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Prognostic Significance of Systemic Cholesterol Profile in Patients with Breast Cancer

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Abstract: Breast cancer ranks as the number one cancer among Indian females with survival as low as 66.1%. Relationship between cholesterol and breast cancer has triggered special interest due to their role in important cellular processes that steer toward carcinogenesis. The interplay between cholesterol and tumor development have been studied in experimental breast cancer models. However, epidemiological data reveal conflicting results, that need to be integrated and put into appropriate viewpoint. This study aims to investigate and corroborate the impact of total cholesterol (TC), triglyceride (TG), VLDL, LDL and HDL cholesterol on the disease-free and overall survival of patients with breast cancer. This study retrospectively analyzed 50 breast cancer patients who underwent radical surgery and attended follow-up visits at KIMS Hospitals. The blood lipid levels such as TC, TG, VLDL, LDL and HDL cholesterol were collected and analyzed from the database of Department of Laboratory Medicine. Potential prognostic factors including age, menopause, grade, receptor status, systemic cholesterol profile etc., were analyzed by univariate and multivariate analysis. TC less than 180mg/dL was associated with disease relapse in univariate analysis. TG, VLDL, LDL and HDL cholesterol were not significantly correlated either to disease-free or overall survival. Low systemic cholesterol level could be a significant prognostic factor for a shorter disease-free survival.

Keywords: Carcinogenesis, Lipoprotein, Cholesterol, Prognosis, Survival

1. Introduction

Breast cancer ranks as the number one cancer among Indian females with rate as high as 25.8 per 100,000 women and mortality of 12.7 per 100,000 women. India continues to have a low survival rate for breast cancer, with only 66.1% women diagnosed with disease between 2010 and 2014 surviving, according to CONCORD-3 study [1].

Life style factors such as obesity, overweight, sedentary life and metabolic syndrome are increasingly considered as important contributing factors for breast cancer, apart from reproductive and hormonal factors [2]. Deranged lipid metabolism could be the plausible link between lifestyle factors and risk for breast cancer. Relationship between cholesterol profile and breast cancer has triggered special interest due to their role in important cellular processes that steer toward carcinogenesis [3].

It has been established that proliferating breast cancer cells have an increased demand for cholesterol. This was accomplished through increased LDLR expression to enhance the cholesterol uptake from the bloodstream [4]. Gallagher et al. [5] have reported that higher LDLR expression was found to be associated with a worse prognosis in breast cancer and have role in disease

progression and disease-free survival. Furthermore, scavenger receptor class B type I (SR-BI), an HDL receptor which mediates cholesterol uptake [6] has also shown to be profusely expressed in breast cancer cells and found related to tumor aggressiveness and poor prognosis in breast cancer. Similarly, triglyceride (TG), as a source for fatty acid oxidation has been proposed to have a role in promoting cell proliferation and tumor growth [7]. However, the relationship between systemic lipid profile and breast cancer development remains ambiguous.

The interplay between cholesterol, lipoproteins and tumor development have been studied in experimental breast cancer models [8]. However, epidemiological data reveal conflicting results, that need to be integrated and put into appropriate viewpoint. Certain studies presented positive association between high total cholesterol (TC), LDL or triglyceride (TG) and the risk of breast cancer [9, 10], while other reported negative associations [11, 12] or even inverse associations [13].

Under this standpoint, we have hypothesized that systemic cholesterol profile could have prognostic significance in patients with breast cancer. In this milieu, we investigated and corroborated the impact of TC, TG, VLDL, LDL and HDL cholesterol levels on the disease-free and overall survival of patients with breast cancer.

2. Materials and Methods

2.1. Study Participants

This study retrospectively analyzed 50 breast cancer patients who underwent radical surgery and attended follow-up visits at the Department of Oncology, Krishna Institute of Medical Sciences, Telangana, India between June 2010 to June 2015. Exclusion criteria included patients older than 70 years, patients who took drugs affecting cholesterol levels and patients who had certain cardiovascular diseases or other chronic ailments other than breast cancer. All the patients underwent radical surgery and administered adjuvant chemotherapy according to their clinicopathological manifestations and molecular subtypes. This study has been approved by the Institutional Ethics Committee and all participants had given written informed consent.

Patients' history, immunohistochemical and pathological reports, surgery approach, laboratory test results and treatment regime were obtained for each participant at baseline. The systemic cholesterol profile was collected and analyzed from the database of Department of Laboratory Medicine, Krishna Institute of Medical Sciences.

2.2. Plasma Lipid Measurements

Total cholesterol (TC), triglyceride (TG), VLDL, LDL and HDL cholesterol were analyzed prior to the surgery. Lipid profile was performed with Beckman Coulter UniCel DxC800 Synchron Clinical Systems using commercial kits from Beckman Coulter Diagnostic products.

2.3. Statistical Analysis

Disease-free survival (DFS) was measured from the date of initial surgery to disease progression (locally or regionally). Overall survival (OS) was measured from the date of entry into the study to the date of death or last follow-up. Shapiro-Wilks test was used to determine whether data sets comes from a normal distribution. Univariate and multivariate analysis were performed to identify those that were significantly associated with prognosis. Quantitative variables such as age and lipid profile were expressed as mean value ± SD. The unpaired Student t test was conducted to compare mean values between survivors and non-survivors. $p < .05$ was considered statistically significant.

3. Results

The tumor related variables such as age, menopausal status, grade, receptor status, systemic cholesterol profile (below and above the normal range) were examined by univariate and multivariate analysis. The results of univariate analysis are presented as Table 1. Age had no impact on DFS or OS when categorized above or below a given age of 50 years. Similarly, menopausal status carried no prognostic significance. Patients presented with stage I showed significantly better DFS and OS as compared to stage II and III. The univariate analysis indicated median DFS of 60, 41 and 31 months ($p = 0.048$) respectively for stage I, II and III. However, in the multivariate analysis, stage did not seem to affect survival significantly (data not shown). Patients with tumors tested positive for estrogen receptor showed better survival than patients with negative tumors, though these differences were not statistically significant for either DFS and OS. Conversely, progesterone/HER2+ receptors' presence or absence, showed no impact on either DFS or OS.

TC below the normal range of 180mg/dL showed significantly shorter median DFS of 26 months as compared to 52 months ($p = 0.039$) when TC level above 180mg/dL. Besides, in the multivariate analysis, total cholesterol level presumed no prognostic significance (data not shown). Analogously, TG, VLDL, LDL and HDL cholesterol were not associated either with DFS or OS.

Of the 50 patients recruited for our study, 24 patients developed disease recurrence (either locally or regionally) and 13 out of 24 patients succumbed to the disease during the follow-up of 60 months. In order to understand the clinical significance of systemic cholesterol profile in the DFS or OS, we analyzed the level of TC, TG, VLDL, LDL and HDL cholesterol and compared between survivors with/without recurrence and non-survivors (Table 2). TC was significantly lower in the survivors with recurrence as compared to survivors without recurrence. More so, it was abysmally low in the non-survivor with level as low as 117mg/dL. Similarly, TG was significantly low in the survivors with recurrence and non-survivors when compared with survivors without recurrence.

Table 1. *Univariate Analysis of Factors associated with DFS and OS in Patients with Breast Cancer.*

Factor	No of Patients	Disease-Free Survival (DFS)			Overall Survival (OS)		
		5-year (%)	Median (Months)	*p*-value	5-year (%)	Median (Months)	*p*-value
Age				0.772			0.526
> 50 years	26	61.54	32		80.76	52	
< 50 years	24	45.83	33		70.83	44	
Menopausal status				0.615			0.921
Pre-menopause	19	47.36	33		84.21	56	
Post-menopause	31	58.06	37		83.87	49	
Stage				0.048			0.493
I	4	100.00	60		100.00	60	
II	23	69.57	41		82.61	52	
III	23	36.09	31		65.22	45	
Oestrogen Receptor				0.078			0.305
Positive	33	60.60	42		78.78	44	
Negative	17	35.29	31		60.58	53	
Progesterone Receptor				0.863			0.791
Positive	29	65.51	34		82.75	50	
Negative	21	66.66	32		66.66	48	
HER2 Receptor				0.764			0.927
Positive	7	57.14	38		85.71	52	
Negative	43	51.16	40		74.42	50	
Total Cholesterol				0.039			0.135
>180 mg/dL	35	26.66	26		80.12	41	
<180 mg/dL	15	60.14	52		66.67	52	
Triglyceride				0.0649			0.351
>150 mg/dL	30	46.67	33		79.97	53	
<150 mg/dL	20	62.44	36		71.01	49	
VLDL-Cholesterol				0.213			0.539
>30 mg/dL	30	46.67	33		79.97	53	
<30 mg/dL	20	55.03	36		70.15	50	
LDL-Cholesterol				0.304			0.319
>130 mg/dL	40	57.53	36		75.19	52	
<130 mg/dL	10	40.00	40		80.00	51	
HDL-Cholesterol				0.278			0.571
>40 mg/dL	34	58.82	35		79.41	49	
<40 mg/dL	16	43.75	34		68.75	54	

Table 2. *Comparison of Systemic Cholesterol Profile between Survivors and Non-survivors.*

Factor	Survivors without Recurrence (n=26)	Survivors with Recurrence (n=11)	Non-survivors (n=13)
Age	50.65 ± 10.54	43.72 ± 8.12	49.66 ± 11.31
Total Cholesterol	148.17 ± 22.32	130.03 ± 22.27[a]	116.28 ± 14.05[b]
Triglyceride	134.58 ± 16.25	115.32 ± 26.70	108.31 ± 18.67[a]
VLDL-Cholesterol	26.31 ± 4.81	22.83 ± 5.59	27.55 ± 7.83
LDL-Cholesterol	92.54 ± 18.41	98.85 ± 14.43	96.35 ± 23.73
HDL-Cholesterol	29.96 ± 5.74	31.11 ± 7.84	34.13 ± 6.61

Data expressed as mean ± Standard Deviation. [a]$p < 0.05$ when compared to survivors without recurrence; [b]$p < 0.01$ when compared to survivors without recurrence.

4. Discussion

The impact of blood cholesterol as a risk factor for breast cancer is contradictory. Still there is lots of ambiguity about the type of cholesterol that contribute to the disease. In this study, we evaluated the effect of systemic cholesterol profile on the disease-free and overall survival of patients with breast cancer. Even though several reports have ascertained the underlying relationship between serum lipids and breast cancer development, studies to delineate the impact of these lipids on their prognosis or survival are scarce. Circulating TC, LDL-cholesterol and HDL-cholesterol appear to play a crucial role in tumor invasiveness or aggressiveness that eventually could skew the final prognosis [14]. Raza et al. [15] have suggested that hyperlipidemia was highly significant in patients with lymph node metastasis. Further studies demonstrated the association of increased risk of cancer recurrence with higher circulating level of TC and LDL-cholesterol [16, 17].

Interestingly, in our study, we found that low systemic TC was associated with shorter DFS and worse prognosis. Conversely, TG, VLDL, LDL and HDL cholesterol assumed no prognostic significance above or below their normal range. Furthermore, when patients were categorized as survivors with/without recurrence and non-survivors, TC and TG were found to be significantly on the lower side in the non-surviving group as compared to survivors. Nonetheless, it is a well-

known fact that highly aggressive breast cancer cells require superfluous supply of cholesterol to fuel their increased metabolic demand which eventually reduce the circulatory cholesterol level [4]. We found that low circulating TC correlates with the increased intracellular cholesterol load within the cancer cells that consecutively increased the release of tumor derived exosomes (Personal Report).

5. Conclusion

Our study revealed the role of systemic cholesterol profile in the prognosis of patients with breast cancer. Patients with stage I disease showed significantly better DFS and OS as compared to stage II and III irrespective of cholesterol profile. However, stage II and III patients with low TC and TG had a higher probability of worse prognosis with shorter DFS. LDL, VLDL and HDL cholesterol were not associated with DFS and/or OS. Our findings thus imply that systemic cholesterol profile of cancer patients should be contemplated with utmost caution as the generalized range may not be advantageous for cancer patients.

Conflict of Interest

The authors declare they have no conflict of interest.

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