De Novo Breast Cancer in Patients With Liver Transplantation: University of Pittsburgh's Experience and Review of the Literature

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De novo **malignancies are one of the current problems in patients with organ transplantation. The incidence has been considered to be higher as a result of increases of oncogenic viruses in immunosuppressed organ recipients. Published reports have shown increased incidence of *de novo* tumors such as malignant lymphomas and cutaneous neoplasms but decreased incidence of breast cancer. A variety of factors affect *de novo* breast cancer development in organ recipients, including immunosuppression, viruses, and underlying disease. The aims of this review are to evaluate the incidence and management of patients with *de novo* breast cancer by giving the University of Pittsburgh's data, and to evaluate the incidence of *de novo* breast cancer in published reports in light of an age-adjusted rate. According to age-adjusted rates presented by the National Cancer Institute's Surveillance, Epidemiology and End Results data, we found increased incidence rate of *de novo* breast cancer in the previously published series. The University of Pittsburgh's incidence rate of *de novo* breast cancer was determined in a fashion similar to that for the Surveillance, Epidemiology and End Results data. Eighty-three percent of all patients were diagnosed at early stages, and it appeared to take longer for *de novo* breast cancer to develop in patients treated with tacrolimus than in patients treated with cyclosporine. In conclusion, surgical treatment of breast cancer in liver recipients is the same as treatment of breast cancer in patients without transplantation. However, the effects of chemotherapy, radiotherapy, and/or tamoxifen remain unclear in transplanted patients and need to be evaluated in larger studies. (*Liver Transpl 2004;10:1–6.*)**

De novo malignancies are considered one of the serious long-term complications of organ transplantation. McKhann first reported the increased incidence of *de novo* malignancies, an observation confirmed shortly thereafter by others.[1–4] A variety of factors are considered responsible for the development of *de novo* malignancies, such as the intensity of the immunosuppressive therapy, the type of transplant, and the use of different immunosuppressive agents. The most frequent cancers among these tumors are malignant lymphomas and cutaneous neoplasms. The observed rate of incidence of *de novo* malignancies in patients with transplantation range from 4.1% to 16% in different series.[5–8] Although decreased incidence of *de novo* breast cancers (BCs) has been reported in the transplant literature,[9,10] there are contradictory data concerning the incidence of BC in those patients compared with the overall population. Some previous studies indicate that the incidence of commonly seen tumors such as carcinoma of the breast is not increased in the transplant population.[10–12]

MEDLINE Search

Our review of published data on the incidence of de novo cancers following transplantation was based on English-language articles in the MEDLINE database. For this purpose, all published reports between 1963–2003 were searched in PubMed-based MEDLINE by using the words *de novo* cancer, transplantation, and liver, and those that presented *de novo* breast cancer were included in the study. In addition, data from the University of Pittsburgh's experience with such cancers was summarized. A 1998 report by Jain et al. has been omitted from the present summary to avoid duplicate presentation of the same BC cases.[5] Patients with recurrence of previous BC, retransplantation, multiorgan transplantation, and transplant patients under the age of 18 years were excluded. Incidence rates of BCs following transplantation were compared with age-specific incidence rates in the general U.S. population using confidence intervals (CIs) based on the Poisson probability distribution.

Abbreviations: BC, breast cancer; CI, confidence interval; Tac, tacrolimus; CsA, cyclosporine; TGF-β, transforming growth factor β; EBV, Epstein-Barr virus; HPV, human papillomavirus; NK, natural killer.

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Table 1. Published Data Regarding *De Novo* Breast Cancer in Liver Transplant Patients and the University of Pittsburgh's Experience

Reference, Year	Number of Liver Transplantations	Female	Mean Age at Transplantation	Number of *De Novo* Breast Cancers
Kelly et al., 1998[10]	888			2
Saigal et al., 2002[11]	1,140		51.5	2
Haagsma et al., 2001[13]	174	106	43	1
Jonas et al., 1997[14]	458	191	46	3
Levy et al., 1993[16]	556			1
Sanchez et al., 2002[17]	1,421		49.7	7
Catena et al., 2001[39]	353			3
Bessa et al., 1997[40]	340			2
Total	5,330		48.6	21
University of Pittsburgh's experience		1,337	52.2	7

Incidence Rates in Published Literature

In the literature, we found 21 *de novo* BCs among 5,330 liver transplant recipients (Tables 1 and 2). The mean age of nine *de novo* BC patients was 54.5 years at diagnosis of cancer.[10,11,13,14,16] The mean age of 13 BC patients was 48.6 years at transplantation.[11,13,14,17] The interval between transplantation and diagnosis of *de novo* BC was available for eight out of the 21 patients in the literature, and the mean interval was 58.9 months (range, 3 months–13 years). Two reports out of eight articles presented the number of female patients.[13,14] Four *de novo* BCs were reported among 297 female patients (1.34 %), and the mean age of these four patients was 52.2 years.

In previously published data, the authors compared the incidence of *de novo* cancer with incidence rates of

Table 2. Data Showing Stage, Treatment, and Outcome of *De Novo* Breast Cancer in the Liver Transplant Recipient

Reference, Year	Stage	Age* (yr)	MI (mo)	Treatment	Ca survi (mo)	Tcr/CsA
Kelly et al., 1998[10]	1	71		M		
	3	46		M + C		
Saigal et al., 2002[11]		59	78		50	CsA
		52	124		11	Tcr
Haagsma et al., 2001[13]		55	156		Died: 11 months	CsA or A
Jonas et al., 1997[14]	T2 N0	43	35	SM	8	CsA
	T1 N1	64	16	SM	26	CsA
	T4 N0	47	3	M + R + H	Recurrence: 45 months	CsA
Levy et al., 1993[16]		54	16	M	54	CsA
Sanchez et al., 2002[17]			43.8		5-year survival: 83%	CsA
Total		54.5	58.9			
University of Pittsburgh's experience	Tis	50.7	40	SM	62.5	
	T1 N0 M0	60.2	40.6	SM + T	84.9	
	T1 N0 M0	63.1	97	SM + C	35.9	
	T1 N0 M0	41.2	43.6	SM + AD	84.6	All Tcr
	T2 N0 M0	50.2	89.4	TM + C	68.7	
	T1 N0 M0	69.5	51.9	TM + AT	9.6	
	T1 N0 M0	61.1	13.0	SM + T	15.0	
Total		56.6	53.6		51.6	

*Mean age at diagnosis of breast cancer.
Abbreviations: MI, mean interval between transplantation and diagnosis of breast cancer; Ca survi, survival of patient with *de novo* breast cancer; Tcr, tacrolimus; CsA, cyclosporine; A, azithioprine; M, mastectomy; C, chemotherapy; SM, segmental mastectomy; R, radiotherapy; H, hormonotherapy; T, tamoxifen; Tis, carcinoma in situ; AD, axillary dissection; TM, total mastectomy.

Table 3. Breast Cancer Incidence: Comparing Three Different Transplantation Populations With General Population

Reference	*De Novo* Breast Cancer/ Total Number of Transplantations	Mean Age (yr)	Study's 95% Confidence Interval	Age-Specific Incidence, 1994–1998
University of Pittsburgh	7/1,337	56.6	210.5–1,078.7	327.2 (white) 289.0 (black)
Haagsma[13] Jonas[14]	4/297	52.8	546.6–3,928.3	277.8 (white) 253.8 (black)

BC in the overall population.[11,14] However, we believe that it would be more appropriate to make this comparison with age taken into account. When we evaluated *de novo* BC incidence with respect to the age-specific incidence rate presented by the National Cancer Institute's Surveillance, Epidemiology and End Results data, we found similar or increased incidence of *de novo* BC among transplant patients.[15] In two studies, while the presented incidence was 4 (1.34%) out of 297 female patients[13,14] whose mean age was 52.2, the expected incidence rate was 0.75 (0.25%) among patients 50–54 years of age, according to Surveillance, Epidemiology and End Results data (Table 1). To determine the incidence among transplant patients and compare it with the age-specific incidence rate in the United States between 1994 and 1998, we evaluated two patient groups separately (Table 3). Group 1 represents the University of Pittsburgh's experience, and group 2 represents two different published studies that evaluated *de novo* BC in female patients with liver transplantation (Tables 1 and 2). In the University of Pittsburgh study, the rate was 0.52%, or 523.5 per 100,000, which is comparable to the rate for the general U.S. population between 55 and 59 years old. The incidence in group 2 seems to be increased with respect to the age-adjusted rates. The estimated 95% CI for group 2 is 546.6–3,928.3, which is higher than the age-specific incidence in the United States from 1994 to 1998 (277.8 whites and 253.8 blacks per 100,000/general population).[15]

Authors' Data, and University of Pittsburgh's Experience

Seven patients (0.52%)were identified retrospectively with *de novo* BC among 1,337 female patients over 18 years of age who underwent orthotopic liver transplantation between August 1989 and December 2001. These figures yield an incidence rate of 523.6 BC per 100,000 patients (95% CI = 210.5 to 1,078.7 BC per 100,000 patients). Because the 95% CI includes the incidence rate of BC in the general population (327.2 in whites and 289 in blacks per 100,000), there is no statistically significant difference between the rates among the Pittsburgh patients and the general population.

The mean age of seven patients was 52.2 years at transplantation and 56.6 years at diagnosis of BC. The mean interval between transplantation and diagnosis of *de novo* BC was 53.6 months. Six of the seven BC cases were diagnosed in stage 1; the seventh was an in situ carcinoma. Five cancers were invasive ductal carcinoma, one was ductal carcinoma in situ, and one was invasive lobular carcinoma. All BC patients underwent surgery and were alive at last follow-up with a mean of 51.6 months. Five patients have survived to more than 5 years, and two were still alive 10 and 15 months after surgery.

Stage, Treatment and Survival

Among 12 BC patients, five whose stages were presented in the literature and seven from the University of Pittsburgh, seven were in stage I, two in stage IIA, two in stage III, and one in stage 0 (Table 2).[10,14] One of the stage III patients had no lymph node or distant metastases (T4 N0 M0). Most (83%) patients were diagnosed at early stages, probably due to closer screening of patients with liver transplantation.

Thirteen BC patients, seven of them in the University of Pittsburgh's experience and six whose therapy was reported in the literature,[10,14,16] underwent surgical therapy. Segmental mastectomy was done in six of these patients. Three patients received chemotherapy, four patients received radiotherapy, and four received hormonotherapy (Table 2). Breast-conserving surgery was achieved in half of the patients (six out of 13). Unfortunately, limited data are available in the organ transplantation literature concerning treatments with chemotherapy and/or radiotherapy and/or use of tamoxifen in BC patients.

The mean interval between transplantation and diagnosis of *de novo* BC was longer for patients who used tacrolimus (Tcr) for immunosuppression than for those who used cyclosporine (CsA). In Pittsburgh's experience, all patients received Tcr and had 53.6 months mean interval for BC diagnosis, which seems longer than the mean interval for patients using CsA (33.7 months in four published reports.[11,14,16,17]

Discussion

De Novo *BC and Immunosuppression*

The immunosuppressive agents most commonly used by the reviewed patients were CsA and Tcr. CsA was used until 1995. Since that year, Tcr has been used for immunosuppression as a first step. CsA and Tcr are produced by fungus species. Although their chemical structures are different, both have similar mechanisms for inhibiting the nuclear factor responsible for activation of IL2 transcription. Thus both inhibit IL-2 gene expression, and the production and generation of cytotoxic cells. It is believed that CsA enhances the risk for carcinogenesis in an autonomous fashion, which is mediated by transforming growth factor β (TGF-β). Although CsA and Tcr both increase TGF-β transcription rates, comparative studies show that the effect is stronger for CsA.[5,18] Azathioprine, the first immunosuppressive agent used in organ transplantation, effectively prevents rejection by inhibiting DNA synthesis as a maintenance agent. However, it has no value as a rescue or induction agent.[19] Mycophenolate mofetil blocks the proliferative response both T and B lymphocytes, inhibits antibody formation, and prevents the generation of cytotoxic T cells.[19]

The relationship between immunosuppressive therapy and the increase of oncogenic viruses have been reported in previous studies. Kelly et al. suggested that immunosuppression leads to increased risk of malignancy because of replication of oncogenic viruses such as Epstein-Barr virus (EBV), herpes simplex 1 and 2, human papillomaviruses (HPV), disturbances of immunity through depression of natural killer (NK) cell activity, chronic antigenic stimulation, impaired immunoregulation, and decreased production of interferon.[10] In the 25th Annual San Antonio Breast Cancer Symposium, two studies showed the importance of mouse mammary-tumor virus-related agent on human mammary carcinogenesis. The authors reported that HPV16 DNA was detected in 26% of core-biopsy proven BC patients with no history of known HPV exposure.[20–22]

Grinstein et al. reported that they found EBV in tissue with typical, atypical ductal and lobular proliferations, and in situ carcinomas. They suggested that EBV may play an oncogenic role in the development of BC.[23] Bonnet et al. showed a positive relationship between EBV infection and hormone-receptor negative tumors, which behave more aggressively than hormone-receptor positive tumor.[24] Labreque et al. also demonstrated the presence of EBV in BC, but found no association between EBV and the histological type of tumor.[25] Desphande et al. analyzed the expression of LMP2A, a membrane protein of EBV, in breast cells but failed to detect expression of any of the EBV viral gene products and suggested that surrogate markers for the identification of cellular- or cytokine-related immune response would be necessary for identifying EBV association with BC.[26] Kleer et al. detected EBV latent membrane protein 1 (LMP1) by immunohistochemical staining and EBV DNA by polymerase chain reaction in 45% (9/20) of fibroadenomas in patients with previous organ transplantation, compared with 0% in the nonimmunocompromised control group.[27] They suggested that EBV infection is specifically localized to epithelial cells. More recently, Murray et al. detected EBV DNA in 19 out of 92 breast tumors.[28] They suggested that the EBV genome is strongly associated with estrogen-receptor (ER)-negative tumors. Among the seven BC patients in University of Pittsburgh's experience,e invasive ductal carcinoma was predominant as in the general population. This tendency may be related to the EBV found in the ductal tissue with ductal proliferation as presented in previous published data.[23]

Stewart et al. suggested that NK cells, a subpopulation of lymphocytes, might act against tumor cells.[29] Jonas et al. showed increased NK cell activity in patients with *de novo* cancer.[14] Pros et al. revealed that NK cell activity could be increased by viral stimulation.[30] It has been shown that NK cell activity is suppressed by alcohol in murine models.[31] Alcohol is also considered to be responsible for the development of *de novo* carcinogenesis. Saigal et al. suggested that a suppressive effect of alcohol on NK cells could promote tumorigenesis.[11] Although NK cells have a role in immunosurveillance, the role of these cells in the development of *de novo* BC and the relationship between NK cells and oncogenic viruses and the immune response against oncogenic viruses remain unclear.

It is possible that *de novo* BC is in part a result of immunosuppression following transplantation, but imunosuppression is not the only factor influencing the development of *de novo* cancer. Chronic kidney failure,

underlying disease before transplantation, early menarche, family history, late menopause, parity, hormone replacement therapy, and long-term exposure to estrogen are also believed to contribute to the development of *de novo* BC. Previous reports have shown the increased estrogen levels in patients with chronic liver disease to be parallel to the expectation of elevated estrogen level as estrogen is metabolized in the liver.[32–35] Becker et al. and Josanni et al. reported elevated estrone and estradiol levels in cirrhotic postmenopausal women.[33,34] Gluud et al. showed that the ratio of estrogen to testosterone increases with declining liver function.[35] Shaaban et al. also reported increased estrogen levels in the patients with chronic liver disease.[36] Long-term exposure to the high levels of estrogen seen in the patients with chronic liver disease may be linked to the increased risk of development of *de novo* breast cancer. The effect of estrogen on the development of *de novo* BC is one possible explanation. However, supporting evidence is difficult to find, perhaps because information about estrogen levels in these patients are not available. Clearly, the development of *de novo* BC needs to be studied in light of many factors.

Underlying disease such as alcoholic cirrhosis has also been responsible for development of *de novo* cancer. Some data suggest a synergistic effect between alcohol and estrogen on the risk of BC.[37] Recently, Saigal showed increased incidence of *de novo* malignancies in patients who underwent transplantation for alcoholic cirrhosis, but no report was found addressing this relationship on development of *de novo* BC.[11] A possible association between primary biliary cirrhosis and BC was previously reported by Wolke et al.[38] In the University of Pittsburgh's experience, three (43%) patients with HCV and two (28%) patients with postnecrotic cirrhosis among *de novo* BC cases (N = 7) were found, and hepatitis accounted for 71% of underlying disease. In contrast to University of Pittsburgh's experience, Kelly reported that *de novo* BC was seen less in HCV patients.[10]

If immunosuppressive treatment enhances BC, it is interesting to ask whether the use of immunosupressive drugs should be reduced. In addition, it would be useful to know whether *de novo* BC would be affected by the type of therapy. However, previous studies have shown no differences among immunosuppressive drugs. Jonas has emphasized that the development of *de novo* cancer is related to immunosupressive protocols such as CsA- or Tcr-based treatment.[14] It has been suggested that immunosuppression dosage be reduced in these patients to the lowest possible level after tumor diagnosis.[9] Because longer exposure to immunosuppressive drugs and the intensity of immunosuppression have been shown to increase development of *de novo* carcinogenesis, this suggestion seems logical.

In conclusion, we found similar *de novo* BC incidence among patients who underwent previous organ transplantation and in the age-matched general population data from the National Cancer Institute's Surveillance, Epidemiology and End Results. This finding contradicts previous reports emphasizing the decrease of BC in transplant patients. Ten out of 12 patients (83%) were diagnosed at early stages, it appeared to take longer for *de novo* breast cancer to develop in patients treated with Tcr than in those treated with CsA. Surgical treatment of BC in liver transplant patients was similar to treatment among patients without previous liver transplantation. Because the age-specific incidence (after 50 years old) is similar to that of the general population, it is worthwhile for patients to obtain a yearly mammography after age 40 to detect breast cancer in an early stage. To make a suggestion about the effects of chemotherapy, radiotherapy and/or tamoxifen in liver transplant patients with breast cancer, larger studies should be done.

References

1. McKhann CF, Jagarlamoody SM. Immunotherapy of cancer-current status. Geriatrics 1970;25:155–160.
2. Murray JE, Wilson RE, Tilney NL, Merrill JP, Cooper WC, Birtch AC, et al. Five years experience in renal transplantation with immunosuppressive drugs: Survival, function, complications, and the role of lymphocytes depletion by thoracic duct fistula. Ann Surg 1968;168:416.
3. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. Transplant Proc 1969; 1:106–112.
4. Starzl TE. Experiences in Hepatic Transplantation. Philadelphia: W.B.Saunders; 1969:348.
5. Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. Transplantation 1998;66:1193–1200.
6. Fung JJ, Jain A, Kwak EJ, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: A major cause of late death. Liver Transplantation 2001;7(suppl 1):109–118.
7. Penn I. Occurrence of cancers in immunosuppressed organ transplant reciepients. In: Terasaki P, Cecka M,eds. Clinical Transplantation. Los Angeles: UCLA, 1990:53–62.
8. Penn I. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant 1993;12(suppl):328–336.
9. Penn I. The problem of cancer in organ transplant recipients. Transplant Sci 1994;4:23–32
10. Kelly DM, Emre S, Guy SR, Miller CM, Schwartz ME, Sheiner PA. Liver transplant recipients are not at increased risk for non-lymphoid solid organ tumors. Cancer 1998;83:1237–1243.
11. Saigal S, Norris S, Muiesan P, Rela M, Heaton N, O'Grady N.

Evidence of differential risk for posttransplantation malignancy on pretansplantation cause in patients undergoing liver transplantation. Liver Transpl 2002;8:482–897.
12. Penn I. Post-transplant malignancy: the role of immunosuppression. Drug Saf 2000;23:101–103.
13. Haagsma E, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, et al. Increased cancer risk after liver transplantation: A population-based study. J Hepatol 2001;34: 84–91.
14. Jonas S, Rayes N, Neuman U, Neuhaus R, Bechtein WO, Guckelberger O, et al. De novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. Cancer 1997;80:1141–1150.
15. Reis LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK (eds.). SEER Cancer Statitics Review, 1973–1998, National Cancer Institute, Bethesda, MD. 2001.
16. Levy M, Backman L, Husberg B, Goldstein R, McMillan R, Gibbs J, et al. De novo malignancy following liver transplantation: A single center study. Transplant Proc 1993;25:1397–1399.
17. Sanchez EQ, Marubashi S, Jung G, Levy MF, Goldstein RM, Molmenti EP, et al. De novo tumors after liver transplantation: A single-institution experience. Liver Transpl 2002;8:285–291.
18. Mohammed MA, Robertson H, Booth TA, Balupuri S, Kirby JA, Talbot D. TGF-beta expression in renal transplant biopsies: A comparative study between cyclosporin-A and tacrolimus. Transplantation 2000;69:614–619.
19. Kirk AD, Sollinger HW. Transplant immunology and immunosuppression. In: SI Schwartz, eds. Principles of Surgery. Vol 1. 7th ed. New York: McGraw-Hill; 1999:362–380.
20. Lushnikova AA, Makhov PB, Kryukova IN, et al. MMTV-related sequence expression in human mammary carcinoma. Breast Cancer Res Treat 2002;76(suppl 1):168.
21. Levine PH, Coronel SM, Pogo BG-T, et al. Increasing evidence a for human breast cancer virus. Breast Cancer Res Treat 2002; 76(suppl 1):168.
22. Damin APS, Alexandre COP, Karam R, et al. Human papillomavirus (HPV) DNA detection by polymerase chain reaction (PCR) in BC: Preliminary results. Breast Cancer Res Treat 2002; 76(suppl 1):169.
23. Grinstein S, Preciado MV, Gattuso P, Chabay PA, Warren WH, De Matteo E, et al. Demonstration of Epstein-Barr virus in carcinomas of various sites. Cancer Res 2002;62:4876–4878.
24. Bonnet M, Guinebretiere J, Kremmer E, Grunewald V, Benhamou E, Contesso G. Detection of Epstein Barr virus in invasive breast cancers. J Natl Cancer Inst 1999;91:1376–1381.
25. Labrecque LG, Barnes DM, Fentiman IS, Griffin BM. Epstein Barr virus epithelial cell tumors: A BC study. Cancer Res 1995; 55:39–45.
26. Deshpande CG, Badve S, Kidwai N, Longnecker R. Lack of expression of the Epstein-Barr Virus (EBV) gene products, EBERs, EBNA1, LMP1, and LMP2A, in BC cells. Lab Invest 2002;82:1193–1199.
27. Kleer CG, Tseng MD, Gutsch DE, Rochford RA, Wu Z, Joynt LK, et al. Detection of Epstein-Barr virus in rapidly growing fibroadenomas of the breast in immunosuppressed host. Mod Pathol 2002 Jul;15:759–764.
28. Murray PG, Lissauer D, Junying J, Davies G, Moore S, Bell A, et al. Reactivity with a monoclonal antibody to Epstein-Barr virus (EBV) nuclear antigen 1 defines a subset of aggressive breast cancers in the absence of the EBV genome. Cancer Res 2003;63: 2338–2343.
29. Stewart T, Tsai S-C J, Grayson H, Henderson R, Opelz G. Incidence of de novo BC in women chronically immunosuppressed after organ transplantation. Lancet 1995;346:796–798.
30. Pros HF, Sterns E, MacGillis DR. Natural killer cell activity in women at 'high risk' for breast cancer, with and without benign breast syndrome. Int J Cancer 1984;34:303–308.
31. Ben-Eliyahu S, Page GG, Yirmiya R, Taylor AN. Acute alcohol intoxication suppresses natural killer cell activity and promotes tumor metastasis. Nat Med 1996;2:457–460.
32. Matti V, Risto P, Mikko S, Matti H, Erkki H, Reino Y. Sex hormones in amenorrheic women with alcoholic disease. J Clin Endocrinol Metab 1984;59:133–137.
33. Becker U, Gluud C, Farholt S, Bennett P, Micic S, Svenstrup B, et al. Menopausal age and sex hormones in postmenopausal women with alcoholic and non-alcoholic liver disease. J Hepatol 1991;13:25–32.
34. Jasonni VM, Bulletti C, Bolelli GF, Franceschetti F, Bonavia M, Ciotti P, et al. Estrone sulfate, estrone and estradiol concentrations in normal and cirrhotic postmenopausal women. Steroids 1983;41:569–573.
35. Gluud C, and the Copenhagen Study Group for Liver Disease. Serum testosterone concentrations in men with alcoholic cirrhosis: Background for variation. Metabolism 1987;35:373–378.
36. Shaaban MM, Ghaneimah SA, Hammad WA, El-Sharkawy MM, Elwan SI, Ahmed YA. Sex steroids in women with liver cirrhosis. Int J Gynaecol Obstet 1980;18:181–184.
37. Colditz GA, Stampfer MJ, Willet WC. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenapausal women. JAMA 1990;264:2648–2653.
38. Wolke AM, Schaffner F, Kapelman B, Sacks HS. Malignancy in primary biliary cirrhosis: High incidence of breast cancer in affected women. Am J Med 1984;76:1075–1078.
39. Catena F, Nardo B, Liviano d'Arcangelo G, Stefoni S, Arpesella G, Faenza A, Cavallari A. De novo malignancies after organ transplantation. Transplant Proc 2001;33:1858–1859.
40. Bessa X, Andreu H, Cirera I, Rimola A, Navasa M, Grande L, et al. De novo tumors in adult patients with hepatic transplant. Gastroenterol Hepatol 1997;20:442–445.