelihood of developing lymphoma, this risk is usually still small.

The following sections describe risk factors for lymphoma:

- age and sex
- family history
- immune system problems
- infections
- previous cancers
- precursor conditions (non-cancerous conditions of lymphocytes)
- other possible causes of lymphoma.
Age and sex

Mutations (genetic changes) build up over your life making you more likely to develop a cancer. Most types of cancer, including lymphoma, become more common as you get older.

Many types of lymphoma are linked to a certain sex. Some types of lymphoma are more common in men. Other types of lymphoma are more common in women. Overall, more men get lymphoma than women. Cancers caused by viruses are often less common in women of childbearing age.

Family history

Lymphoma is not inherited – it is not passed from parent to child. However, your risk of developing lymphoma is slightly higher if you have a close relative (parent, brother or sister, or child) who has had lymphoma. This increased risk is usually not linked to a particular gene. Research suggests the increased risk may be caused by inheriting several polymorphisms (genetic differences between different people) that all contribute a small increase in risk. These polymorphisms are often in genes of the immune system. Lifestyle factors may also contribute to this increase in risk.

Immune system problems

Your immune system protects you against infections. It also helps your body get rid of cells that are not needed, such as those that are damaged or are not working properly. Conditions that cause problems with your immune system can make it more likely that lymphocytes grow out of control, resulting in lymphoma. Medical conditions that cause problems with your immune system include:

- conditions that are treated with immunosuppressive drugs
- immunodeficiency disorders
- autoimmune problems.
Immunosuppressive drugs

People who have an organ transplant or an allogeneic (donor) stem cell transplant take immunosuppressive drugs (drugs that dampen the immune system). Immunosuppressive drugs prevent your body reacting badly against (rejecting) the donor organ or cells.

Some people take immunosuppressive drugs for other reasons, for example for autoimmune conditions. Being on immunosuppressive drugs can increase your risk of developing lymphoma. The increased risk varies considerably depending on factors like what type of transplant you had and how much immunosuppression you need. Lymphomas that develop after a transplant are called post-transplant lymphoproliferative disorders (PTLDs).

Immunodeficiency disorders

Primary immunodeficiency disorders are problems that you are born with or that have a genetic cause (they are due to changes in your genes). There are lots of different types of primary immunodeficiency disorders, for example, ataxia telangiectasia and Wiskott-Aldrich syndrome.

The risk of developing lymphoma is higher than usual for most people with primary immunodeficiency, but it varies according to each disorder. They are generally rare disorders, so they account for very few cases of lymphoma.

Most primary immunodeficiency disorders are usually diagnosed when people are very young. Some types of primary immunodeficiency become more obvious as you get older and are usually diagnosed in adulthood, for example, common variable immunodeficiency (CVID).

PID UK have more information on primary immunodeficiency disorders, including information on cancer and primary immunodeficiency.

Secondary immunodeficiency disorders are immune system problems caused by something else, for example HIV or chemotherapy.

HIV and lymphoma

Human immunodeficiency virus (HIV) infection is associated with an increased risk of lymphoma.
People with HIV are less able to fight infections that are linked to certain types of cancer, and some lymphomas in people with HIV are caused by viruses. For example, in some people, the *Epstein-Barr virus* (EBV) is associated with the development of lymphoma. Lymphoma can also develop in people with HIV because the infection causes changes in the immune system so that it doesn’t work properly.

Several types of lymphoma are ‘AIDS-defining malignancies’. Acquired immunodeficiency syndrome (AIDS) is an advanced stage of HIV. If you have HIV and develop certain infections or cancers, you are diagnosed with AIDS. Since the introduction of anti-retroviral treatments (ART) for HIV, the risk of developing these AIDS-defining forms of lymphoma has reduced. However, there has been an increase in the risk of developing other types of lymphoma, including *EBV-associated Hodgkin lymphoma*. Researchers are trying to find out why this is.

**Autoimmune disorders**

Some people have conditions that cause their immune system to be overactive and attack parts of their own body. These are called autoimmune disorders.

Some autoimmune disorders can cause chronic inflammation. Inflammation happens when your body reacts to an injury and is trying to repair itself. This inflammation may contribute to the development of lymphoma.

In many cases, the risk of complications like lymphoma is thought to be higher in people with more severe forms of these conditions. This may be because these people have more inflammation than those with less severe forms. However, these people are also more likely to be receiving *immunosuppressive drugs*, which may also account for the increased risk of lymphoma.

Autoimmune disorders with links to lymphoma include:

- **Sjögren’s syndrome**, which increases the risk of developing *splenic marginal zone lymphoma* and *MALT lymphoma* of the salivary gland or lung
• Hashimoto’s thyroiditis, which increases the risk of MALT lymphoma of the thyroid

• coeliac disease, which can cause enteropathy-associated T-cell lymphoma (EATL)

• rheumatoid arthritis and systemic lupus erythematosus, which are both linked to splenic marginal zone lymphoma and diffuse large B-cell lymphoma (DLBCL).

People with other autoimmune disorders, such as Crohn’s disease, might also be at increased risk of lymphoma. This usually depends on the type of treatment and severity of the disorder.

It is important to stress that the vast majority of people with autoimmune disorders, including those listed above, do not develop lymphoma.

Infections

Lymphoma itself is not infectious. You cannot catch lymphoma and you cannot pass it on to someone else.

Some viruses can cause lymphoma in some people. The viruses can be found in the lymphoma cells. Other viruses and bacteria can contribute to the development of lymphoma if they cause chronic (long-term) reactions from your immune system.

It is important to note that many of these infections are very common and do not cause lymphoma in most people. Other factors are also involved in the development of lymphoma.

Infections that can cause lymphoma include:

• Epstein–Barr virus (EBV), the virus that causes glandular fever. Most people in the world are infected by EBV and the infection does not usually cause any symptoms. EBV is found in the lymphoma cells of:
  • the type of Burkitt lymphoma seen in children in Africa and sometimes in the sporadic type of Burkitt lymphoma (the type seen in the UK)
- some **Hodgkin lymphomas** – in the UK, around a third of Hodgkin lymphomas are linked to EBV
- **HIV-associated lymphoma**
- **post-transplant lymphoproliferative disorder** (PTLD)
- some **T-cell lymphomas**.

- HTLV-1 (human T-lymphotropic virus type 1) is found in people with **adult T-cell leukaemia/lymphoma**. This virus and this type of lymphoma are rare in the UK. They are more common in other parts of the world, like southern Japan, the Caribbean basin, Central and South America, parts of central Africa, Iran and Romania.
- HHV-8 (human herpesvirus 8) is linked with a rare form of lymphoma called primary effusion lymphoma and with an illness called ‘**multicentric Castleman’s disease**’ – both are uncommon but are sometimes seen in people with a weakened immune system.

Infections that can indirectly cause lymphoma by over-stimulating the immune system include:

- **Hepatitis C virus** (HCV), which is seen in some people with marginal zone lymphoma, for example **nodal marginal zone lymphoma** and **splenic marginal zone lymphoma**.
- **Helicobacter pylori**, bacteria that cause inflammation and ulcers in the stomach, which are often found in people with gastric **MALT lymphoma**.
- **Chlamydia psittaci**, an infection that can be caught from birds (including pet birds like parrots), which is linked with **MALT lymphoma** in the lacrimal (tear) gland and around the eye.
- **Campylobacter jejuni**, a common cause of **food poisoning**, is linked to **MALT lymphoma** in the bowel.
- **Borrelia burgdorferi**, which causes **Lyme disease**, is linked to **MALT lymphoma** in the skin.

Greater exposure during adulthood to infections that typically affect children (for example, in teachers) has also been proposed as a possible risk factor for lymphoma.
Previous cancers

Some people who have had cancer develop a second, different cancer at a later time. A second cancer is different to relapse, which is when the original cancer comes back.

Having risk factors for the first cancer might mean you are at greater risk of developing another cancer.

Second cancers can also be late effects of treatment, which means they only develop many months or years after treatment. This can happen because treatments like chemotherapy and radiotherapy damage cells, including lymphocytes. Treatment for cancer can therefore increase your risk of developing a second cancer in the future.

If you have had treatment for cancer, your medical team should give you information on what to look out for and how to reduce your risk of developing late effects.

Non-cancerous conditions of white blood cells

Some non-cancerous conditions cause abnormal or high numbers of white blood cells. Some of these conditions can later develop into a lymphoma. For example:

- Multicentric Castleman’s disease can develop into non-Hodgkin lymphoma or Hodgkin lymphoma.
- Monoclonal B-lymphocytosis can develop into chronic lymphocytic leukaemia (CLL).
Other possible causes of lymphoma

Many studies have looked for other possible causes of lymphoma. Sometimes one or two studies suggest a possible link, but then other studies find something different.

There are lots of different types of lymphoma and many are rare diseases. Studies often group lymphomas as Hodgkin or non-Hodgkin lymphoma, but each subtype of lymphoma has different causes. This makes it difficult to unpick the causes of each type and can explain some of the differences between findings of different studies.

The International Lymphoma Epidemiology Consortium (InterLymph) is an international group of scientists who research lymphoma risk factors. Key findings from their scientific meetings are available from the Lymphoma Coalition.

Many people worry about causes of cancer that are reported in the news. For example, processed meats and wireless or mobile phone signals. In most cases, there is little evidence that these factors can cause lymphoma.

The following risk factors have been studied and may have some links with the development of lymphoma. However, there is no strong evidence for any of these risk factors and any increase in risk is likely to be very small. It may be that any increased risks are due to these factors causing inflammation in your body. Chronic (long-term) inflammation can contribute to the development of lymphoma.

Chemicals

Industrial chemicals, pesticides and hair dyes are possible risk factors for developing lymphoma, but evidence is limited. As these chemicals are more commonly used in certain jobs, studies have also looked at the work that people do. Some studies have suggested links, but these are likely to apply only to certain types of lymphoma and certain chemicals. It is very difficult to determine exactly which factors are important in developing lymphoma as there are very few people with each type of lymphoma exposed to each type of chemical. It is likely, however, that any increased risks are small.

For instance, people who used hair dyes in the 1970s or earlier may be slightly more likely to develop lymphoma. It is likely that hair dyes used more recently are safer, but it takes many years to find out. Farmworkers or
those who live on farms may be slightly more likely to develop certain types of lymphoma, perhaps due to pesticides, other chemicals and viruses that might spread from animals. Breast implants have also been associated with a rare type of lymphoma – breast implant-associated anaplastic large cell lymphoma.

Scientists are continuing to study which chemicals may be linked to the development of lymphoma.

**Lifestyle**

Some lifestyle factors have been linked with an increased risk of developing lymphoma but evidence is limited. It is likely that any increased risks are small. However, many of the following factors are important in the development of various types of cancer.

Keeping a healthy lifestyle by maintaining a healthy weight, exercising regularly, eating a healthy diet and not smoking can reduce your risk of many health problems.

- Smokers have a slightly increased risk of some types of lymphoma.
- A diet with high levels of red meat, animal fat and dairy products could be linked to the development of some cancers, including lymphoma.
- Taking regular exercise reduces the risk of developing lots of types of cancer. There is some evidence that physical exercise can lower your risk of developing lymphoma too.
- Some cancers are more common in people who are obese. Evidence of a link with lymphoma has been found in some studies and not in others. There is not enough evidence to say if this only applies to people who are very overweight. It could be that the increased risk of lymphoma is due to poor diet and lack of exercise.

No strong links between lymphoma and other factors like alcohol, or tea or coffee consumption have been identified.

In most cases, the cause of lymphoma is not known. There is little or no evidence to suggest that anything you have done – or not done – has caused you to develop lymphoma. Talk to your doctor if you are worried about the possible cause of your lymphoma or about the risk for someone close to you.
References

These are some of the sources we used to prepare this information. The full list of sources is available on request. Please contact us by email at publications@lymphoma-action.org.uk or phone on 01296 619409 if you would like a copy.


Further reading

- Diagnosis and staging of lymphoma
- Glossary
- Symptoms of lymphoma
- The immune system
- The lymphatic system
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