ACCEPTABILITY AND YIELD OF BIRTH COHORT SCREENING FOR HEPATITIS C IN A CANADIAN COLORECTAL CANCER SCREENING POPULATION

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ABSTRACT

Background: Hepatitis C virus (HCV) screening is recommended in patients born between 1945 and 1965 ('baby boomers'). Since these individuals are often screened for colorectal cancer (CRC), dual screening for HCV may enhance case identification. Our objectives were to assess the acceptability and yield of HCV screening among patients undergoing CRC screening.

Methods: Patients referred for CRC screening colonoscopy completed an anonymous survey regarding the acceptability of HCV screening, risk factors, and prior testing. The impact of demographics and HCV risk factors on screen willingness were determined using logistic regression, and stored serum on 483 patients who had undergone CRC screening were tested for HCV antibodies.

Results: Among 1,012 survey respondents (median age 56 years, 90% baby boomers, 87% Caucasian, 22% immigrants), 123 patients (12%) reported prior HCV testing. Nine of these patients (0.9%; 1.0% of baby boomers) were previously diagnosed with HCV, of whom 5 (56%) reported risk factors. Excluding these patients, 90% would consent to blood or salivary HCV testing. After adjustment for age, gender, and immigrant status, Caucasians (odds ratio [OR] 3.38; 95% CI 1.81-6.32) and patients with risk factors (>1 vs. 0: OR 3.67; 1.12-12.02) had higher screening acceptance. Among 483 patients screened for CRC, three were anti-HCV positive (0.6% [95% CI 0.1-1.8%]; 0.8% [0.2-2.4%]) of baby boomers).

Interpretation: Acceptance of HCV screening is high among Canadians undergoing CRC screening. However, the relatively low HCV prevalence suggests that the cost-effectiveness of birth cohort screening in this population warrants evaluation.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation in Canada [1]. These complications are expected to increase dramatically over the next decade [2] and cause more years of life lost due to mortality and suboptimal health compared with any other infectious disease [3]. Canadian guidelines advocate HCV testing in individuals with evidence of liver disease or risk factors including injection drug use (IDU), receipt of blood products before 1992, and immigrants from endemic countries [4]. However, several characteristics of HCV suggest that more widespread screening may be beneficial. First, HCV infection is common. Although the exact prevalence is unknown, at least 250,000 Canadians (0.8% of the population) are likely infected [2]. Second, most patients are asymptomatic until advanced liver disease has developed; thus, many HCV cases are unaware of their infection (60% to 70% in Canada and the U.S.) [5, 6]. Third, therapies are available that cure the virus in 70-80% of patients [4], arrest progression of liver disease, and reduce mortality [7]. Based on these characteristics, recent U.S. guidelines advocated one time screening for HCV antibodies in individuals born between 1945 and 1965 ('baby boomers'), plus risk factor-based screening [8]. This birth cohort has a high prevalence of HCV (3.6% in the U.S.), accounts for 75% of cases, and has the greatest risk of HCV-related mortality [9, 10]. The Canadian Liver Foundation has endorsed similar recommendations [11].

Prior to adopting birth-cohort screening in Canada, the prevalence of HCV and the feasibility of this approach require confirmation. Our study sought to address these issues among patients undergoing colonoscopy for colorectal cancer (CRC) screening. This unique clinical setting

offers several advantages relevant to birth-cohort HCV screening. Since CRC screening is recommended for individuals starting at age 50 – many of whom undergo colonoscopy at regular intervals - this patient population is enriched with baby boomers [12]. Second, patients who undergo CRC screening are engaged in care and have demonstrated acceptance of preventive interventions. Finally, gastroenterologists are in a distinctive position as they are both experts on viral hepatitis and perform screening colonoscopies. Unlike primary care-based HCV screening, this environment ensures direct linkage to counseling and antiviral therapy for infected cases.

METHODS

Study Setting

The Forzani and MacPhail Colon Cancer Screening Centre (CCSC) is a non-hospital endoscopy unit located in Calgary, Alberta that is dedicated to providing CRC screening-related colonoscopies (~19,000 annually) to residents of Calgary and surrounding communities (population ~1.5 million) [13]. The CCSC accepts referrals for asymptomatic, generally healthy individuals eligible for CRC screening-related colonoscopy, including those at average or increased risk of CRC, for investigation of positive fecal occult blood tests, and surveillance for those with a history of adenomatous polyps or CRC. Colonoscopy for the investigation of symptoms, dysplasia surveillance in patients with inflammatory bowel disease, or for patients with major comorbidities that preclude colonoscopy in a non-hospital setting (e.g. decompensated cirrhosis) is not provided.

Prior to colonoscopy at the CCSC, referred patients attend an education session regarding CRC, including screening options and colonoscopy preparation [13]. For the first part of this study, we invited all individuals presenting for this session during May 2013 to complete an anonymous questionnaire that included demographic information and questions regarding the acceptability of HCV screening by blood and/or saliva-based assays, risk factors for infection (e.g. IDU, blood transfusion, etc.), and previous testing for and pre-existing diagnoses of HCV (see Appendix for the questionnaire). Pre-existing HCV diagnoses could not be confirmed due to the anonymous nature of the survey. Patients were also asked about their willingness to be evaluated by a liver specialist if found to be HCV-positive.

The CCSC also maintains a bio-repository that includes demographic, lifestyle and health information (excluding HCV status), plus serum specimens (stored at -80 ºC) on consenting individuals who have undergone colonoscopy for CRC screening. Patients within the bio-repository are similar to the general population of screened patients. For the second part of the study, we randomly selected 496 individuals who had provided serum specimens to the bio-repository between February 2011 and August 2012. As these patients had not specifically consented to HCV testing, we contacted them by mail to outline the purpose of the study and request permission to test their serum for HCV. Patients wishing to opt out were asked to return a pre-addressed letter within one month of the initial mailing. In total, 8 subjects declined participation and the invitation letter from five subjects was returned undeliverable. Therefore, 13 subjects were excluded leaving 483 specimens (97%) available for testing. In these patients, testing for anti-HCV antibodies was performed using the Architect anti-HCV CMIA assay (Abbott Laboratories; Abbott Park, IL) with confirmation by the MONOLISA Anti-HCV

Plus assay (Bio-Rad Laboratories; Montreal, PQ). In patients who were anti-HCV positive on both assays, chronic HCV infection (i.e. persistent viremia) was confirmed by testing the serum for HCV RNA using the Abbott RealTime HCV Version 4.0 assay (lower limit of virus detection, 12 IU/mL).

Statistical Analyses

Data are presented as medians (interquartile range [IQR]) or proportions. Between groups comparisons were made using Fisher's exact or Mann-Whitney tests. In the first part of the study, the primary outcome measure was the willingness to be screened for anti-HCV antibodies by either blood or saliva-based assays. Using logistic regression analysis, we determined the associations between the following factors and screen willingness: age, sex, race (Caucasian vs. other), immigrant status (Canadian vs. foreign-born), marital status (married/common-law vs. other), education (university vs. lower), and the number of self-reported risk factors for HCV including IDU, blood transfusion, tattoos, incarceration, infected family member or spouse, and sexual contact with an HCV-positive partner (categorized as 0, 1, and ≥2 risk factors). Independent predictors of willingness to be screened were determined using a logistic regression model including age, gender, and variables significant (P<0.05) in univariate analyses. Associations are presented with odds ratios (OR) and 95% confidence intervals (CI). In the second part of the study, the proportions of individuals with positive anti-HCV antibodies and positive serum HCV RNA were calculated with exact binomial 95% CIs. Subgroup analyses were conducted according to birth cohort (1945-1965 [baby boomers] vs. other). All statistical analyses were performed using Stata v11.0 (StataCorp; College Station, TX). Two-sided P-values less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

During May 2013, 1,012 individuals referred for CRC screening colonoscopy at the CCSC completed the questionnaire regarding HCV screening. Fifty-two percent of respondents were male and the median age was 56 years (IQR 53-62); 90% were baby boomers. The majority (87%) was Caucasian, 22% were immigrants, and 42% had a university degree. Twenty-six percent of respondents (n=266) reported at least one risk factor for HCV infection. With the exception of prior blood transfusions (9%) and tattoos (9%), risk factors were uncommon (IDU [2.2%], infected family member [1.5%] or spouse [0.2%], incarceration [0.7%], and sexual contact with an infected partner [0.5%]).

Self-Reported HCV Infection

Among 123 survey respondents (12%) reporting previous HCV testing, 9 patients (7.3%) disclosed a known diagnosis of HCV. If confirmed (and the remaining patients tested negative), these infections would correspond to an HCV prevalence of 0.9% (95% CI 0.4-1.7% [9/1,012]) overall and 1.0% (95% CI 0.5-1.9% [9/914]) among baby boomers. Five of these patients (56%) reported HCV risk factors, including IDU in four patients, and an infected family member/blood transfusion in one patient.

Acceptability of HCV Screening

Excluding the 9 patients with self-reported HCV infection, 90% of survey respondents (903/1,003) would consent to HCV antibody screening by blood (85%) or saliva-based testing (89%; *P*=0.009 vs. blood). Ninety-two percent of individuals (919/1,003) would consent to

evaluation by a specialist if found to be HCV-positive. Table 1 outlines the characteristics of patients referred for CRC screening according to their willingness to undergo HCV screening. In univariate analysis, Caucasian race, non-immigrant status, and an increasing number of HCV risk factors were associated with a willingness to be screened. After adjustment for age and gender, Caucasians were more likely to accept HCV screening (OR 3.38; 95% CI 1.81-6.32); immigrant status was not significant (OR 0.70; 95% CI 0.39-1.26). Compared to patients with no reported HCV risk factors, patients with one (OR 2.79; 95% CI 1.30-5.96) or at least two risk factors (OR 3.67; 95% CI 1.12-12.02) were more likely to accept HCV screening.

Prevalence of HCV in Patients Screened for Colorectal Cancer

Serum samples from 483 patients who had undergone CRC screening colonoscopy were tested for anti-HCV antibodies. The median age was 56 years (IQR 56-61), 77% (n=370) were baby boomers, 48% were male, 26% were immigrants, and 43% had a university education. In total, four patients were anti-HCV-positive on initial screening, of which three were confirmed, corresponding to an anti-HCV prevalence of 0.6% (95% CI 0.1-1.8% [3/483]) overall and 0.8% (95% CI 0.2-2.4% [3/370]) among baby boomers. The three anti-HCV positive patients were male, baby boomers, and one was foreign-born. HCV RNA was positive in two of these cases (52,971 IU/mL and 9,728,627 IU/mL, respectively), corresponding to a prevalence of chronic HCV infection (i.e. viremia) of 0.4% (95% CI 0.05-1.5%) overall and 0.5% (0.07-2.0%) among baby boomers.

INTERPRETATION

Main Findings

Our study confirms that acceptability of HCV screening is high among Canadian patients undergoing colonoscopy for CRC screening. However, the prevalence of HCV was lower than expected, suggesting that birth-cohort screening in this patient population may not be the optimal means of improving case identification globally in Canada. On the other hand, these individuals are engaged in preventive care and would potentially be more likely to accept and complete anti-HCV therapy than other target screening populations.

Among patients referred for CRC screening colonoscopy at a non-hospital endoscopy facility, 90% would be willing to undergo dual screening for HCV by either blood or saliva-based assays. Patients with risk factors for HCV were more likely to accept screening, suggesting that risk factor-based screening could be effective if appropriately conducted. However, frequently cited barriers to this approach including lack of physician time and knowledge about HCV risk factors, as well as patient reluctance to disclose risk factors were at least partially addressed by our administration of an anonymous survey [14]. We also observed that immigrant patients were less likely to accept screening, although this difference did not persist after adjustment for race; Caucasians were more accepting of screening. Other studies have demonstrated reduced screening of immigrants (e.g. for breast and cervical cancer) [15, 16], perhaps due to fear of stigmatization or repercussions regarding immigration status [17]. Not surprisingly, patients were more likely to accept HCV screening via salivary tests – not yet available in Canada - compared with blood tests, presumably due to their non-invasive nature [18]. Although this issue is less important in this setting since patients could have blood drawn

with insertion of their intravenous line pre-colonoscopy, the use of salivary tests when available may be preferable in other settings such as outreach programs, particularly among injection drug users who may have compromised venous access [19].

The observed rates of self-reported HCV infection (0.9% overall and 1.0% of baby boomers) and anti-HCV positivity of screened blood samples (0.6% overall and 0.8% of baby boomers) are lower than we expected, particularly if one considers only chronically infected (i.e. viremic) patients (0.4% overall and 0.5% of baby boomers). In British Columbia, 1.4% of HCV antibody tests were positive (3.0% of baby boomers) [20] and U.S. estimates of HCV prevalence from the National Health and Nutrition Examination Survey are significantly higher (1.6% overall and 3.6% of baby boomers) [9]. There are several potential explanations for these differences. Importantly, the prevalence of HCV in Canada may be lower than some have suggested. Our results are in keeping with modeled estimates from Remis (0.8% overall and 1.2% of baby boomers) [2]. Moreover, in the only seroprevalence study of randomly-selected individuals in Canada, the Canadian Health Measures Survey (CHMS) reported an anti-HCV prevalence of 0.5% overall and 0.8% among individuals aged 50-79 years [6]. However, our study and the CHMS under-sampled some high-risk groups including injection drug users, incarcerated individuals, the homeless, and Aboriginals. Although the immigrant population in our study (and in the CHMS) [6] was similar to the Canadian population, ours was a highly educated cohort engaged in their health care. Therefore, the generalizability of our findings may be questioned. Moreover, due to the relatively small sample size of our study, the confidence intervals surrounding our prevalence estimates are wide. For example, the HCV prevalence in baby boomers and overall could be as high as 2.4% and 1.8%, respectively. Despite these

uncertainties, the main unanswered question is whether HCV screening among patients undergoing CRC screening (and in general) is cost-effective. In the U.S., primary care-based baby boomer screening has been advocated based on an incremental cost-effectiveness ratio of approximately $36,000 versus risk factor-based screening [5]. Whether combined screening for HCV and CRC is cost-effective in Canada warrants formal analysis, particularly in light of differences in HCV prevalence and the costs of HCV screening and treatment in Canada versus the U.S. Similar to advanced CRC, the costs of managing end-stage liver disease secondary to HCV is high. Moreover, the fact that patients undergoing CRC screening are already engaged in care with HCV treatment experts, thus reducing the necessity of additional referral and appointments, must be considered.

Limitations

As mentioned, the ability to draw inferences regarding the prevalence of HCV in Canada is limited by the small sample size and specific nature of our study population. In addition, 8 patients (1.6%) declined study participation and five could not be contacted. If these patients declined due to known hepatitis C or perceived risks factors for infection, our prevalence figures could be underestimates.

Conclusions

In summary, acceptance of HCV screening is high among Canadian patients undergoing CRC screening. However, the relatively low HCV prevalence suggests that the cost-effectiveness of birth cohort screening in this population warrants evaluation prior to the widespread adoption of this approach.

CONTRIBUTORS

Robert Myers, Pam Crotty, Susanna Town, Mark Swain, Steven Heitman, and Robert Hilsden helped conceive and design the study and interpreted the data. Robert Myers, Pam Crotty, Susanna Town, Janine English, Kevin Fonseca, Raymond Tellier, S. Elizabeth McGregor, Steven Heitman, and Robert Hilsden acquired the data. Robert Myers analyzed the data and drafted the manuscript. All of the authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication.

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COMPETING INTERESTS

Robert Myers and Mark Swain have received consultation, research, and/or speaking fees from Vertex, Merck, Roche, Gilead, Janssen, Abbvie, and Boehringer-Ingelheim, all of whom produce products for the treatment of HCV. No competing interests were declared by the other authors.

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TABLES

Table 1: Characteristics of Patients Referred for Colorectal Cancer Screening According to Willingness to Undergo HCV Screening

Variable †	Total Cohort (n=1,012)	Willing to be Screened (n=903) *	Unwilling to be Screened (n=100) *	Unadjusted Odds Ratio for Willingness to be Screened (95% CI) *
Male	52% (529)	52% (474)	51% (51)	1.09 (0.74-1.59)
Age, *years*	56 (53-62)	56 (53-62)	57 (53-61)	0.99 (0.96-1.02)
Baby boomer (born 1945-1965)	90% (914)	90% (814)	91% (91)	0.81 (0.38-1.73)
Caucasian race	87% (876)	89% (803)	66% (65)	**4.25 (2.66-6.79)**
Immigrant	22% (221)	20% (177)	42% (42)	**0.34 (0.22-0.52)**
University education	42% (399)	40% (358)	38% (38)	0.94 (0.60-1.47)
Married or common-law	82% (831)	82% (741)	83% (83)	0.90 (0.52-1.59)
HCV risk factors				
0	74% (746)	72% (653)	89% (89)	Ref
1	17% (169)	18% (158)	8% (8)	**2.69 (1.28-5.66)**
≥2	10% (97)	10% (92)	3% (3)	**4.18 (1.30-13.5)**

Data are median (IQR) or proportions (% [n]).

* Excludes 9 patients with a self-reported diagnosis of HCV.

† Gender, age, race, immigrant status, marital status, and education level missing in 1, 2, 6, 1, 5, and 69 respondents, respectively.