Review Article

A Review on Cholesterol content in Breast Cancer

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ABSTRACT

Breast cancer is growing among the women all over the world now a day. High cholesterol and obesity are important risk factors for cancer development. Many studies have suggested that our day to day dietary sources are rich in cholesterol ultimately leading to breast cancer. Cholesterol accelerates and enhances tumour formation. In addition, tumours are more aggressive and tumour angiogenesis is enhanced. The present study examined the role of cholesterol in the regulation of tumour progression in a model of mammary tumour formation. An association between high cholesterol and breast cancer has been found in study of more than 1 million patients over 14 year time. There are many studies done till date which suggests that there is some association found between high cholesterol and diseases, especially breast cancer. It is still to be confirmed that all cholesterol sources can lead to life-threatening cancer.

Keywords: Cholesterol, Breast Cancer, tumour, statins, hyperlipidaemia, hormone-estrogen

INTRODUCTION

Cholesterol, it's an Ancient Greek word in which chole means bile and stereos means solid, is an organic molecule. Cholesterol is a waxy, fat-like substance found in all cells of our body which needs the cholesterol to make hormones, vitamins (D), and substances that help us digest foods. Cholesterol protects membrane integrity/cell-viability and thus be able to change shape and move about (unlike bacteria and plant cells which are restricted by their cell walls)[1].

Dietary Sources

Animal fats are complex mixtures of triglycerides, with lesser amounts of phospholipids and cholesterol. As a consequence, all foods containing animal fat contain cholesterol to varying extents. Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp. Human breast milk also contains significant quantities of cholesterol.

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems[2]. There are 100 different known cancer that affect humans, nearly20% of cancers are due to infection such as hepatitis B, C, human papillomavirus, cholesterol etc[3].

Some of the known cancers are brain cancer, throat cancer, breast cancer, lung cancer, skin cancer, vaginal cancer, vulvar cancer, stomach cancer, thymus cancer etc. A basic mechanism or the pathway for biosynthesis of cholesterol initiates through common enzymes like acetyl Coenzyme etc. Hydroxymethylglutaryl-coenzyme A is the precursor for cholesterol synthesis. HMG-CoAHMG-CoA Reductase catalyses production of mevalonate from HMG-CoA. The carboxyl group of hydroxymethyl glutarate that is in ester linkage to the thiol of coenzyme A is reduced first to an aldehyde and then to an alcohol. This can be better understood by looking into figure 1.

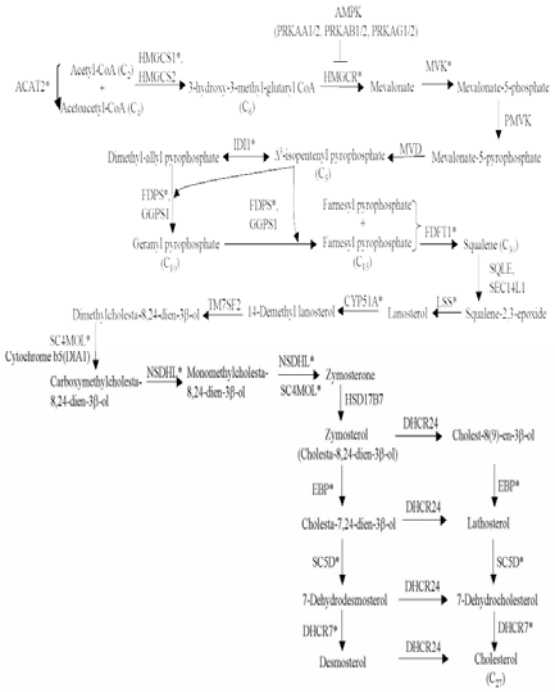

Figure 1: Biosynthesis of cholesterol[4]

Table 1: levels of cholesterol in human[5]

Level mg/dl	Level mmol/L	Interpretation
<200	<5.2	Desirable level corresponding to lower risk for heart disease
200-240	5.2-6.2	Borderline high risk
>240	>6.2	High Risk

Breast cancer refers to a malignant tumour that has developed from cells in the breast[6]. The Symptoms are

lump in the breast, change in breast shape, dimpling of the skin, and fluid coming from the nipple, red scaly patch on the skin, unexplained weight loss and abnormal bleeding. The risk factor includes obesity, early age at first menstruation, lack of physical exercise, having children late or not at all, drinking alcohol, hormones replacement therapy, Ionizing radiation. Other than that the cholesterol level should be maintained in human body because there is particular range of the cholesterol that has a greater risk to cause cancer as mentioned in table no. 1.

Detailed Analysis

Breast cancer is related to obesity caused by high cholesterol[7]. A new role of cholesterol in the activation of a cellular signalling pathway that has been linked to breast cancer was described[8]. CANONICAL WNT signalling is a pathway that promotes cell growth and divisions and is most active in embryonic cells during development. Over activity of this signalling leads to cancer. Researchers discovered a binding site for cholesterol on a protein called DISHEVELLED. It is like a switch on a track – when the signal reaches Dishevelled, the signal is directed along either canonical or non-canonical. They realized that cholesterol is able to bind specifically to Dishevelled, so interest came in the topic of cholesterol as a potential determinant of WNT signalling pathway getting activated. The researchers also noticed that localized increase in cholesterol within the cell membrane seemed to selecting promote canonical WNT signalling. Things like high fat diets which boost cholesterol have been linked to elevated incidence of cancer[9]. The concern that are driven by canonical WNT signalling includes colon cancer, lung cancer and most commonly breast cancer.

Hormones responsible for Breast Cancer

There is a molecule, not cholesterol but a metabolite of cholesterol called 27HC(hydroxycholesterol) that mimics the hormone estrogen and can independently drive the growth of breast cancer[10]. The hormone estrogen feeds to 75% of breast cancer there is an involvement of 27HC in breast tumour growth and as well as aggressiveness of the cancer to spread to other organs using mouse models. They noticed that cholesterol metabolite was inhibited when the animals were not supplemented with 27HC. 27HC can be made in other places in the body and transported to the tumours[11]. Gene expression studies revealed a potential association between 27HC exposure and the development of resistance to the antiestrogen tamoxifen. Their data also highlights how increased 27HC may reduce the effectiveness of aromatase inhibitors, which are among the most commonly used breast cancer therapeutics. When the human breast tissue tumour becomes more aggressive then it increases the affinity of the enzyme to make 27HCgrowth[12]. Cholesterol metabolite 27HC promotes tumour growth in estrogen-receptor positive breast cancer was previously believed to be stimulated primarily by the female sex hormones estrogen and its commonly treated using endocrine-based medications that starves tumour of estrogen. Estrogen receptor positive breast cancer is prevalent following menopause. The discovery that 27HC as another driver of breast cancer is important information which can be used to develop new therapies that inhibit 27HC action of production, in effect cutting the cancer off from the key growth stimulators. 1 Million New cases of breast cancer are diagnosed each year and about two-third of those are hormone receptor positive[13]. 27HC stimulates the growth of breast cancer cells by hijacking growth promoting mechanism triggered by estrogen receptor.

Enzymes involved in Breast Cancer

An enzyme called CYP7B1, metabolized 27HC. CYP7B1 is diminished in breast tumour compared with normal breast tissue[14]. There is more than 7-fold poorer overall survival in women whose tumours display low CYP7B1, compared with women with high tumour CYP7B1[15]. It was found that in those without a risk factor for cancer normal level of cholesterol in the blood are 1.6g/l whereas with the risk factor, cholesterol level dropped to 1.3g/l.

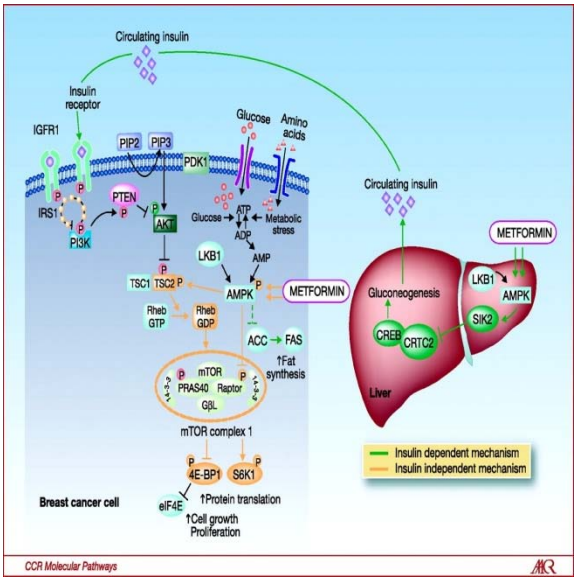

Figure 2: Mechanism of breast cancer[16a]

Computational Study on Breast Cancer

A woman's risk of developing breast or ovarian cancer is greatly increased if she inherits a deleterious (harmful) mutation in the BRCA1 gene or the BRCA2 gene. BRCA1 and BRCA2 are the human genes that produce tumour suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material. When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. BRCA1 and BRCA2 mutations account for about 20 to 25 per cent hereditary breast cancers and about 5 to 10 % of all breast cancers. There are basically two

types of mechanism that involves in formation of breast cancer cell one is insulin dependent mechanism and another is insulin independent mechanism that are briefly explained in figure no.2.

Role of Drugs in Treatment

NSAIDs may lower breast cancer recurrence rate in overweight caused by high cholesterol[17]. Recurrence of hormone –related breast cancer was cut by half in women having high cholesterol who regularly use aspirin or other non-steroidal anti-inflammatory drugs according to a study. The study found that BMI greater than 30 and had estrogen-receptor alpha and positive breast cancer had a 52% lower rate of recurrence and a 28 months delay in time to recurrence if they were taking aspirin or other NSAIDs. Using blood from obese patients, some researchers conducted experiments in the lab to recreate a tumours environment containing breast cancer cells that promote inflammation. They found that factors associated with high cholesterol initiates a network of signalling within a tumour environment to promote growth. Researchers used data from 440 women diagnosed with invasive ER?-positive breast cancer and treated at university of Texas Health Science Centre of the women. A by-product of cholesterol function like the hormones estrogen fuel the growth and spread of the most common types of breast cancers, many researchers did their research in mouse models and tumour cells[18]. These scientists linked high cholesterol and Breast cancer, especially in post-menopausal women, suggests that dietary changes or therapies to reduce cholesterol may also offer a simple, accessible way to reduce breast cancer risk. There is a simple way to reduce breast cancer by keeping the cholesterol level in check either by using statins or taking a healthy diet High level of HDL (high density lipoprotein) has been linked to increased breast cancer levels. If the activity of HDL receptors is blocked in breast cancer we may be able to limit the harmful effect of HDL while maintaining levels that are beneficial for blood vessels[19]. To study the effect of HDL on cancer cells at the molecular level exposed the breast cancer cells to HDL and noticed the signalling pathways involved in cancer progression were activated and those cells began to migrate in an experimental model. The HDL receptor called SR-BI in the cells can be expressed less imitated by using silencing RNA to reduce receptor level. Reduced SR-BI in the cells is associated with reduced tumour formation. So the SR-BI should be blocked in the breast cancer cell line with the drug called BLT-1. This supports the idea that HDL plays a role in the development of aggressive breast cancer and that inhibiting its function via SR-BI in breast cancer cells may still stop cancer. Statins are the most common treatment to reduce cholesterol level in blood.

The cholesterol lowering drugs are already known to reduce the risk of heart attack and strokes. The drugs are cheap and already taken by around 7 million people in UK. Being overweight is already known to be a risky factor for developing breast cancer. People are more likely to have high cholesterols. Researchers say that they are potentially leading towards clinical trial in 10-15 years to test the effect of statins on the incidence of breast cancer. If such a trial is successful, statins may have role in prevention of breast cancer, especially in high cholesterol women. It is still too early to say whether lowering cholesterol, for e.g. through the use of statins can reduce the risk of breast cancer but this study is promising in this field.

Sovereignty of the Disease

The researchers conducted an analysis on about 1 million patients across UK between 2000-2013 from ACALM clinical database. There were 664,159 women and these 22938 had Hyperlipidaemia and 9312 had breast cancer. Some 530 women with Hyperlipidaemia developed breast cancer. They found that having Hyperlipidaemia increased risk of breast cancer by 1.64 times[20]. High cholesterol levels in the blood increases the chance of developing breast cancer by 64%. University of Texas Health Science Centre of the women studied 58.5% were obese, 25.8% were overweight, 31% took aspirin, 42% statins and 25% omega-3 fatty acid. There was an indication of protection from aspirin and other NSAID.

Breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmadabad, Calcutta and Trivandrum where it constitutes > 30% of all cancers in females[21].

Pathology: Invasive ductal carcinoma not otherwise specified (IDC NOS) was found to be the most common type (88%) followed by infiltrating lobular carcinoma (3.7%), colloid carcinoma (1.1%), and ductal carcinoma in situ (DCIS) (1.1%) and metaplastic types (0.9%)[22]. 70% patients were reported as having grade III disease[23].

Westernization of lifestyle has led to an increase in the incidence of breast cancer in India. Thus, the Indian breast cancer patients have higher loco-regional recurrences and poorer over-all survival.

CONCLUSION

In the past few years, there is an increase in the cholesterol level in almost every individual irrespective of age. Because of the food they have every day. If the connection between high cholesterol and breast cancer is validated, the next step would be to see if lowering cholesterol with statins can reduce the risk of developing cancer.

People should always take a safe side and avoid having a high cholesterol diet as it does not only leads to cancer, but also various diseases like strokes and heart attacks. Researchers are trying their level best to have a success in this topic.

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