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Hepatitis C virus seroprevalence in the general female population from 8 countries

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Abstract

Background—Hepatitis C virus (HCV) infection is a significant global health issue because it is widespread and persistent and can cause serious liver diseases.

Objectives—The aim of this study is to estimate HCV prevalence in women from the general population in different geographical areas worldwide and to assess the potential role of sexual behaviour in the virus transmission.

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Competing interests:
All authors: No reported conflicts

Ethical approval:
The parent studies had been approved by the institutional review board (IRB) of the local institutions; IARC and NCI IRBs also approved the analysis here presented. Informed consent was obtained from all subjects, all study protocols and procedures were in accordance with the Declaration of Helsinki.

Potential conflicts of interests. All authors: No reported conflicts.

Study design—Each participating centre recruited a random sample of women from the general population aged from less than 20 to more than 75 years. The study included 8,130 women from 8 countries with information on sociodemographic factors, reproductive and sexual behaviour, smoking habit and HPV DNA through individual interviews. A blood sample was also collected to perform serological tests. We estimated the prevalence ratios associated to HCV to evaluate the effect of sexual behaviour in viral transmission.

Results—Women were reactive to a minimum of two HCV antigens, including at least one non structural protein were considered as positive (33% of the samples were classified as positive, 40% as negative, and 27% as indeterminate (N=402), that were considered as not positive). The age-adjusted HCV seroprevalence varied significantly by regions (0.3 % in Argentina to 21.1% in Nigeria). We found no association between HCV prevalence and age, educational level, smoking habit and any of the available variables for sexual behaviour and reproductive history.

Conclusions—This large study showed heterogeneous distribution of HCV seroprevalence in female and provides evidence of the null impact of sexual behaviour in HCV transmission.

Keywords

hepatitis C virus; seroprevalence; sexual behaviour

BACKGROUND

Hepatitis C virus (HCV) is transmitted by a blood-borne RNA virus identified in the late 1980s. HCV infection is a significant global health concern because it is widespread, and persistent HCV infection can cause serious liver diseases such as cirrhosis and hepatocellular carcinoma. It is estimated that about 2-3% of the world's population is HCV-infected and that about 130 million individuals are chronic carriers and consequently at risk of developing liver cirrhosis or cancer. (1)

HCV prevalence estimates range from less than 1% in industrialised areas in North America, Northern/Western Europe and Australia to more than 15% in Egypt, Pakistan, and Mongolia (2). Seven HCV genotypes are known; types 1, 2, 3 are diffused worldwide while the others are generally limited to specific geographic areas. Genotype distribution presents ethnic variability and underlines different pathways of virus transmission (1,3).

HCV infection is mainly acquired by parenteral route through the use of injectable drugs and/ or nosocomial transmission due to unsafe medical and dental procedures, and other practices involving non-sterile instruments more common in limited resources settings (1). Implementation of routine HCV screening in blood donors and use of disposable needles have substantially decreased new infections via blood transfusion in many countries.

Current understanding of the natural history of HCV is still far from comprehensive. Even though it has been shown that HCV is rarely sexually transmitted, compared to other parentally transmitted viruses, such as hepatitis B or HIV (4), the role of heterosexual intercourse in HCV infection acquisition remains controversial.

OBJECTIVES

The goal of this analysis is to estimate HCV prevalence in women from the general population in different geographical areas worldwide and to evaluate the potential role of sexual behaviour in the transmission of the infection using data from the IARC International Human Papillomavirus (HPV) prevalence survey and the NCI Costa Rica HPV Natural History Study.

STUDY DESIGN

Participants

Between 1994 and 2005 the International Agency for Research on Cancer (IARC) coordinated a study to estimate the prevalence of genital HPV infection in different geographical regions with contrasting cervical cancer incidence rates. The description of the recruitment has been previously published (5). Briefly, each participating centre recruited a random sample of women from the general population stratified in 11 groups aged from less than 20 to more than 75 years.In Costa Rica, a stratified random sample of subjects participating in a larger cohort study was selected. Information on sexual, reproductive, and socio-demographic history as well as tobacco use was collected through individual interviews. A blood sample was also collected to perform serological tests. Participation rates varied across the sites: Lampang 71%, Ho Chi Minh 88%, Korea 74%, Songkla 48%, Spain 60%, Costa Rica 91%, Colombia 95%, Argentina 50% and Nigeria 48.4%. The parent studies had been approved by the institutional review board (IRB) of the local institutions; IARC and NCI IRBs also approved the analysis here presented. Informed consent was obtained from all subjects, all study protocols and procedures were in accordance with the Declaration of Helsinki.

Specimens and laboratory testing

Plasma samples were shipped to the Viral Oncology Section laboratory at Frederick National Laboratory for Cancer Research and tested for antibodies against HCV relying on a screening assay and a confirmatory test, both based on a previously reported assay (6).

A pool of four peptides from the core structural protein (C1 and C2) and the non-structural proteins NS4 and NS5 was used in a screening assay; Plasma displaying reactivity in the screening assay was tested using a confirmatory test, consisting of four ELISAs utilizing the same peptides individually. Both screening and confirmatory assays were validated using commercial panels; comprising 279 sera from HCV infected individuals or normal blood donors. Specifically, the following panels were used : the HCV Worldwide Performance Panel WWHV301 (BBI, now Seracare, Milford, MA), which includes samples from the US, Argentina, sub-Saharan Africa, China and Egypt with genotypes 1-4 and various subtypes; the HCV Seroconversion Panel PHV920(M) (SeroLogicals, now Seracare, Milford, MA); and a panel of sera from HCV-uninfected healthy blood donors (The Binding Sites, San Diego, CA), Panels are characterised by the manufacturers using HCV genotype, RNA, and antibody assays; sera from infected subjects had antibody levels between 0.1 and >5 signal-to-cut-off ratios (s/co).

Optimal cut-offs were chosen to maximize overall assay discrimination (maximum Younden index). The confirmatory assay was scored following criteria similar to those utilized in confirmatory RIBA assays (7). Samples with no reactivity to any individual peptide were deemed negative. Samples with reactivity to at least two different HCV antigens (C1 and C2 were considered as one antigen) were scored as positive. Finally, samples were classified as indeterminate if reactivity was observed for only one antigen. Samples displaying no reactivity in the screening assay were not tested in the confirmatory assay and scored as HCV negative.

In a subset of (79 serologically positive) samples, we tested for HCV RNA using a real time rtPCR assay (Miley et al, personal communication). Briefly, primers and probes designed to conserved regions in the 5'UTR with over 95% nucleotide sequence identity in over 100 HCV sequences of genotypes 1 to 7 were utilized in an assay employing as standard a plasmid encoding for a replication incompetent HCV genome. Serological and molecular methods are further detailed in supplementary materials.

Statistical analysis

The HCV prevalence was estimated by geographical region and I^2 test was used to quantify variability in HCV prevalence due to the heterogeneity among geographical regions. Due to the statistically significant heterogeneity observed among geographical regions no pooled estimate was provided. The prevalence ratios and 95% confidence intervals (PR, 95% CI) for HCV positivity were evaluated for educational level, reproductive and sexual behaviour, smoking and HPV status. Geographical regions with 5 or less HCV positive women were excluded from the PR analyses. We provide P-value for test for linear trend for ordinal and continuous variable, otherwise P-value for chi-squared test is provided. All P-values reported are for two-sided tests. We carried out a sensitivity analysis excluding indeterminate subjects without observing any impact on the estimate of HCV prevalence by geographical region (data not shown). All data analyses were performed using STATA computer software (version 10.1).

RESULTS

Of the 13,639 initially recruited, a total of 8,130 women were tested for this study. The main reason for exclusion was the unavailability of plasma samples. The confirmatory test scored 40% of the samples as negative (N=595), 33% as positive (N=491) and 27% as indeterminate (N=402), that were considered as not positive. The overall mean age was 40 years (SD 15.55). We observed that 97.5% of the variability in HCV prevalence was due to heterogeneity among geographical regions and consequently, stratified analyses by geographical region were provided instead of pooled estimates. Table 1 shows the distribution of HCV adjusted prevalence by age and stratified by geographical region. The HCV prevalence ranged from 21.1 (95%CI, 18.8 to 23.7) in Nigeria to 0.3 (95%CI, 0.1 to 1.0) in Argentina. For the remaining geographical regions, HCV prevalence varied from 0.6% in Spain to 4.7% in Ho Chi Minh City, Vietnam. Women from Nigeria were 61 times more likely to be HCV positive than women from Argentina. Overall, there were no statistically significant differences in the number of antigens scored as positive by

geographical region (p-value 0.3). Table 2 shows stratified HCV prevalence ratio and 95% confidence interval by demographic, sexual and reproductive behaviour and HPV DNA. We did not observe any impact on the PR of HCV positivity due to any of the behavioural characteristics evaluated. We suspected some of the prevalence is due to false positives in our assay, possibly due to exposure to other flaviviruses. We therefore tested a small subset of antibody positive samples by rtPCR without observing any amplification HCV RNA

DISCUSSION

This study confirms the heterogeneity of the HCV seroprevalence worldwide showing a 61-fold disparity between Nigeria and Argentina and provides evidence of null contribution of sexual behaviour in the transmission of HCV infection. None of the other exposures explored (reproductive history, demographical factors, HPV DNA and tobacco consumption) was associated to HCV seroprevalence.

The HCV seroprevalence observed (4% approximately) in Vietnam (Ho Chi Minh) and in Thailand (Lampang and Songkla) are consistent with those reported in previous studies (8). It is probable that the estimate in Ho Chi Minh reflects a higher concentration intravenous drug users in the city and does not reflect the HCV prevalence (8), across the country. Limited data on intravenous drugs users or others risk groups are available from Thailand (9).

Again, the 3.1% HCV prevalence in Busan (Korea) represents a two-fold higher point estimate than the one reported in the nationwide seroepidemiology of Hepatitis C in 2009 (10).

Our estimates for HCV prevalence in Colombia and Costa Rica are consistent with those previously reported (1-2.5%) but somehow lower than what has been published in Argentina (0.34 vs 2-2.5 in literature) (11). Data for Spain was also consistent with that reported in western European countries (1.6%) (12). However in Nigeria, the HCV prevalence was considerably higher than that estimated in other epidemiological studies in Sub-saharan Africa (13). Whether this difference corresponds to a true high prevalence that has been formerly underdetected or due to cross reactivity with other Flaviviridae like hepatitis G, West Nile virus or Yellow fever virus requires further evaluation.

It is likely that there is a global underestimation of HCV burden particularly in low- and medium-resource countries with limited information on HCV prevalence based on well-designed population-based studies.

Most often, HCV prevalence studies are based on specific young population such as blood donors or pregnant women although young adults and adults are more likely to be HCV infected by contaminated blood and needles than children (2). Contrary to HBV, late age at infection does not protect from becoming chronic carrier and having high risk of developing hepatocellular carcinoma. Although no vaccines against HCV are available, most HCV transmission could be avoided. Population-based data on HCV prevalence are incomplete and often biased towards an underestimate of the real infection burden. So far, HCV testing has been recommended mainly for intravenous drug users (12) with the advent of new

therapies, indications for HCV testing should be broadened as recently decided by the U.S. Centers for Disease Control and Prevention (14).

We would like to underline the main limitations and strength of our study. We did not have information on potential parenteral paths of transmission as this information was not available in the parent study which was designed mainly to explore sexual behaviour. Unfortunately the study did not test for HIV infection, which is comorbid with HCV infection in many settings, and could compromise the validity or generalizability of our findings. However, based on the parent study's design and findings on sexual behaviour, we are confident that our study sample is representative of the general, low HIV risk population.

One limitation of or results is the potential overestimation of HCV prevalence in Nigeria. Two potential artefacts should be considered. Firstly, the possibility of cross reactivity between HCV and other Flaviviridae like GB virus-C, dengue virus, Japanese encephalitis virus, West Nile virus or yellow fever virus. Our failure to amplify HCV RNA from antibody positive Nigerian samples reinforces this possibility. Secondly, false-positive results are reported to occur at a rate of 10-20% and are usually seen in low-risk blood donors with of autoimmune disease, hypergammaglobulinemia. Plasmodium falciparum, endemic in Nigeria, can result in hypergammaglobulinemia and thus could partially explain our high HCV prevalence in Nigeria. Aceti et al. observed a high rate of false HCV positive results in patients with *Plasmodium Falciparum* (15).

In conclusion, this large study confirms the significant geographical heterogeneity of HCV seroprevalence globally and does not identify any effect of sexual behaviour on the transmission of HCV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Hihglights

- We assessed HCV seropositivity in 8,130 women from different geographical areas.
- We reported a major heterogeneity of the HCV seroprevalence worldwide.
- We provided evidence of no effect of sexual behaviour in HCV transmission.
- None of the other exposures explored was associated to HCV seroprevalence.
- We found a very high HCV prevalence in Nigeria probably due to cross reactivity.

Table 1

HCV prevalence and number of HCV antigens positive by geographical area

GEOGRAPHIC AREA	HCV prevalence[1]				Number of positive antigens n (%)		
	N total	N (Pos)	(%)	95% CI	2	3	4
HoChiMinh	571	27	4.7	[3.3 to 6.8]	7 (1.2)	15 (2.6)	5 (0.9)
Spain	314	2	0.6	[0.2 to 2.5]	0 (0)	2 (0.6)	0 (0)
Lampang	1178	50	4.2	[3.2 to 5.5]	8 (0.7)	26 (2.2)	16 (1.3)
Argentina	884	3	0.3	[0.1 to 1.0]	1 (0.1)	1 (0.1)	1 (0.1)
Nigeria	1080	229	21.1	[18.8 to 23.7]	68 (6.3)	98 (9.1)	63 (5.7)
Colombia	1840	46	2.5	[1.9 to 3.3]	7 (0.4)	27 (1.5)	12 (0.6)
Songkla	970	14	1.4	[0.8 to 2.4]	2 (0.2)	8 (0.8)	4 (0.4)
Korea	931	29	3.1	[2.2 to 4.4]	6 (0.6)	17 (1.8)	6 (0.7)
Costa Rica	362	5	1.4	[0.6 to 3.3]	2 (0.6)	3 (0.8)	0 (0)

[1] Adjusted by age (continuous)

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Table 2

Prevalence Odds Ratio for Hepatitis virus C and risk factors by geographical region

	HochiMinh			Lampang			Nigeria		
Risk factor	**Total (N)**	**HCV positive (n, %)**	**PR, 95% CI[1]**	**Total (N)**	**HCV positive (n, %)**	**PR, 95% CI[1]**	**Total (N)**	**HCV positive (n, %)**	**PR, 95% CI[1]**
Age at interview, years	**571**	**27 (5)**		**1178**	**50 (4)**		**1080**	**229 (20)**	
<35	237	6 (3)	Ref	491	16 (3)	Ref	394	80 (20)	Ref
35-44	212	17 (8)	3.17 (1.27 to 7.89)	166	8 (5)	1.48 (0.64 to 3.39)	158	24 (15)	0.75 (0.49 to 1.14)
>44	122	4 (3)	1.30 (0.37 to 4.50)	521	26 (5)	1.53 (0.83 to 2.82)	528	125 (24)	1.17 (0.91 to 1.49)
p-value association		**0.01**			0.4			0.06	
Educational level	**570**	**27 (5)**		**1178**	**50 (4)**		**1080**	**229 (20)**	
Primary	149	7 (5)	Ref	651	31 (5)	Ref	303	67 (22)	Ref
Secondary or higher	389	19 (5)	1.08 (0.44 to 2.56)	279	8 (3)	0.74 (0.31 to 1.78)	293	51 (17)	0.79 (0.57 to 1.10)
None	32	1 (3)	0.61 (0.07 to 4.94)	248	11 (4)	0.78 (0.37 to 1.66)	484	111 (23)	1.04 (0.69 to 1.57)
p-value association		0.9			0.4			0.2	
Age at first sexual intercourse	**571**	**27 (5)**		**1178**	**50 (4)**		**1080**	**229 (20)**	
<18	36	4 (11)	Ref	247	8 (3)	Ref	264	58 (22)	Ref
18-20	173	10 (6)	0.52 (0.17 to 1.59)	400	23 (6)	1.72 (0.78 to 3,80)	544	118 (22)	0 .93 (0.70 to 1.25)
21-23	160	3 (2)	0.17 (0.04 to 0.73)	179	9 (5)	1.49 (0.58 to 3,79)	150	32 (21)	0.90 (0.60 to 1.34)
>24	202	10 (5)	0.44 (0.15 to 1.35)	352	10 (3)	0.92 (0.37 to 2.32)	122	21 (17)	0.72 (0.45 to 1.15)
p-value association		0.09			0.2			0.7	
Total number of sexual partner	**568**	**27 (5)**		**973**	**47 (5)**		**1063**	**226 (20)**	
<=1	539	25 (5)	Ref	822	37 (5)	Ref	554	121 (22)	Ref
2-4	29	2 (7)	1.48 (0.37 to 5.96)	149	10 (7)	1.47 (0.75 to 2.90)	478	96 (20)	0.91 (0.72 to 1.15)
over 5	0	0	----	2	0 (0)	----	31	9 (29)	1.32 (0.75 to 2.34)
p-value association		0.6			0.5			0.4	
Number of births	**571**	**27 (5)**		**1178**	**50 (4)**		**1080**	**229 (20)**	
<=1	200	9 (5)	Ref	310	18 (6)	Ref	208	49 (24)	Ref

Risk factor	HochiMinh Total (N)	HochiMinh HCV positive (n, %)	HochiMinh PR, 95% CI[1]	Lampang Total (N)	Lampang HCV positive (n, %)	Lampang PR, 95% CI[1]	Nigeria Total (N)	Nigeria HCV positive (n, %)	Nigeria PR, 95% CI[1]
2	166	9 (5)	1.14 (0.44 to 2.92)	266	11 (4)	0.61 (0.29 to 1.28)	98	22 (22)	0.93 (0.60 to 1.45)
>3	205	9 (4)	0.86 (0.30 to 2.56)	602	21 (3)	0.43 (0.21 to 0.85)	774	118 (22)	0.73 (0.53 to 1.10)
p-value association		0.9			0.3			0.6	
Smoking status	**571**	**27 (5)**		**1178**	**50 (4)**		**1076**	**227 (20)**	
Never	562	26 (5)	Ref	885	36 (4)	Ref	1057	220 (21)	Ref
Ever	9	1 (11)	2.35 (0.35 to 15.63)	293	14 (5)	0.89 (044 to 1.83)	19	7 (37)	1.68 (0.91 to 3.11)
p-value association		0.4			0.6			0.09	
HPV DNA [2]	**571**	**27 (5)**		**974**	**47 (5)**		**1029**	**215 (20)**	
No	530	24 (5)	Ref	895	42 (5)	Ref	796	169 (21)	Ref
Yes	41	3 (7)	1.68 (0.52 to 5.45)	79	5 (6)	1.42 (0.56 to 3.46)	233	46 (21)	0.93 (0.70 to 1.25)
p-value association		0.4			0.5			0.6	

Risk factor	Colombia Total (N)	Colombia HCV positive (n, %)	Colombia PR, 95% CI[1]	Songkla Total (N)	Songkla HCV positive (n, %)	Songkla PR, 95% CI[1]	Korea Total (N)	Korea HCV positive (n, %)	Korea PR, 95% CI[1]
Age at interview, years	**1840**	**46 (3)**		**970**	**14 (1)**		**931**	**29 (3)**	
<35	1202	29 (2)	Ref	284	4 (1)	Ref	186	2 (1)	---
35-44	484	13 (3)	1.11 (0.58 to 2.12)	194	4 (2)	1.46 (0.37 to 5.78)	294	11 (4)	3.48 (0.78 to 15.52)
>44	154	4 (3)	1.08 (0.38 to 3.02)	492	6 (1)	0.87 (0.25 to 3.04)	451	16 (4)	3.30 (0.77 to 14.21)
p-value association		0.9			0.7			0.2	
Educational level	**1840**	**44 (2)**		**969**	**14 (1)**		**931**	**29 (3)**	
Primary	525	10 (2)	Ref	615	9 (1)	Ref	260	12 (5)	Ref
Secondary or higher	1182	31 (3)	1.41 (0.67 to 2.98)	151	1 (1)	0.41 (0.05 to 3.30)	626	16 (3)	0.62 (0.25 to 1.51)
None	57	3 (5)	2.58 (0.66 to 9.43)	203	4 (2)	1.57 (0.44 to 5.58)	45	1 (2)	0.47 (0.06 to 3.56)
p-value association		0.3			0.6			0.3	
Age at first sexual intercourse	**1840**	**46 (3)**		**970**	**14 (1)**		**931**	**29 (3)**	
<18	782	19 (2)	Ref	235	3 (1)	Ref	14	1 (7)	Ref

Risk factor	Colombia Total (N)	Colombia HCV positive (n, %)	Colombia PR, 95% CI[1]	Songkla Total (N)	Songkla HCV positive (n, %)	Songkla PR, 95% CI[1]	Korea Total (N)	Korea HCV positive (n, %)	Korea PR, 95% CI[1]
18-20	511	9 (2)	0.78 (0.34 to 1.76)	411	6 (1)	1.17 (0.29 to 4.69)	167	4 (2)	0.38 (0.05 to 3.22)
21-23	278	10 (4)	1.59 (0.70 to 3.60)	175	2 (1)	0.92 (0.15 to 5.57)	284	10 (4)	0.61 (0.08 to 4.64)
>24	269	8 (3)	1.29 (0.54 to 3.06)	149	3 (2)	1.66 (0.32 to 8.32)	466	14 (3)	0.57 (0.07 to 4.39)
p-value association		0.4			0.9			0.70	
Total number of sexual partner	**1756**	**44 (3)**		**964**	**14 (1)**		**879**	**28 (3)**	
<=1	1096	28 (3)	Ref	864	9 (1)	Ref	758	25 (3)	Ref
2-4	233	5 (2)	0.85 (0.33 to 2.19)	97	5 (5)	5.34 (1.74 to 15.18)	119	3 (3)	0.77 (0.24 to 2.52)
over 5	428	11 (3)	1.03 (0.52 to 2.06)	3	0 (0)	----	2	0 (0)	----
p-value association		0.9			**0.006**			0.9	
Number of births	**1840**	**46 (3)**		**970**	**14 (1)**		**934**	**29 (3)**	
<=1	659	21 (3)	Ref	178	2 (1)	Ref	140	3 (2)	Ref
2	508	13 (3)	0.71 (0.34 to 1.50)	200	3 (2)	1.35 (0.23 to 8.05)	382	15 (4)	1.70 (0.5 to 5.79)
>3	673	12 (2)	0.43 (0.19 to 0.99)	592	9 (1)	1.26 (0.15 to 10.39)	380	11 (3)	1.04 (0.28 to 3.91)
p-value association		0.3			0.9			0.7	

Risk factor	Colombia Total (N)	Colombia HCV positive (n, %)	Colombia PR, 95% CI1	Songkla Total (N)	Songkla HCV positive (n, %)	Songkla PR, 95% CI1	Korea Total (N)	Korea HCV positive (n, %)	Korea PR, 95% CI1
Smoking status	**1764**	**44 (2)**		**970**	**14 (1)**		**931**	**29 (3)**	
Never	1297	38 (3)	Ref	918	13 (1)	Ref	878	27 (3)	Ref
Ever	467	6 (1)	0.43 (0.18 to 1.03)	52	1 (2)	1.39 (0.18 to 10.67)	53	2 (4)	1.16 (0.28 to 4.78)
p-value association		**0.05**			0.8			0.8	
HPV DNA [2]	**1840**	**46 (3)**		**964**	**14 (1)**		**844**	**27 (3)**	
No	1552	40 (3)	Ref	933	12 (1)	Ref	756	22 (3)	Ref
Yes	288	6 (2)	0.79 (0.33 to 1.87)	31	2 (6)	5.05 (1.18 to 21.61)	88	5 (6)	1.97 (0.77 to 5.08)
p-value association		0.6			**0.02**			0.2	

Geographical regions with 5 or less HCV positive women were excluded of 229 the PR analyses.

[1] Prevalence Ratio and 95% confidence interval

^{2}HPV DNA: Human Papiloma Virus DNA