Ambiguity of Plasma Cholesterol Levels as a Biomarker of Prostate Cancer

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The character of circulating cholesterol as a biomarker of prostate tumorigenesis is ambiguous. Inconsistent results have been reported for the association of serum cholesterol with prostate cancer. Results from several studies suggest that men with higher circulating cholesterol are more at risk of developing prostate cancer, while other studies reported increased risk of death from prostate cancer by men with low plasma cholesterol concentrations. More bewildering were results, which showed no association between total cholesterol or its sub-fractions and the risk of prostate cancer. Various attempts to explain the phenomena have compounded the problem by claiming that circulating cholesterol levels are suitable biomarkers of overall prostate cancer, and in some instances, prognostic markers of only aggressive prostate cancer. Then, what do we accept? Several explanations have been put forward to justify this apparent uncertainty and they are considered here briefly.

The Case for High Circulating Cholesterol and Prostate Cancer

Various studies suggest that high cholesterol is a modifiable risk factor for prostate cancer, and is subject to potential "reverse causality" as undetected disease modifies cholesterol level ahead of diagnosis [1]. In this case, the prevailing evidence seems to suggest that men with higher plasma cholesterol are at greater risk of developing high-grade or aggressive prostate cancer, than the overall risk of developing the disease. Some very interesting studies observed that the association between hypercholesterolemia and prostate cancer was stronger only in men diagnosed before 50 years and in those older than 65 years [2]. These studies have proposed two major mechanisms for explaining the occurrence. The first explanation being that prostate cancer cells over accumulates cholesterol in their cell membrane, forming lipid rafts, which facilitates pro-carcinogenic cell signaling. Secondly, it was explained that high cholesterol level is vital for carcinogenesis because it activates several signals, including those within the sonic hedgehog, and the Akt Pathways. In contrast, subjects having lower cholesterol level were deemed to possess inhibited pro-carcinogenic activities in their prostate cells. Additional justification for a relationship between hypercholesterolemia and prostate cancer comes from the position of cholesterol as a precursor of steroid hormones and androgens in particular, suggesting that higher circulating levels of cholesterol affects increased androgen synthesis, and irregular growth of prostate cancer cells is driven by abundant androgens. An exciting and very recent corollary to this was the discovery that prostate cancer cells synthesize their own androgens, in sufficient quantities to activate the androgen receptor [3]. Since cholesterol is the precursor of androgens, its excess was regarded to very likely boost *de novo* androgen synthesis, and to reinforce disease progression. Further, hypercholesterolemia is believed to contribute to prostate carcinogenesis by virtue of its association with higher serum prostate specific antigen (PSA) levels. This is supported by observation that treatment with statins (cholesterol-lowering drugs) quite often lowers PSA levels. Regrettably, the mechanism by which enriched serum cholesterol elevates PSA or conversely, the reduction of serum PSA by low serum cholesterol is not yet understood. Lastly, other explanations of the relationship between hypercholesterolemia and prostate cancer have rather shifted the culpability to obesity, overfeeding, physical stature, and dyslipidemia. Another major boost

to the role of hypercholesterolemia in prostate cancer is the inverse relationship between statins use and the progression, or significant reduction in the risk of advanced prostate cancer. With this, the implicit role of cholesterol in prostate cancer is suggested as the promotion of its progression to advanced disease.

As insightful as some of these explanations may seem, they appear inadequate in many respects or fail to exist in isolation. For instance, at all instances of enrichment of circulating cholesterol, it would be expected that several cell proliferation signals, or increased steroid synthesis would dominate in steroidogenic cells, leading to carcinogenesis or worse still advanced tumors. Holding *de novo* cholesterol synthesis constant, it is compelling to inquire whether enriched circulating cholesterol constantly draws a parallel with extra-hepatic or enriched peripheral tissue cholesterol. On the other hand, it is logical to inquire about the status of the intrinsic mechanisms for enriched cholesterol efflux from all the peripheral tissues, including the prostate. An affirmative answer to the first inquiry would generally imply that; hypercholesterolemia stimulates pro-carcinogenic signaling in all or most instances. If the opposite is true, then we may well presume that the direct influence of hypercholesterolemia on prostate tumor progression is secondary to that of confounding factors, which promote cholesterol imbalance or deregulated efflux from peripheral tissues. Although many of these confounding factors that support intracellular cholesterol enrichment are yet to be identified, it will again be logical to consider in retrospect many of the molecules within the cholesterol trafficking and efflux arrangements. Emerging evidence suggests that dysfunctional forms of lipoproteins together with ATP-binding cassette, sub-family A, member 1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), both of which are major transporters involved in cholesterol efflux and peripheral lipid homeostasis, could disorganize the recognized cholesterol homeostasis mechanism, leading to intracellular cholesterol enrichment. Interestingly, recent reports are inclined towards accepting that allelic variants of the apolipoprotein E (apoE) gene characterize the degree of cholesterol efflux from peripheral tissues. ApoE is the systemic primary cholesterol carrier, and in peripheral tissues, its function in cholesterol efflux is to lower cellular cholesterol levels [4]. Overall, dysfunctional forms of some of these confounding factors may dictate the often observed over accumulation of membrane cholesterol in disregard to existing intrinsic mechanisms for reverse cholesterol transport, leading to pro-carcinogenic cell signaling. Supporting the attempts to explain the gaps in how hypercholesterolemia supports pro-carcinogenic

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signaling by defying the intrinsic arrangement for maintaining cholesterol equilibrium, another question arises as to why peripheral tissue cholesterol stuffing permits higher circulating cholesterol level. It is expected that in dysfunctional cells, intracellular cholesterol repletion would engender cholesterol depletion within circulation. This assumption may validate studies suggesting that low circulating cholesterol level is a promising biomarker of prostate cancer.

The Case for Low Circulating Cholesterol and Prostate Cancer

In sharp contrast to the foregoing, low serum cholesterol levels have in several other studies been implicated as possible biomarkers of increased susceptibility to various cancers, including cancer of the prostate [5]. The relative risk for cancer is believed to be highest in the lowest tertile of serum cholesterol and lowest in the highest. Specifically, cancer mortality rates are said to increase at serum cholesterol levels below 160 mg/dl [6]. A more detailed investigation of the trend in cholesterol levels across disease phases has been provided by studies in breast cancer. A very remarkable aspect of such studies was the observation that higher plasma total cholesterol levels were attained at the early stages of the disease, while lower levels followed thereafter. This suggested the progressive nature of cholesterol disequilibrium in various carcinogenesis. Thus, studies on the course of cholesterol imbalance are necessary to arrive at a consensus for determining the exact stage for evaluating serum cholesterol and its use as a biomarker for prostate carcinogenesis.

Yet again, several attempts have been made to justify the relationship between low blood cholesterol concentrations and cancer. A curious explanation states clearly that the observed relationship could be associated with the low levels of circulating vitamin E and/or carotenoids which feature regularly in such conditions, and not to any direct effect of serum cholesterol. This argument relies on the fact that circulating levels of vitamin E and several carotenoids are consistently correlated with serum cholesterol levels. The glitch in such argument is that there was complete disregard for the role of cholesterol in pro-carcinogenic signaling, making its presence insignificant. Several other explanations for the association of low circulating cholesterol levels with increased prostate cancer risk, including the "preexisting cancer effect", have not been able to rationalize the observed low serum cholesterol and the concomitant cell membrane-rich cholesterol levels that determine lipid rafts formation and pro-carcinogenic cell signaling. To bridge the gap between low serum cholesterol and prostate carcinogenesis would entail investigating the coexistence of low circulating cholesterol with high intracellular cholesterol levels in prostate cancer cells. Further analysis of the events within the cholesterol trafficking mechanism and cholesterol-controlled cell signaling events may attest to the existence of an inverse relationship between low serum cholesterol and prostate carcinogenesis. The absence of any link between these events will support the suggestion that serum cholesterol is not associated with the overall incidence of prostate cancer.

The Case for No Association between Circulating Cholesterol and Prostate Cancer

Very early prospective studies of various cancer types found no evidence that low circulating cholesterol increased the risk of cancer, but believed that cancer in some way lowers serum cholesterol [7]. However, most of the studies found increased, though statistically insignificant occurrence of cancer at low circulating cholesterol levels, and consequently attributed it to preclinical cancer. These inverse associations were found during the first years of follow-up, especially for rapidly developing cancers [8]. Interestingly, attributing cholesterol-cancer manifestation to preclinical or "preexisting cancer effect" suggests the realization of cholesterol trafficking. Despite observation of the relationship between cholesterol trafficking and prostate cancer, the cross talk between them has not been elucidated. A detailed investigation of how cholesterol drives prostate cancer would be significant in establishing its role as a biomarker of prostate cancer.

In conclusion, and from the multitude of evidence available, there is no doubt that cholesterol affects prostate cancer growth. What is in question is the discrepancy between various studies on the subject, suggesting a positive, others negative and yet others, no correlation between circulating cholesterol level and the risk or existence of prostate cancer. Such discrepancy in results demolishes any evidence on the use of circulating cholesterol levels as a marker of the disease. Given the apparent progressive nature of cholesterol disequilibrium in diverse cancers, it will be prudent to seriously consider the trend in cholesterol flux across the entire spectrum of the disease progression, in order to establish the choice of cholesterol value and interval that befits its use as a biomarker of prostate cancer.

References

1. Shafique K, McLoone P, Qureshi K, Leung H, Hart C, et al. (2012) Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. BMC Cancer 12: 25.

2. Bravi F, Scotti L, Bosetti C, Talamini R, Negri E, et al. (2006) Self-reported history of hypercholesterolemia and gallstones and the risk of prostate cancer. Ann Oncol 17: 1014-1017.

3. Mostaghel EA, Solomon KR, Pelton K, Freeman MR, Montgomery RB (2012) Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors. PLoS One 7: e30062.

4. Lee CY, Tse W, Smith JD, Landreth GE (2012) Apolipoprotein E promotes β-amyloid trafficking and degradation by modulating microglial cholesterol levels. J Biol Chem 287: 2032-2044.

5. Eichholzer M, Stahelin HB, Gutzwiller F, Ludin E, Bernasconi F (2000) Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-y follow-up of the prospective Basel study. Am J Clin Nutr 71: 569-574.

6. Moore RJ, Chamberlain RM, Khuri FR (2004) Apolipoprotein E and the risk of breast cancer in African-American and non-Hispanic white women. A review. Oncology 66: 79-93.

7. Hiatt RA, Fireman BH (1986) Serum cholesterol and the incidence of cancer in a large cohort. J Chronic Dis 39: 861-870.

8. Knekt P, Reunanen A, Aromaa A, Heliovaara M, Hakulinen T, et al. (1988) Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. J Clin Epidemiol 41: 519-530.