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Research Article

INCIDENCE/CO MORBIDITY OF ISCHEMIC HEART DISEASES (IHD)/MYOCARDIAL INFARCT (MI)/CARDIOVASCULAR DISORDERS IN SMOKING CANCER PATIENTS AND VICE VERSA – A REVIEW

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A B S T R A C T

While using the search phrase "Ischemic Heart Diseases" combined with "Myocardial Infarct", "Cardiovascular Disorders", "Diabetes Mellitus", "Cancer" or "Smoking" in PubMed when using the MeSH search mode yielded some reports on mild reports on association in relation with Cardiovascular diseases and Smoking Cancer patients. However, a hand search yields clinical reports on incidence of Ischemic Heart Diseases in Smoking Cancer patientsand vice versa that were published over two decades ago. An investigation of this topic should proceed via two specific methods: a review of the published work, and a study of general tumour pathogenesis.

Patient education and periodic general and oral cancer examinations by medical and dental professionals respectively are necessary to reduce diagnostic delay and improve prognosis. This review emphasizes the important role of medical and dental professionals of being aware that the Incidence/ Co morbidity of Ischemic heart diseases (IHD)/Myocardial Infarct/cardiovascular disorders/ hypertension in smoking cancer patients. And there is an enigma surrounding the Co morbidity of Cardiovascular disorders in smoking cancer patients which is yet to be discovered. Some related questions have been discussed in this review.

INTRODUCTION

Smoking as a cause of increased risk for Ischemic heart disease is well known and several studies show the decrease in risk for heart disease in people who stop smoking over a period of time ranging from 5-15 years and the risk reaching the levels of nonsmokers. Increase in the risk of cancer among smokers is also well established. This has led to the interest in incidence of cancer in myocardial infarction patients and the occurrence of ischemic heart disease in cancer patients and their relationship to smoking and quitting. This has been traced to multiple factors such as continued smoking, radiation, chemotherapy and the use of increasingly high dose low ionizing radiation in diagnostics in both these populations. While there are few studies in the western scientific literature in this direction there are not many if not no studies in this direction from India. This acquires importance in the fact that the incidence of Ischemic heart disease in the south Asian population especially Indian is on the rise and the increase in metabolic syndrome makes Indians riskier than their western counterparts to heart disease atherosclerosis and probably cancer also. So, a study going into the incidence of IHD in cancer patients or cancer in Ischemic Heart Disease (IHD) patients or a simultaneous occurrence of both will be of relevance and of extreme importance in all aspects of healthcare Myocardial Infarction incidence is present in cancer patients. Mostly in smoking cancer patients. Chemotherapeutic drugs may also lead to myocardial infarction. In one of the review articles', as per clinical trials on 1625 cancer patients -- 6.5% of the subjects had a myocardial infarction. Lung cancer, ovarian cancer and prostate cancer are in which IHD are commonly found. In India the cases are occurring more day by day. Very Low-Density Lipoprotein (VLDL) and Low-Density Lipoprotein (LDL) deposition in the body also causes MI in cancer patients[1].

The pathophysiology is of chronic inflammation in response to injury with abnormal cell proliferation due to presence of cancer. Endothelial dysfunction leads to loss of protective mechanisms, monocyte/macrophage & T-cell migration, uptake of low-densitylipoprotein (LDL) cholesterol & its oxidation, uptake of oxidized LDL by macrophages, smooth muscle cell migration &proliferation,& deposition of collagen[1].

Objective: Our objective is to check for the previous studies if conducted with this regard in other geographical regions

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mainly focusing on the Incidence/ Co morbidity of Ischemic heart diseases (IHD)/Myocardial Infarct/cardiovascular disorders/ hypertension in smoking cancer patients and work on further deeper for finding out the exact reason behind this co morbidity and to go ahead for finding out for genetic mutations in that co morbidity, early diagnosis and treatment plan in our research. To check out tumor biology influenced by co morbidity. In India, till date not a research or study is conducted on this topic but unfortunately Indians are at a high risk of having co morbidity related to CVS, IHD due to diet, genetic mutation and heredity. In Indians due to presence of stomach pot belly,obesity, excessive fat deposition, VLDL and LDL deposition, severe smoking habits, and hereditary are the major factors for co morbidities like IHD, CVS disorders, Hypertension and Myocardial Infarct in smoking cancer patients as such.

Some unanswered questions pertaining to this topic were mentioned by Mette Sogaard *et al*[9] – So these will be our

Major objectives that have to be fulfilled

1. Why not some cancers do not have myocardial infarction incidence?
2. Is negative prognostic impact of co morbidity attributable to co morbidity related deaths or does co morbidity also influence cancer specific mortality?
3. How tumor biology is influenced by co morbidity?
4. How much of negative prognostic impact of co morbidity is explained by differences in socioeconomic position, lifestyle, and social support?
5. Is co morbidity associated with less access to specialized care?
6. Does treatment at increasingly specialized cancer centres improve cancer survival mainly in patients without severe co morbidity?
7. Are apparent disparities in cancer treatment among patients with co morbidity related to physicians' recommendations, patients' preferences, and /or decreased compliance?
8. Is co morbidity associated with high risk of cancer treatment toxicity, given the limited participation of patients with co morbidity in randomized clinical trials?
9. How do individual co morbidities – alone and in combination – impact cancer patients' clinical courses?
10. Does the prognostic effect of specific co morbidities vary according to cancer type?
11. How do duration and severity of co morbidity influence cancer prognosis?
12. How co morbidity is most accurately measured in cancer patients?

DISCUSSION

As per study conducted by The Post-Graduate Education Center, Tokushima University Hospital, Tokushima, Japan on two young cancer suffering patients who had an acute myocardial infarction the report mentioned that the incidence of thrombus formation in cancer patients varies among investigators: 1–11%. Thrombus formation is frequent in digestive, pancreatic, lung, and blood cancer patients[2]. Some studies also suggested the following mechanisms like in the presence of cancer, tumor cells directly act on thrombin, promoting blood coagulation where the coagulation capacity is enhanced through interactions between tumor cells and platelets and the coagulation capacity is enhanced through the enhancement of von Willebrand factor and inflammatory cytokines[2]. Some Anti-cancer drugs also includes the vascular toxicity.

Research study conducted on myocardial infarction in early stages of breast cancer women by Oncologic Centre, Karolinska Hospital, Stockholm, Sweden, Institute of Environmental Medicine, Karolinska Institute, Stockholm. Sweden, and Department of Surgery, Karolinska Hospital, Stockholm, Sweden: Researchers state that there was no indication of an increased risk of acute myocardial infarction with the radiation therapy among the women treated with conservative surgery[3]. However, due to the small number of events the study could not exclude the possibility that cardiac problems may arise in some patients with left sided cancers who have their heart located anteriorly in the mediastinum[3]. Individual, three-dimensional dose pIanning represents one method to identify such patients and is basic to technical changes aimed at decreasing the cardiac radiation dose volume.

Study performedat the Massachusetts Medical Society and published in The New England Journal of Medicine[4] on Oct 3,1996concludes that the CARE trial demonstrates that treatment with pravastatin can substantially reduce the burden of cardiovascular disease in patients with a history of myocardial infarction[4]. The study gives new importance to cholesterol-lowering therapy by demonstrating a significant reduction in the incidence of coronary events in patients with cholesterol levels of less than 240 mg perDeciliter4. This group includes the majority of survivors of myocardial infarction.

Smoking Cessation and Decreased Risk of Coronary Heart Disease[5]: Cigarette smoking is a well-established risk factor for coronary heart disease (CHD) in men and women (U.S. Department of Health and Human Services, 1983)[5]. Although cessation of smoking reduces morbidity and mortality from CHD (U.S. Department of Health and Human Services, 1990), there have been conflicting reports of the time required for the excess risk to return to the level of never-smokers. Some of smoking's effects that increase CHD risk (for example, increased platelet activation, elevated carbon monoxide levels, and coronary artery spasm) are immediately reversible, but other effects are either irreversible or are only slowly reversible (for example, development and progression of atherosclerosis) (McBride, 1992)[5]. Hence, it is possible that the smoker who stops will experience a component of rapid decline in risk compared with those who continue to smoke and a further component of risk that gradually falls to the level of never-smokers. The available prospective epidemiological data are predominantly in middle-aged men, and they suggest that smoking cessation is accompanied by a halving of CHD risk after 1 year. These data also show that an additional 15 years are required for the risk to decline to the level of never smokers (U.S. Department of Health and Human Services, 1990). However, a recent prospective study in predominantly elderly subjects suggested that risk in former smokers returns to that of never-smokers within 5 years of cessation (LaCroix *et al*., 1991). Further, several case-control studies, limited to nonfatal myocardial infarction (MI), have suggested that the excess CHD risk among former smokers dissipates completely

less than 5 years after cessation (Rosenberg *et al*., 1985 and 1990; Dobson *et al*., 1991)[5].

Smoking Cessation and Decreased Risk of Stroke[5]: Smoking is an established risk factor for stroke in both men and women (Shinton and Beevers, 1989). Based on a review of the available evidence, a U.S. Surgeon General's report, *The Health Benefits of Smoking Cessation. A Report of the Surgeon General,1990* concluded that smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking (U.S. Department of Health and Human Services, 1990)[5].

Jerry W. Hussong *et al*[6], infers that the angiogenesis plays a key role in solidtumor growth and metastasis which is a highly regulated process under the tight control of inducers and inhibitors. They also state that it involves degradation of the parent venule basement membrane, endothelial cell proliferation and migration, development of sprouts, and generation of new basement membrane. Recent studies suggest the role for angiogenesis in the pathophysiology of hematologic malignancies[6]. Vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) are two of the best characterized angiogenic factors. They are produced by a number of neoplastic and non-neoplastic cell types. Acute myeloid leukemia (AML) cells express VEGF. Furthermore, elevated levels of bFGF were detected in urine from patients with acute lymphoblastic leukemia (ALL) and lymphoma. In children with ALL, elevated levels of bFGF in the urine were associated with increased density of bone marrow vessels. The purpose of the current study was to determine the extent of angiogenesis in AML. Their results show increased vessel density in bone marrow specimens from patients with AML, thus suggesting a possible role for angiogenesis in the pathophysiology of this disease[6]. And also, there was a positive correlation between the percentage of marrow blasts and vessel score. Both VEGF and bFGF are among the most potent mitogens for endothelial cells and stimulators of angiogenesis. They also work synergistically to stimulate angiogenesis. Most of the early work on angiogenesis was done in solidtumors[6]. More recently, a mounting body of evidence has been accumulating suggesting a role for angiogenesis in the pathophysiology of hematopoietic malignancies. Children with ALL have increased angiogenesis in their marrow and increased urinary levels of bFGF.

Studypublished on Effects of Co morbidity and Smoking on the Survival of Lung Cancer Patients: "The article "Never-Smokers with Lung Cancer: Epidemiologic Evidence of a Distinct Disease Entity" by Toh *et al*[7], recently published in the Journal of Clinical Oncology was of greatinterest to us. They reported that non–small-cell lung cancer of thenever smoker is different from the non–small-cell lung cancer of theever smoker in terms of epidemiologic features as well as survival[7].Furthermore, the effect of co morbidity on the survival of lung cancer patients is expected to become more important as survival continues to improve. In addition, there was substantial evidence that co morbidities from smoking were significantly related to the poor survival of lung cancer patients.Smoking is well known to have a major role in the carcinogenesis and progression of lung cancer[7]. Therefore, it is not surprising that a never-smoker would have different characteristics from an ever smoker even in survival. In this regard, the never-smoker was shown to have a longer survival in retrospective hospital-based cancer cohorts. However, despite the interesting observation by Toh *et al*[7], it is unclear why the presence of co morbidity was not associated with survival and smoking status. Some co morbidities, such as cardiovascular disease or chronic obstructive pulmonary disease which can act as potential hazards when providing appropriate treatment to lung cancer patients, have been shown to be clearly attributable to smoking.

A prospective cohort study with a large population needs to answer the following questions: do co morbidities or their severity interact with smoking to affect the survival of lung cancer patients? Does smoking and co morbidities, especially those related to smoking, affect survival independently or are they confounding as one? It is time to address the issue of evaluating co morbidities in patients with lung cancer.

Some more studies done on Risk factors for morbidity after pulmonary resection for lung cancer in younger and elderly patients, Kazuya Takamochi *et al*[8], from the Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan, performed a research study to evaluate the perioperative morbidity, mortality, and risk factors for morbidity after lung cancer resection in younger and elderly patients. This study retrospectively reviewed 1073 patients with non-small cell lung cancers (NSCLC) who underwent pulmonary resection. The risk factors for morbidity were analyzed independently in groups of 664 younger (-70 years) patients and 409 elderly (G70 years) patients. Co-morbidities, such as hypertension, ischemic heart disease, and renal insufficiency were more frequently observed in the elderly group in comparison to the younger group[8]. Co-morbidities, such as hypertension, ischemic heart disease, and renal insufficiency were more frequently observed in the elderly group in comparison to the younger group. Multivariate analyses revealed the risk factors for morbidity to be % forced expiratory volume in 1 s (FEV), the extent of pulmonary resection and tumor histology in the younger group, and smoking, hypertension, renal insufficiency and % diffusing capacity of the lung to carbon monoxide (DLCO) in the elderly group, respectively. In conclusion, the rate of perioperative morbidity and mortality after NSCLC resection in elderly patients were similar to those in younger patients8. However, perioperative management should be cautiously performed while considering the risk factors for morbidity especially in elderly patients because they frequently have various co-morbidities. The study was conducted by having a barring between morbidity and mortality[8].

A review by Mette Sogaard *et al*[9], after a meta-analysis by referring 2500 articles on co morbidity and cancer, they affirm that only few researchers investigated the prognostic impact of comorbidity as a primary aim. Most studies found that cancer patients with comorbidity had poorer survival than those without comorbidity, with 5-year mortality hazard ratios ranging from 1.1 to 5.8. Few studies examined the influence of specific chronic conditions. In general, comorbidity does not appear to be associated with more aggressive types of cancer or other differences in tumor biology[9]. Presence of specific severe comorbidities or psychiatric disorders were found to be associated with delayed cancer diagnosis in some studies, while chronic diseases requiring regular medical visits were associated with earlier cancer detection in others. Another finding was that patients with comorbidity do not receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy as often as patients without comorbidity, and

their chance of completing a course of cancer treatment is lower. Postoperative complications and mortality are higher in patients with comorbidity[9]. It is unclear from the literature whether the apparent undertreatment reflects appropriate consideration of greater toxicity risk, poorer clinical quality, patient preferences, or poor adherence among patients with comorbidity[9].

Overall Summary from the above articles: Despite increasing recognition of the impact of comorbid illnesses on the prognosis of cancer patients, challenges remain. A large number of studies reported suboptimal treatment among patients with comorbidity across tumor sites and stages of disease. However, because most studies examined diagnosis, treatment, physician and/or patient preferences, but not all factors, it is unclear whether suboptimal cancer treatment reflects appropriate consideration of increased risk of toxicity due to comorbid illness, patient preferences, lower quality of clinical care, or poor adherence. Consequently, a number of questions remain unanswered about the relationship between comorbidity and cancer outcome. To adequately address these questions, studies are needed that elucidate whether comorbidity in general or only specific diseases or disease combinations are associated with poorer survival. Thus, studies with a more specific focus should be undertaken, including those that address the impact of an individual comorbidity on treatment provided to a homogenous population of cancer patients (ie, with comparable stage and tumor type). This is true about in our case also. Some unanswered questions on this topic of co morbidity (Table 1).

Is the negative prognostic impact of comorbidity attributable to comorbidity-related deaths or does comorbidity also influence cancer-specific mortality?
How is tumor biology influenced by comorbidity?
How much of the negative prognostic impact of comorbidity is explained by differences in socioeconomic position, lifestyle, and social support?
Is comorbidity associated with less access to specialized care?
Does treatment at increasingly specialized cancer centers improve cancer survival mainly in patients without severe comorbidity?
Are apparent disparities in cancer treatment among patients with comorbidity related to physician recommendations, patients' preferences, and/or decreased compliance?
Is comorbidity associated with higher risk of cancer treatment toxicity, given the limited participation of patients with comorbidity in randomized clinical trials?
How do individual comorbidities – alone and in combination – impact cancer patients' clinical courses?
Does the prognostic effect of specific comorbidities vary according to cancer type?
How do duration and severity of comorbidity influence cancer prognosis?
How is comorbidity most accurately measured in cancer patients?

Table 1 Some unanswered questions on this topic of co morbidity

C. Martin TAMMEMAGI *et al*[10],evaluated the impact of co morbidity on lung cancer survival.Co morbidity has a major impact on survival in early- and late-stage disease, and even infrequent deleterious co morbidities are important collectively. Co morbidity count and the Charlson index failed to capture much information. Clinical practice and trials need to consider the effect of co morbidity in lung cancer patients[10]. They concluded that the Lung cancer is strongly associated with smoking, a major cause of co morbidity. Hence, the diversity and count of co morbidities may be greater in lung cancer patients. Lung cancer has a relatively short course, and indolent co morbidities may not have the opportunity to exert deleterious effects. The respiratory tract of lung cancer patients is compromised by the cancer, and additional pulmonary co morbidities may not be tolerated as well as by patients free of tumors in their lungs[10]. Thus, the co morbidity indexes that were developed and validated in non-lung cancer patients may not perform well in lung cancer patients. The findings of the current study support this view[10]. For example: hypertension, coronary artery disease, myocardial infarct, cerebrovascular disease and diabetes, perceived to be of major importance in other studies or in established co morbidity indexes, were not found to be important predictors of survival in lung cancer patients. Moreover, the current study indicates that even if an index is significantly predictive of a health outcome and does so in adose-response fashion, it may be far from optimal.

Research study done by Terry F Pechacek *et al*[11], states that **e**xposure to secondhand smoke increases the risk of fatal and non-fatal coronary heart disease in non-smokers by about 30%. Because coronary heart disease is a leading cause of death in many countries, even relatively small increases in risk from this one factor can result in a large population burden of disease attributable to exposure to tobacco smoke. While the substantial cardiovascular risks posed by active smoking are now almost universally accepted, the tobacco industry and some other observers continue to question the idea that secondhand smoke can cause cardiovascular disease and death[11]. Notwithstanding the substantial clinical and experimental evidence regarding the adverse cardiovascular effects of exposure to secondhand smoke, some have argued that an association between low level environmental exposures and health outcomes should be more critically evaluated, particularly when the relative risk for the exposure is below 2.0. In addition, the risk of coronary heart disease associated with the typical self reported level of exposure to secondhand smoke (for example, that of a non-smoker living with a smoker) can seem disproportionate. It is more than one third of the risk associated with smoking cigarettes a day, even though the measured exposure to tobacco smoke among non-smokers is only about 1% of the exposure from smoking 20 cigarettes a day[11].

As per study done by Mark J. Eisenberg *et al*[12],patients exposed to low-dose ionizing radiation from cardiac imaging and therapeutic procedures after acute myocardial infarction may be at increased risk of cancer. Results states that out of the 82,861 patients included in the cohort, 77% underwent at least one cardiac imaging or therapeutic procedure involving low-dose ionizing radiation in the first year after acute myocardial infarction. The cumulative exposure to radiation from cardiac procedures was 5.3 milli Sieverts (mSv) per patient year,of which 84% occurred during the first year after acute myocardial infarction. A total of 12 020 incident cancers were diagnosed during the follow-up period. There was a dose dependent relation between exposure to radiation from cardiac procedures and subsequent risk of cancer. For every 10 mSv of low-dose ionizing radiation, there was a 3% increase in the risk of age- and sex-adjusted cancer over a mean follow-up period of five years (hazard ratio 1.003 per milliSievert, 95% confidence interval 1.002–1.004)[12]. Study **interprets that e**xposure to low-dose ionizing radiation from cardiac imaging and therapeutic procedures after acute myocardial infarction is associated with an increased risk of cancer[12].

CONCLUSION

So, we believe that these above-mentioned original studies and review articles will be a torch bearer andboost to furtherresearch workin mere future. And our future further interests are to check for the incidence ofthe co morbidities like IHD, CVS disorders, hypertension and Myocardial infarctin different cancers and cancerous lesions and work on further deeper for finding out the exact reason behind this co morbidity and to go ahead for finding out for genetic mutations in that co morbidity, early diagnosis and treatment plan in our research. And we would also like to find out the answers for still unanswered questions as mentioned in the above-mentioned study -- The impact of co morbidity on cancer survival: a review which has been described in Table 1.

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