Characteristics of non-hepatic cancers in cirrhotic patients

Sirozlu hastalarda gelişen karaciğer dışı kanserlerin özellikleri

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Background and Aims: *Besides the incidence of hepatocellular carcinoma, the incidence of some non-hepatic cancers also increases in patients with cirrhosis. We evaluated whether there was an increase in the incidence of non-hepatic cancers in patients with cirrhosis diagnosed before transplantation in our center.* ***Materials and Methods:*** *In this retrospective study, a total sample of 1017 patients with cirrhosis who were followed up at our center was reviewed, of which the data of 37 patients who did not develop non-hepatic cancer were evaluated, and the incidence of cancer was determined. These data were compared with the incidence rate of cancer at our hospital.* ***Results:*** *The incidence of non-hepatic cancers was found to be increased by 4-fold in males and by 9-fold in females (overall 7.5-fold) among patients with cirrhosis compared with that in the control group ($p < 0.05$). Comparison based on the type of cancers in cirrhotic patients revealed an increase by 93-fold for leukemia, 33-fold for lymphoma, 31-fold for gallbladder cancers, 15.5-fold for gastric cancers, 12-fold for renal cell cancers, 10-fold for sarcomas, 9-fold for urinary bladder cancers, ~6-fold for pancreatic, laryngeal, endometrial, and lung cancers, 4-fold for prostate cancers ($p < 0.05$), 2.5-fold for colon cancers, and 1.2-fold for breast cancers ($p > 0.05$).* ***Conclusion:*** *There was an increase in the incidence of all non-hepatic cancers, primarily lymphoma and leukemia, in patients with cirrhosis.*

Key words: *Cirrhosis, non-hepatic cancers, hepatocellular carcinoma*

Giriş ve Amaç: *Sirozlu hastalarda hepatosellüler karsinom görülme sıklığının artmasının yanında bazı karaciğer dışı kanserlerin görülme sıklığı da artmaktadır. Bizim merkezimizde transplantasyon öncesi takip edilen karaciğer sirozlu hastalarda karaciğer dışı kanserlerin artıp artmadığını değerlendirdik.* ***Gereç ve Yöntem:*** *Bu retrospektif çalışmada merkezimizde takip edilen 1017 sirozlu hastadan karaciğer dışı kanser gelişen 37 hastanın verileri değerlendirildi ve kanser insidans oranları belirlendi. Bu veriler hastanemize ait kanser insidans oranları ile karşılaştırıldı.* ***Bulgular:*** *Karaciğer dışı kanserlerin görülme sıklığı kontrol grubuna göre erkeklerde 4 kat, kadınlarda 9 kat, toplamda ise 7,5 kat artmış idi ($p <0,05$). Sirozlu hastalarda kanser türlerine göre kıyaslandığında ise lösemilerde 93 kat, lenfomalarda 33 kat, safra kesesi kanserlerinde 31 kat, mide kanserlerinde 15,5 kat, renal hücreli kanserlerde 12 kat, sarkomlarda 10 kat, mesane kanserlerinde 9 kat, pankreas, larinks, endometrium ve akciğer kanserlerinde yaklaşık 6 kat, prostat kanserlerinde 4 kat ($p <0,05$), kolon kanserlerinde 2,5 kat, meme kanserlerinde ise 1,2 kat artış söz konusu idi ($p >0,05$).* ***Sonuç:*** *Sonuç olarak sirozlu hastalarda başta lenfoma ve lösemi olmak üzere bütün karaciğer dışı kanserlerin görülme sıklığı önemli oranda artmış olarak bulundu.*

Anahtar kelimeler: *Siroz, hepatosellüler karsinom, karaciğer dışı kanserler*

INTRODUCTION

Cirrhosis is defined as the late phase of progressive liver fibrosis that is characterized by an impaired architecture of the liver and the development of regenerative nodules (1). The risk of developing hepatocellular carcinoma (HCC) is increased in cirrhotic patients so as the incidence of non-hepatic cancers (NHC). Berman et al. investigated hepatic and non-hepatic cancers in a cohort of 952 cirrhotic patients and found that 1, 3 and 5-years incidence rates were 1.2%, 4.4%, and 7.8% for HCC and 2.2%, 4.5%, and 6.8% for NHC. The most prevalent NHC were breast cancer, lung cancer, and lymphoma (3). Kalaitzakis et al. conducted a study in 1019 cirrhotic patients and found that the incidence of cholangiocarcinoma was 13-folds, esophagus cancer was 8-folds, pancreatic cancer was 5-folds, colorectal and lung cancers were 4-folds higher in cirrhotic patients compared to the normal population (4). The risk of developing cancer in cirrhotic patients is due to changes in hormonal levels, decreased metabolism of carcinogens, and alterations in the immune response. In our study, we evaluated data on NHC detected in patients with cirrhosis of various etiologies. We aimed to investigate whether the incidence of NHC is increased or not in cirrhotic patients compared to cancers in noncirrhotic patients in Turkey.

MATERIALS and METHODS

This study was approved by the research council and ethics committee of the Ankara Başkent University of Medical and Health Sciences (Project no: KA12/ 52). In this

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Manuscript: 09.11.2018 · **Accepted:** 17.12.2018

DOI: 10.17941/agd.501918

study, we included retrospective data of patients older than 18 years admitted to the Ankara hospital, Baskent University from January 1995 to November 2011. We obtained archived data of 1076 cirrhotic patients. Etiology of cirrhosis, Child stage, the age of diagnosis, follow-up duration, NHC site, and concomitant HCC were recorded. Cirrhotic patients who underwent transplantation and later developed NHC were excluded. Since we intended to assess if the incidence of NHC increased in cirrhotic patients, we created a control group. We evaluated the data of patients diagnosed with cancer and reported to the Turkish Association of Cancer Research. From this list of patients, we included those over the age of 18 years, admitted to our hospital in 2005, and were noncirrhotic. Using this data, we calculated the incidence rates for all relevant types of cancer in our hospital. In addition, we compared these incidence rates with the incidence rates of cancers detected in cirrhotic patients. We used SPSS for Windows 15.0 (Microsoft, Washington, USA) for the statistical analyses. Data were presented as numbers, percentages, incidence, and comparisons.

RESULTS

The present study evaluated retrospective data of 1076 patients: 689 males (64%) and 387 females (36%), between 18 and 90 years old that were admitted to our hospital from 1995 to 2011. NHC was detected in 37 patients: 24 males (64.9%) and 13 females (35.1%).

In the control group, we obtained the data of 516 patients (306 males and 210 females) diagnosed with various types of cancer out of a total of 90380 patients (33750 males and 56630 females) admitted to our hospital in 2005. The incidence of developing cancer among these patients was 0.90% for males and 0.37% for females with an overall mean incidence of 0.57%. The mean age of cancer development in the control group was 57.5±18.7 (18-92) years.

The mean age of cirrhotic patients was 60.9±15.5 (19-91) years. The mean age of 37 cirrhotic patients diagnosed with NHC was 63.0±13.7 (26-91) years. The difference in the mean age between the cirrhotic patients developing NHC and the control group patient developing cancer was statistically insignificant ($p > 0.05$). The follow-up duration ranged from 1 to 30 years with a mean follow-up period of 6.4 years. The time of NHC development after the diagnosis of cirrhosis ranged from 1 to 16 years with a mean time of 3.2 years.

Distribution of cirrhotic patients with NHC according to the Child stage was as follows: Child A 35.2%, Child B 37.8%, and Child C 27%. Of the patients with NHC, 26% and 21% were infected with HBV and HCV, respectively. The total prevalence of cirrhotic patients with a viral etiology was 47%.

The distribution of etiologic factors in cirrhotic patients with NHC is shown in Figure 1.

The incidence of developing any kind of cancer (excluding HCC) among cirrhotic patients was 3.4% for males and 3.3% for females with a total incidence of 3.4%. Concomitant HCC was present in only 2 out of 37 pa-

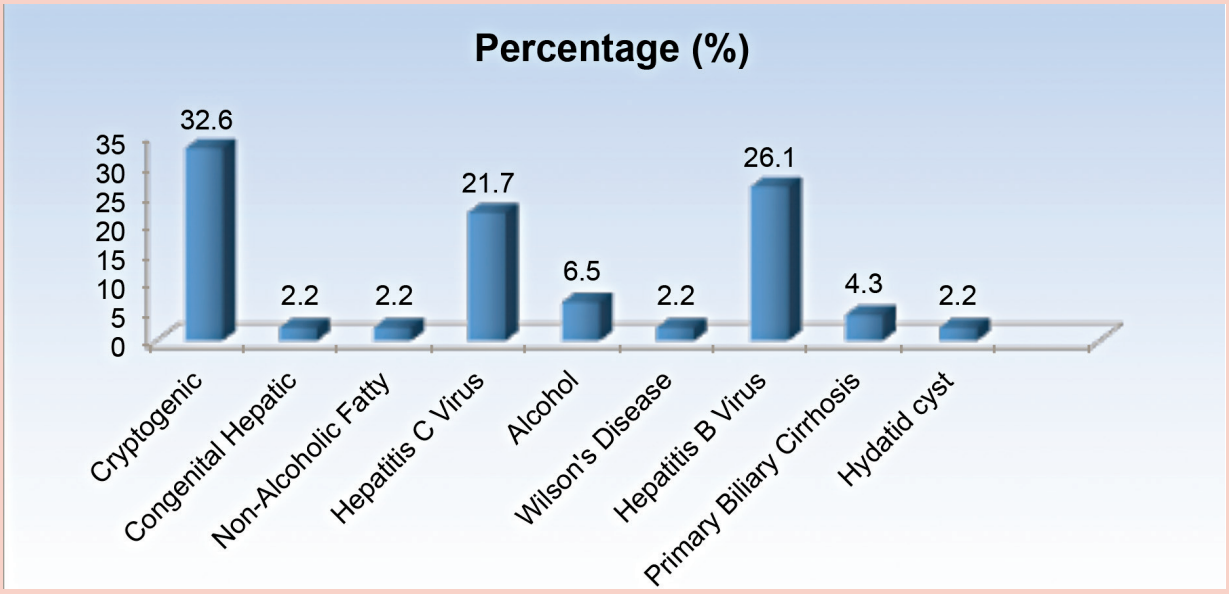

Figure 1. Number and type of factors in cirrhotic patients where NHC was detected.

tients with NHC. One patient had renal cell carcinoma and the other had prostate carcinoma. In these 37 patients, hematological cancers accounted for 27%, gastrointestinal cancers accounted for 24.3%, genitourinary cancers accounted for 24.3%, and thoracic-breast cancers accounted for 10%. In patients with NHC, the incidence of leukemia was 16.2%, gastric cancer was 13.5%, and lymphoma was 10.8%. Lung cancer, bladder cancer, renal cell carcinoma, and prostate cancer was 8.1%. Pancreas cancer and gallbladder cancer was 2.7%.

When comparing cirrhotic patients with the control group in terms of NHC incidence rates according to the region of cancer, an increase of 5-folds was found in head-neck cancers, 4-folds in thorax-breast cancers, 6-folds in GI cancers, 63-folds in hematological cancers, 5-folds in genitourinary cancers, 3-folds in gynecological cancers, 6-folds in skin cancers, and 21-folds in musculoskeletal cancers ($p < 0.05$). The overall increase in the incidence rates was 4-folds in males and 9-folds in females with a mean overall incidence rate of 7.5-fold ($p < 0.05$). When comparing groups according to the cancer type, an increase by 93-folds was observed in leukemia; 33-folds in lymphomas; 31-folds in gallbladder cancers; 15.5-folds in gastric cancers; 12-folds in renal cell carcinomas;10-folds in sarcomas; 9-folds in bladder carcinomas; 6-folds in pancreas, larynx, endometrium, and lung carcinomas; 4-folds in prostate carcinoma ($p < 0.05$); 2.5-folds in colon carcinomas ($p = 0.085$); and 1.2-fold in breast carcinomas ($p = 0.428$). The increase fold in colon and breast cancer was not statistically significant. The differences between cirrhotic patients and the control group are shown in Figures 2 and 3 according to the cancer type and body region.

While the number of cases was adequate when the cancers were classified according to the groups, we should bear in mind that the number of cases was inadequate in the subgroups regarding the type of cancer.

DISCUSSION

In cirrhotic patients, besides the higher incidence of HCC, the incidence of NHC is also increased. It is not clear whether cirrhosis itself or exposure to the etiological factor of cirrhosis or the hormonal and metabolic changes

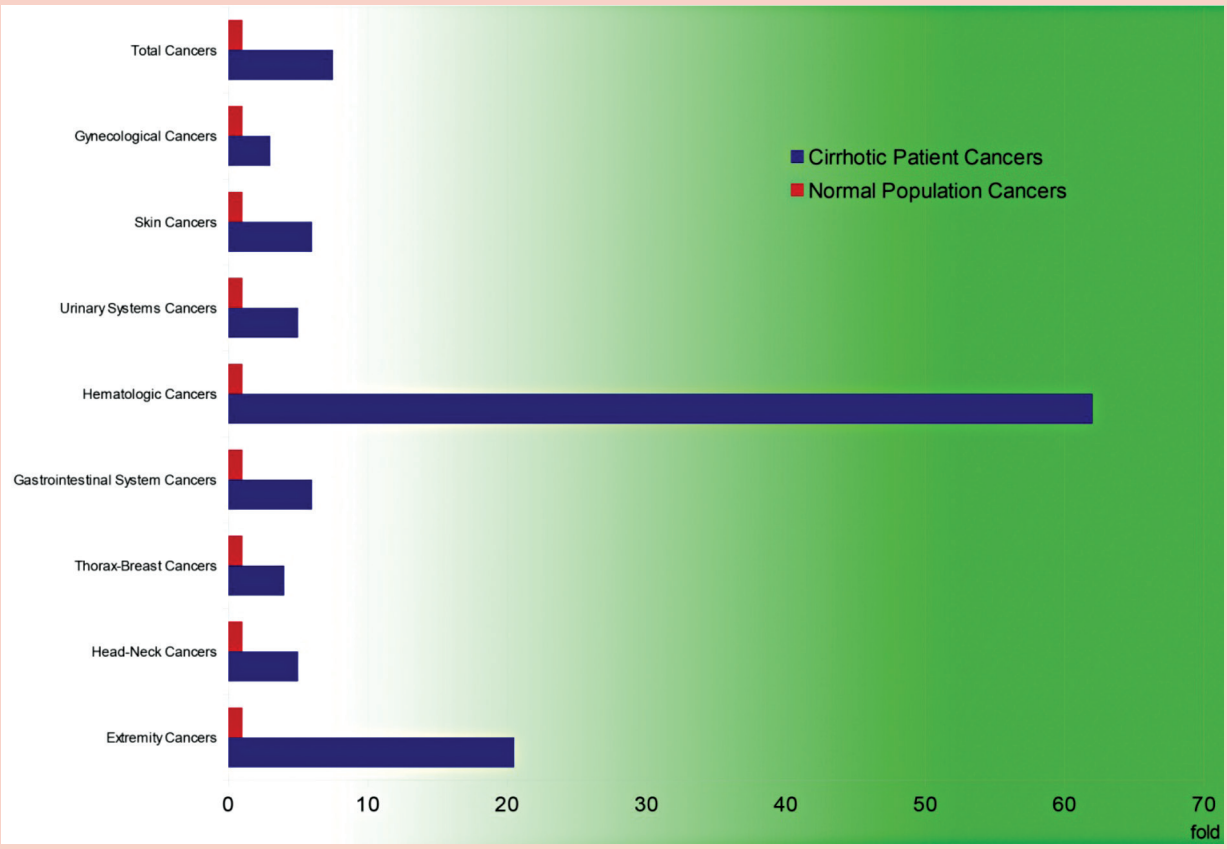

Figure 2. Comparative results of the non-hepatic cancers in cirrhotic patients and the control group according to the body region.

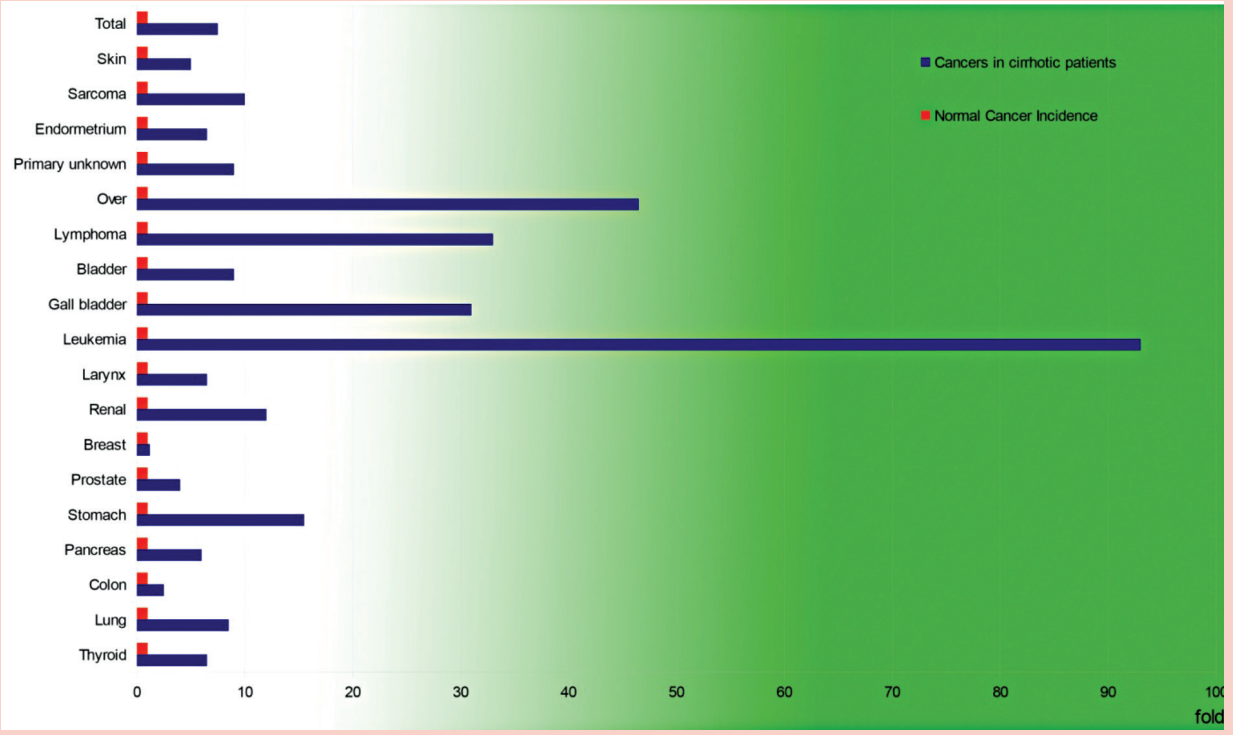

Figure 3. Comparative results of NHC developing in cirrhotic patients and the control group according to the type of cancer.

due to cirrhosis plays the main role in this oncogenesis process. Sorensen et al. conducted a study in cirrhotic patients in Denmark and determined a 25-fold increase in the risk of HCC, whereas the risk of cholangiocarcinoma increased by 10-folds. A mild elevation was found in lung, larynx, pharynx, oral cavity, pancreas, bladder, and renal cancers in alcoholic cirrhotic patients, which were related to alcohol and tobacco consumption (7).

In the present study, there was an overall mean of 7.5-folds increase in the risk of NHC with a 4-fold increase in males and 9-folds increase in females. This was consistent with the literature data. However, female/male distribution was not specified in previous studies, it is difficult to explain the 2-fold risk increment that we found in females. This could be due to the female ratio of approximately 1/3 and male ratio of 2/3 in the 1076 cirrhotic patients we analyzed. The high risk of developing cancer in cirrhotic female patients could also be related to hormonal level changes.

Considering affinity of the virus to hematopoietic cells, it can be stated that HBV might have a role in the pathogenesis of some hematological malignancies developed in patients with HBV-related hepatitis and cirrhosis (9). Considering the probable role of HBV in the development of lymphoma, it is important to know that the virus infects hematopoietic and lymphoid cells and is replicated thereafter. Moreover, the presence of HBV nucleic acids was demonstrated during acute infections in tissues such as lymph node, spleen, gonads, thyroid gland, kidney, pancreas, and adrenal gland (10,11). HBV binds to mononuclear cells (12) and may infect hematopoietic cells and their precursors (13,14). Hepatitis B virus-deoxyribonucleic acid (HBV-DNA) was detected in all major subgroups of mononuclear cells in peripheral blood during acute and chronic HBV infections (15,16). Hepatitis B surface antigen (HBs Ag) and Hepatitis B core antigen (HBc Ag) have been detected in the precursors of mononuclear cells in the blood (17,18). These findings reveal that the lymphoid system is an important reservoir for HBV (19). Although the relation between HBV and non-Hodgkin lymphoma (NHL) has not been investigated as well as in HCV, the majority of studies demonstrated a positive correlation between HBV infection and NHL.

HCV alone or together with other factors (infection, environmental, and genetics) may trigger immunological changes. Viral antigens may produce a chronic stimulus in the immune system by molecular imitation or changing autoantibodies. Lymphotropic characteristics of HCV may explain the relationship between the virus and some immune-lymphoproliferative diseases. The presence of

circulating immune complexes and antibodies may explain the autoimmune findings that are frequently encountered in monoclonal gammopathies, such as chronic lymphocytic leukemia and low-grade NHL. In 1994 an Italian study detected HCV, which is replicated in serum and peripheral lymphocytes, in one-third of the patients with B-cell lymphoma of various grades (22,23). This finding was of great significance since the prevalence of HCV infection was two times higher in HL (3%) when compared to normal healthy population (1.5%). The presence of HCV genomic sequences was detected in serum and neoplastic tissues (bone marrow and lymph node) both in idiopathic B-cell lymphomas and HCV-related malignant lymphomas (24-26). Similar outcomes were reported in other European countries (27-29) and Japan (30,31). Since HCV infection often becomes chronic and remains latent in the lymphocytes, it might play a role in the development of lymphoma.

In the comparison of cirrhosis patients and the control group, an increase in the incidence of all types of cancers was observed; however, the increase in the incidence of hematological cancers was the highest. This was consistent with an increased incidence of lympho-hematological cancers in cirrhotic patients reported in the literature. Out of 10 patients with hematological cancer, 5 had multiple myeloma, 4 had lymphoma, and 1 had leukemia. Interestingly, none of these patients had HBV-related cirrhosis, whereas 3 had HCV-related cirrhosis, 5 had cryptogenic cirrhosis, 1 had alcoholic cirrhosis, and 1 had cirrhosis secondary to a hydatid cyst. Although the fact that HBV and HCV trigger lymphoproliferative diseases was demonstrated in several studies, the results of the present study were consistent with the studies mentioning no correlation between them. The cause of cirrhosis was HBV in 3 out of 9 patients with GI cancer, 6 patients had non-viral cirrhosis.

When comparing the groups according to the type of cancer, in previous studies the most frequent increase was in breast cancer. In our study, 1.2-folds increase in breast cancer did not attain a statistically significant level. The low number of breast cancer cases may be due to the fact that the number of women patients followed for cirrhosis is low. Increase in lymphomas and lung cancer was consistent with our findings. Similarly, the lowest increase was observed in colon cancer and was consistent with our findings. The high incidence of lympho-hematological cancers in cirrhosis patients could be verified in our study. However, we observed no direct correlation between the type of malignancy and cirrhosis of HBV or HCV origin. The increased incidence of gallbladder cancers can be attributed to viral etiologies and was consistent with cases reported in the literature. The high incidence of GI cancers was also consistent with our findings; however, we encountered no publication reporting an increase only in the incidence of gastric cancers. The etiology of cirrhosis was HBV in 2, alcohol in 1 and cryptogenic in the remaining 2 out of 5 patients with gastric cancer. In the literature, it is reported that there is a tendency of malignancies in case of chronic HBV and HCV infections, which is not contradictory to the data in our study.

The distribution of cirrhotic patients among Child stages was similar and no significant difference was determined in terms of NHC incidence. The incidence rates found in the present study are representative of a section of the patients in our hospital and the Ankara province, these findings are relevant because they expose a substantial increment in NHCs. Performing liver transplantation to appropriate patients and eradication of hepatotropic viruses might lead to a reduction in this type of cancer. It is clear that more works need to be done in this issue.

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