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Letter to the Editor

Is there any optimum value of lepidic parameters for cancer risk and progress?

The influence of lipid parameters on cancer, is, everything but clear. While several studies report a positive association between types of cancer and cholesterol levels, other studies, suggest that there is no such clear association, and other studies, suggest a negative, rather than positive, association. There is a need of a less simplistic, more complex, assumption between pathologies and controlling factors that is not a linear relation in a single explanatory variable, such as the concentration of total, HDL or LDL cholesterol, of cancer risk or progress.

According to Ref. [1], high cholesterol levels are associated with an increased short-term risk of prostate cancer, while, opposite, long-term risk, may be diminished. The explanatory variables are arranged into 3 bins (tertiles). After a 3-year lag time, men in the second and third tertiles of total cholesterol had a 27% and 26% increased risk of prostate cancer, respectively, compared with those in the first tertile. Without considering lag time, men in the highest tertile of total cholesterol and those with highest LDL cholesterol levels had a 42% and 38% increased risk of risk of prostate cancer, compared to those with the lowest tertile or the lowest LDL cholesterol level. In a 20-year lag time, men in the highest total cholesterol had a 62% decreased overall risk of prostate cancer compared with those in lowest tertile. In a 10-year lag time, no significant association was found between the lipid measurements and risk of prostate cancer. In mathematical terms, a linear regression between the specific cancer risk, and the cholesterol concentrations does not work explaining a more complex pattern that is thought.

Ref. [1] is not the exception, but the norm, of works trying to link risk or progress of certain types of cancer and cholesterol. Ref. [2] discusses the link between altered cholesterol metabolism and epigenetic modification during breast cancer progression. While it is sure that cholesterol plays an important role in the development of breast cancer, the link between the two factors is not well understood. Ref. [3] reports of the controversial relationship between HDL cholesterol and cancer incidence and mortality. There have been studies that have revealed a significant inverse association between HDL cholesterol and cancer risk. However, there have also been several confounding factors and opposite results. Hence, also here, it is impossible to derive definitive conclusions.

The influence of lipid parameters on cancer, is, everything but clear. Some studies, such as Ref. [4], report an association between cancer and cholesterol levels in the direction that higher cholesterol levels translate in an increased risk, or progress, of types of cancer. Some other studies, such as Ref. [5], suggest that there is no such clear unique association. Some other studies, such as Ref. [6], suggest that higher cholesterol levels translate in a reduced risk, or a regress, of types of cancer.

Ref. [4], that is based on an animal model, discovered that increasing cholesterol in mice influences the growth of stem cells in the intestines, facilitating tumors to form much faster. The connection between dietary cholesterol and colon cancer is suggested by other works. By increasing cholesterol levels, cells divide more rapidly, causing an acceleration of colon tumor formation. This molecular pathway may play similar role in other cancers. Ref. [6], reporting of human studies, offer a different perspective. The association between total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer project (Me-Can) is based on data of 289,273 male and 288,057 female participants. In male, higher total serum cholesterol concentrations are borderline significantly associated with decreasing risk of total cancer. Significant inverse associations are observed for cancers of the liver/intrahepatic bile duct, pancreas cancer, skin non-melanoma and lymph/hematopoietic tissue cancers. In females, higher total serum cholesterol concentrations are associated with decreasing risk of total cancer and for gallbladder, breast, skin melanoma and lymph/hematopoietic tissue cancers.

While cholesterol level is certainly higher in cancer cells, it is uncertain if this is positive or negative. Epidemiologic studies suggest a positive association between elevated serum cholesterol and risk for certain cancer types. Other epidemiologic studies suggest no or negative association. To further complicate the matter, statins were speculated to have not only indirect, but also direct carcinogenic properties. This dramatically conflicting evidence, especially of epidemiologic studies, explains the current ambiguity regarding the role of cholesterol in cancer, very well exemplified by the latest statement by the American Institute for Cancer Research. They say that while higher cholesterol may be linked to increased risk of heart disease, no similar link has been shown between cholesterol and cancer risk.

We know that cancer and cholesterol are related, but we do not know how they are related. The issue is generated by the assumption of a simplistic linear relation between cholesterol concentration, and the risk or progress of types of cancer. What is evident from the many examples reported in the literature, is the need of a less crude, more complex, assumption, between pathologies and controlling factors, with nonlinear regressions in multiple, continuous, variables, very likely able to provide better answers that associating cancer to tertiles.

Cholesterol assists with various purposes, including production of vitamin D, digestion, production of hormones, cell integrity and function. Both LDL and HDL cholesterol help the immune system and carry nutrients. However, by increasing cholesterol levels, cancer cells also reproduce much faster. Dietary cholesterol is positively associated with the risk of cancer, albeit dietary surveys in

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humans are unreliable, and extrapolation to humans of mice experiments is difficult because blood cholesterol levels in humans are not driven by dietary cholesterol. Intracellular cholesterol is certainly more relevant than dietary cholesterol in cancer. Deregulation of cholesterol homeostasis may increase the risk, or progress, of cancer. Intracellular cholesterol level in cancer cell may be more relevant than serum cholesterol. Intracellular cholesterol homeostasis varies among different cancer types. As HDL particles have been demonstrated to be superior to HDL concentration as a predictor of cardiovascular disease, Ref. [7], and similarly LDL particles have been demonstrated to affect end-stage renal disease more than the LDL concentration, Ref. [8], correlation should also involve number of HDL and LDL particles in addition to total, HDL and LDL cholesterol concentrations.

It is likely that different patients, at different stages of their specific pathology, may have different, optimal levels of cholesterol related parameters, and departure from the specific optimal levels, more than the simple concentration of total, HDL or LDL cholesterol, or also number of HDL and LDL particles, may increase the risk or progress of different types of cancer.

The role of cholesterol in cancer, is everything but clear, with positive, negative, or unclear effects, of increasing cholesterol concentration on the risk and progress of types of cancer. As cholesterol has positive and negative effects, and the trade-off is everything but linear. This is the reason why the many attempts to linearly relate cancer risk or progress to cholesterol concentration have failed. There is the opportunity of optimal lepidic parameters to be discovered through nonlinear regressions. These optimal parameters may differ from patient to patient and from pathology to pathology, with the departure from these values, more than the absolute values, determining the risk or the progress of types of cancer.

References

[1] Murtola TJ, Kasurinen TV, Talala K, Taari K, Tammela TL, Auvinen A. Serum cholesterol and prostate cancer risk in the Finnish randomized study of screening for prostate cancer. Prostate Cancer Prostatic Dis 2018:1.
[2] Munir MT, Ponce C, Powell CA, Tarafdar K, Yanagita T, Choudhury M, et al. The contribution of cholesterol and epigenetic changes to the pathophysiology of breast cancer. J Steroid Biochem Mol Biol 2018;183:1–9.
[3] Pirro M, Ricciuti B, Rader DJ, Catapano AL, Sahebkar A, Banach M. High density lipoprotein cholesterol and cancer: marker or causative? Prog Lipid Res 2018;1:54–69.
[4] Wang B, Rong X, Palladino EN, Wang J, Fogelman AM, Martín MG, et al. Phospholipid remodeling and cholesterol availability regulate intestinal stemness and tumorigenesis. Cell Stem Cell 2018;22(2):206–20.
[5] Kuzu OF, Noory MA, Robertson GP. The role of cholesterol in cancer. Cancer Res 2016. https://doi.org/10.1158/0008-5472.CAN-15-2613.
[6] Strohmaier S, Edlinger M, Manjer J, Stocks T, Bjørge T, Borena W, et al. Total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer Project (Me-Can). PLoS One 2013;8(1), e54242.
[7] Kontush A. HDL particle number and size as predictors of cardiovascular disease. Front Pharmacol 2015;6:218.
[8] Bowden RG, Wilson RL, Beaujean AA. LDL particle size and number compared with LDL cholesterol and risk categorization in end-stage renal disease patients. J Nephrol 2011;24(6):771.

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