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BRIEF ARTICLE

Is chronic hepatitis C virus infection a risk factor for breast cancer?

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Abstract

AIM: To evaluate the prevalence of breast tumors in adult females with chronic hepatitis C virus (HCV) infection.

METHODS: Prospective, single-center study, based on female outpatients consulting in a liver unit, for 1 year. The study group included females with present and/or past history of chronic infection by HCV. Patients with spontaneous recovery were excluded. Chronic hepatitis had been proved by liver biopsy in the majority of cases and/or biological markers of inflammation and fibrosis. The control group included female patients with other well documented chronic liver diseases: chronic hepatitis B, alcoholic liver disease, autoimmune hepatitis, hemochromatosis, non alcoholic liver disease, chronic cholangitis. Participating patients were prospectively questioned during consultation about past breast history and follow-up by mammography.

RESULTS: Breast carcinoma was recorded in 17/294 patients with HCV infection (5.8%, 95% CI: 3.1-8.4) *vs* 5/107 control patients (4.7%, 95% CI: 0.67-8.67). Benign tumors of the breast (mastosis, nodules, cysts) were recorded in 75/294 patients with HCV infection (25.5%, 95% CI: 20.5-30.5) *vs* 21/107 (19.6%, 95% CI: 12.1-27.1) in the control group. No lesion was noted in 202 patients with HCV (68.7%, 95% CI: 63.4-74) *vs* 81 control patients (75.7%, 95% CI: 67.6-83.8). Despite a trend to an increased prevalence in the group with HCV infection, the difference was not significant compared to the control group (P = NS). In patients over 40 years, the results were, respectively, as follows: breast cancer associated with HCV: 17/266 patients (6.3%, 95% CI: 3.4-9.3) *vs* 5/95 patients (5.2%, 95% CI: 0.7-9.7) in the control group; benign breast tumors: 72/266 patients with HCV infection (27%, 95% CI: 21.7-32.4) *vs* 18/95 patients (18.9%, 95% CI: 11-26.8) in the control group; no breast lesion 177/266 (66.5%, 95% CI: 60.9-72.2) in patients with HCV infection *vs* 72/95 (75.7%, 95% CI: 67.1-84.4) in the control group. The differences were not significant (P = NS).

CONCLUSION: These results suggest that chronic HCV infection is not a strong promoter of breast carcinoma in adult females of any age.

Key words: Breast tumors; Breast cancer; Hepatitis C virus infection; Risk factor

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INTRODUCTION

Several viruses have been involved in the occurrence of cancers[1]. For instance, human papilloma virus has been directly implicated in uterus cancer; poliomavirus in mesothelioma and brain tumors; Epstein-Barr virus in B-cell lymphoproliferative disease and nasopharyngeal carcinoma; herpes virus in Kaposi sarcoma[1]. Hepatitis C virus (HCV) is well-known to cause chronic hepatitis, cirrhosis and hepatocarcinoma[2-5]. The prevalence of HCV in France, as in other Western European countries, is around 1% and is estimated to be 1.6% in the United States[6-8]. The potential link between HCV infection and the risk of developing malignancy other than hepatocarcinoma has been recently raised in several studies[9-13]. There are several lines of evidence showing a role in the occurrence in non-Hodgkin lymphoma and lymphoproliferative diseases[9,10]. Recent studies argue for an increasing risk of intra-hepatic cholangiocarcinoma[11] and thyroid cancer[12]. The prevalence of HCV has been evaluated in elderly patients with tumors different from hepatocarcinoma and non-Hodgkin lymphoma (colorectal, prostate, breast, bladder, kidney)[13]. Among 236 patients, 87 (36%) were positive for HCV, a higher prevalence than in the patients of the control group (10%)[13]. A statistically significant difference was observed with kidney cancer, prostate cancer, and bladder cancer[13]. Finally, the link between hepatocarcinoma and another tumor has been assessed in a retrospective study including 37 patients[14]. Five patients (13.5%) had developed another primary cancer before or after hepatocarcinoma: kidney cancer, breast cancer, colorectal cancer, prostate cancer, or lymphoma. A common point between these 5 patients was HCV chronic infection. This suggested that HCV chronic infection may not only promote hepatocarcinoma, but also other solid tumors[14].

Therefore the aim of this study was to assess the frequency of breast tumors in adult females with chronic infection by HCV and whether this disease may be a promoting factor for the onset of benign or malignant breast tumors.

MATERIALS AND METHODS

This was a prospective, single-center study performed over 1 year in female patient aged ⩾ 20 years, consulting in the Liver Unit of Montpellier School of Medicine, France, for chronic liver diseases. The study group included patients with present or past chronic infection by HCV.

Patients

Inclusions criteria: Age ⩾ 20 years, the evidence of chronic infection by HCV based on the presence of serum anti-HCV antibodies, detection of serum HCV RNA by PCR tested on several occasions for a period longer than 1 year; chronic hepatitis C proved by liver biopsy (75% of patients) or non-invasive methods (25% of patients) including biological markers of inflammation and fibrosis of the liver such as Fibrotest-Actitest® and/or elastographic examination (Fibroscan®) as recently published[15-17]; agreement of the patient for participation in the study.

Exclusion criteria: A spontaneous recovery from HCV; co-infection by hepatitis B virus or human immunodeficiency virus; absence of capacity to understand or to answer the questions in the inquiry.

The control group included females seen sequentially and prospectively during the same period and affected by chronic liver disease over 1 year, with well defined characteristics based on clinical, radiological and histological features [chronic hepatitis B, chronic alcoholic liver disease, auto-immune hepatitis, hemochromatosis, non alcoholic fatty liver disease (NAFLD), chronic cholangitis, *etc.*].

Methods

The following information was collected during the consultation by using a questionnaire: past history of breast cancer or benign breast tumor; which type if any (adenoma, mastosis, cyst); performed examinations or treatment (mammography, biopsy, surgery); potential participation in a tumor detection program by mammography. Indeed, in our geographic area, there is a detection program for breast lesions with systematic mammography every 2 years for females over 40 years.

Statistical analysis

The data processing was performed using SAS software packages version 8.1. A general descriptive analysis was done for every parameter of the study. The distribution of qualitative variables (such as breast tumors) between groups was compared using χ^2 test. When the calculated frequency of the categorical data of the contingency table did not allow the use of the χ^2 test, Fisher's exact test was performed. A P level < 0.05 was considered as significant. Stratification was performed according to age brackets: 20 to 40 years, 41 to 60 years and more than 60 years. Unilateral and bilateral power was calculated *a posteriori*.

RESULTS

Four hundred and one patients fulfilled inclusion criteria and all agreed to participate in the study. The study group with HCV infection included 294 patients; the control group included 107 patients with the following chronic liver diseases: NAFLD, 32 cases; chronic hepatitis B, 10 cases; primary biliary cirrhosis, 17 cases; auto-immune chronic hepatitis, 13 cases; chronic alcoholic liver disease, 4 cases; chronic cholangitis, 9 cases; hemochromatosis, 4 cases; and other chronic liver diseases, 18 cases.

Patients' ages ranged from 21 to 84 years (median 58 years) in the HCV group and from 23 to 84 years (median 56 years) in the control group. The distribution by age was comparable in the two groups with a predominance of patients between 40 and 70 years: 20-40 years, n = 36 (8.9%) *vs* n =

Table 1 Characteristics of the 294 patients with chronic hepatitis C

	All patients
Median age (yr)	58 (21-84)
HCV Genotype	
HCV 1	63%
HCV 2	11%
HCV 3	19%
HCV 4-5	7%
Severity of liver disease[1]	
F0-F2	70%
F3	16%
F4	14%
HCV treatment	
Never treated	30%
Past or ongoing treatment	70%

[1]The extent of fibrosis has been expressed according to the METAVIR scale as previously described[15]. HCV: Hepatitis C virus.

15 (9.7%); 41-60 years, n = 132 (33%) *vs* n = 52 (45.9%); > 60 years, n = 126 (42.8%) *vs* n = 40 (37.4%). Other main characteristics of patients with chronic HCV infection, including genotype, severity of fibrosis and anti-viral treatment history, are shown in Table 1. They are similar to the features collected in the data bank of patients with HCV infection in our regional HCV network (3280 patients)[18]. In the control group, the percentage of chronic liver diseases reaching the stage of cirrhosis (stage F4 of METAVIR scale) was 13% (14/107 cases), which was similar to the HCV group (14%) (Table 1).

The programme of mammography for patient aged over 40 years was followed in 212/266 patients (79.7%) of the HCV group and in 74/99 patients (77.8%) of the control group. In younger patients, mammography had only been performed because of symptoms, in less than 15% of patients of both groups.

The prevalence of breast tumors is shown in Table 2. Among all patients, breast cancer was recorded in 5.8% (95% CI: 3.1-8.4) of HCV group patients *vs* 4.7% (95% CI: 0.67-8.67), a benign breast tumor in 25.5% (95% CI: 20.5-30.5) in the HCV group *vs* 19.6% (95% CI: 12.1-27.1) in the control group, no evidence of breast lesion in 68.7% (95% CI: 63.4-74) of patients in the HCV group *vs* 75.7% (95% CI: 67.6-83.8) in the control group. Despite a trend for a higher prevalence of malignant or benign tumors in the HCV group, there was no significant statistical difference with the control group (Table 2). Familial history of breast cancer was recorded only in 1 of the 17 patients in the HCV group and none in the 5 cases of the control group.

The same analysis was performed according age brackets as presented in Table 3. No breast cancer was recorded in females younger than 40 years in the two groups. The frequency was low for females between 41 and 60 years, with a mild predominance but no significant difference in the HCV group compared to the control group: 3.4% (95% CI: 0.5-6.4) *vs* 1.8% (95% CI: 0-5.3). Females older than 60 years exhibited the highest prevalence with 10.0% without any difference between the two groups. In all patients over 40 years, breast cancer in the HCV group was 17/266 patients (6.3%, 95% CI: 3.4-9.3) *vs* 5/95 (5.2%, 95% CI: 0.7-9.7) in the control group.

For benign breast tumors, frequency also varied according to age brackets: it was slightly lower in the HCV group *vs* the control group for females between 20 and 40 years. In contrast, it was slightly higher in the other two age brackets but the difference was not statistically significant.

The absence of breast tumors was slightly higher in females aged between 41 and 60 years, and older than 60 years in the control group *vs* the HCV group but the difference was not statistically significant.

DISCUSSION

In many parts of the world, breast cancer is the most frequent form of cancer in females[19-22]. Similarly in France, there are 49 000 new cases/year and 11 000 deaths for a population of 60 million inhabitants[23-25]. The incidence is 101 cases/100 000 females[25]. Overall, cancer occurs in one female out of 11. As with many other cancers, the risk increases with age (less than 10% of breast cancers are detected in patients younger than 40 years[21-24]. Then the incidence increases with age[21-24]. These observations justify a systematic detection in females from 50 years. The causes of breast cancer are poorly known. Nevertheless, some risk factors have been identified[25-28]: benign breast diseases, fertility (females without pregnancy or with first pregnancy later than 30 years old exhibit a higher risk), obesity particularly after menopause[25]. Familial and genetic factors may also increase the risk, in particular through a gene mutation (BRCA1-BRCA2)[28]. The role of oral contraceptives has been discussed[21-27]. The increase in risk has been mainly observed in oral contraceptive users with a family history of breast cancer[28].

The role of HCV in breast cancer has been recently raised[14] for the following reasons. Chronic HCV infection is clearly involved in the occurrence of hepatocarcinoma and lymphoma[3,4-10] and in several other solid tumors[11-13]. Some cases of breast cancer were observed in a recent study of patients with HCV[14] and several cases have been recorded during the regular follow-up of the large cohort of patients with chronic HCV infection seen in the Liver Unit of Montpellier School of Medicine (personal observation). This led to the present prospective study knowing that a program of systematic detection of breast tumors by mammography every 2 years in all females older than 40 years has been in place in our geographic area for nearly 20 years.

Global results of this study show a breast cancer frequency of 5.8% in adult females with chronic HCV infection. Intentionally, we included a group of young females, aged 20-40 years, to detect a potential signal in an age population known to not exhibit a particular risk. No malignant lesion was recorded. However, only a small proportion of these patients had undergone mammography. Therefore, the detection of a tumor was mainly based on

Table 2 Prevalence of breast tumors

	Patients with HCV infection (n = 294)		Patients with other chronic liver diseases (n = 107)		P value
	n (%)	95% CI	n (%)	95% CI	
Breast cancer - all patients	17 (5.8)	3.1-8.4	5 (4.7)	0.67-8.67	NS
Benign breast tumors	75 (25.5)	20.5-30.5	21 (19.6)	12.1-27.1	NS
No breast lesion	202 (68.7)	63.4-74	81 (75.7)	67.6-83.8	NS

HCV: Hepatitis C virus; NS: Not significant.

Table 3 Prevalence of breast tumors according to age

Age of patients (yr)	Patients with chronic HCV infection (n = 294)		Patients with other chronic liver diseases (n = 107)		P value
	n (%)	95% CI	n (%)	95% CI	
Breast cancer					
20-40	0/28 (0)		0/12 (0)		NS
41-60	5/146 (3.4)	0.5-6.4	1/55 (1.8)	0-5.3	NS
> 60	12/120 (10.0)	4.6-15.4	4/40 (10.0)	0.7-19.3	NS
Benign breast tumors					
20-40	3/28 (10.7)	0-22.2	3/12 (25.0)	0.5-49.5	NS
41-60	41/146 (28.1)	20.8-35.3	12/55 (21.8)	10.9-32.7	NS
> 60	31/120 (25.8)	18-33.7	6/40 (15.0)	3.9-26.1	NS
No breast lesion					
20-40	25/28 (89.3)	77.8-100	9/12 (75.0)	50.5-99.5	NS
40-60	100/146 (68.5)	60.9-76	42/55 (76.4)	65.1-87.6	NS
> 60	77/120 (64.2)	55.6-72.7	30/40 (75.0)	61.6-88.4	NS

HCV: Hepatitis C virus; NS: Not significant.

its clinical expression. This sub-group representing about 10% of the overall group has slightly lowered the global prevalence. Indeed, the prevalence of all patients aged more than 40 years is 6.3% and reaches its highest rate, 10%, in females aged more than 60 years. The prevalence may have been underestimated since the mammography program was not followed in 20% of patients. Results observed in the HCV group were similar to those found in the control group, including females with other types of chronic liver diseases and having the same breast tumor detection program. We observed a similar low frequency in younger patients and the same proportion of patients who did not follow the mammography program. Therefore, this did not influence the comparison between groups. Finally, a familial history of breast cancer was recorded in a single patient with breast cancer (in the HCV group). This factor does not appear to have influenced the result of our study. Overall, these data do not support the idea that HCV chronic infection is a factor which contributes markedly to breast cancer. This view is also reinforced by the fact that prevalence of breast cancer found in this study is within the range of those found in general French and occidental populations[19-24]. Nevertheless, the interpretation of the results needs to be balanced by some limitations, in particular the relatively low number of patients in the control group and the absence of a priori calculation of the number of patients required to show a significant difference between groups with high power. This is largely caused by the fact that the prevalence of breast cancer in patients with chronic liver diseases in general and in HCV infection in particular, was completely unknown when the study was started. Therefore, our study does not allow us to draw definite conclusions. Nevertheless, it may serve as basis to set a more powerful study with matched control groups.

In summary, results of this study allowed the evaluation of the prevalence of breast cancer in patients with HCV chronic infection and suggest that HCV is not a strong promoter of breast carcinoma in adult females of any age.

COMMENTS

Background

Chronic infection by hepatitis C virus (HCV) exhibits a high frequency worldwide and represents a major cause of chronic liver disease leading to cirrhosis and hepatocarcinoma. Its influence on the onset of malignant tumors is under investigation.

Research frontiers

Several recent studies suggest that HCV chronic infection can not only cause hepatocarcinoma and lymphoma but may also promote the onset of several other solid tumors involving biliary ducts, thyroid, prostate, kidney and bladder.

Innovations and breakthroughs

The prevalence of breast cancer in patients with chronic liver diseases in general and HCV chronic infection in particular, is unknown. The relationship between HCV infection and breast cancer has been recently suggested by anecdotal cases. This is the first study designed to evaluate the prevalence of breast malignant and benign tumors in female patients and to assess whether HCV chronic infection is a risk factor. The study has been performed prospectively, using other chronic liver diseases as the control group. The results show the same prevalence of breast tumors in both groups which suggests that HCV does not appear as a strong promoting factor.

Applications

This study has allowed us to estimate the prevalence of breast cancer in females with chronic HCV infection. The interpretation of the results is balanced

by the number of patients included in the study and statistical power. Nevertheless, this constitutes a step to design new studies with matched control groups including a much larger number of patients to evaluate a potential low impact of HCV in breast malignancy.

Peer review

The authors evaluated the association between HCV infection and breast cancer. The study included 294 patients with HCV infection. Control subjects were 107 women seen in the same liver clinic over a 1-year period. Overall, there was no difference in the frequency of breast cancer or benign breast lesions between HCV-infected patients and control subjects. The hypothesis is interesting, but the study has limitations as discussed.

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