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ORIGINAL ARTICLE

Colorectal Cancer Survivors' Receptivity toward Genomic Testing and Targeted Use of Non-Steroidal Anti-Inflammatory Drugs to Prevent Cancer Recurrence

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Abstract

Genomic testing and targeted use of non-steroidal anti-inflammatory drugs (NSAIDs) may mitigate cancer recurrence risks. This study examines colorectal cancer (CRC) survivors' interest and receptivity to these strategies. Patients diagnosed with stage I-III CRC in 2004–2012 were recruited through the New Mexico Cancer Registry to complete a cancer survivorship experiences survey. We assessed interest in genomic testing, daily aspirin (ASA) and NSAID use, and receptivity to future daily ASA/NSAIDs. Descriptive statistics and multivariable logistic regression models estimated factors associated with genomic testing interest. Receptivity to future ASA/NSAIDs use was estimated for non-users of ASA/NSAIDs. Among CRC survivors (n = 273), 83% endorsed interest in genomic testing, 25% were ASA users and 47% ASA/NSAIDs users. In our final model, genomic testing interest was associated with being uncoupled [OR = 4.11; 95% CI = 1.49–11.35], low income [OR = 0.35, 95% CI: 0.14–0.88], smoking history [OR = 0.35, 95% CI: 0.14–0.90], low [OR: 0.33, 95% CI: 0.07–1.43] and moderate [OR: 0.26, 95% CI: 0.11–0.61] health literacy, and personal CRC risk worry [OR: 2.86, 95% CI: 1.63–5.02, p = 0.0002]. In our final model, ASA use was associated with age [OR: 1.05, 95% CI: 1.01–1.10] and cardiovascular disease history [OR: 2.42, 95% CI: 1.23–4.73, p = 0.010]. Among non-users ASA/NSAIDs, 83% reported receptivity to ASA/NSAIDs to reduce cancer risks, and no significant correlates were identified. The majority of survivors' expressed genomic testing interest and endorsed receptivity toward ASA/NSAIDs use for cancer risk management. Further research to optimize ASA/NSAIDs use guided by genomic testing is warranted.

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INTRODUCTION

In the USA, there are 1.5 million CRC survivors, and this growing population requires long-term surveillance for recurrence and secondary cancers. (Miller et al. 2019) Genomic tests are used to identify inherited genetic variations (germline) and acquired tumor genetic alterations (somatic) in cancer care. With this information, precise pharmacological therapies can be targeted to improve clinical outcomes (e.g., drug safety, personalized supportive care, etc.). (Relling and Evans 2015) Findings from a recent Commission on Cancer Initiative found that 20% of patients receiving curative resection for Stage I-III CRCs had a recurrence within five years, and most occurred before the two-year time point. (Zafar et al. 2020) Moreover, studies suggest as many as 50% of CRC survivors report cancer recurrence fears, (Fisher et al. 2016) and as many as one-third of CRC survivors reported "high" levels of recurrence fears associated with lower quality of life. (Custers et al. 2016; Simard et al. 2013) Fear of recurrence has been shown to be associated with interest in germline testing among breast cancer survivors and survivors of cancers likely of heritable origin (inclusive of CRC survivors). (Bartley et al. 2021) However, there remains a gap in research investigating the acceptability of genomic testing and targeted use of aspirin/non-steroidal anti-inflammatories in recurrence risk management in the broader CRC population.

Genomic testing in CRC survivorship is an evolving landscape. In current clinical practice, tumor genomic sequencing is recommended to screen for Lynch syndrome and to guide the therapeutic management. (Engstrom et al. 2009; Abrha et al. 2020) The clinical criteria for germline testing for a Lynch syndrome diagnosis (e.g., Bethesda and Amsterdam criteria) were revised as new evidence has emerged. (Boland et al. 1998; Jung et al. 2016; Rodriguez-Bigas et al. 1997; Umar et al. 2004) Challenges with the application of selective screening criteria for germline testing have been identified (e.g., limited family history, not all cases meet the high-risk criteria, inconsistent referral, and evaluation among high-risk). (Stoffel et al. 2009; Cross et al. 2013) In response, several expert guidelines recommend universal Lynch syndrome screening. (EGAPP Working Group 2009; Palomaki et al. 2009). Evidence about the application of NSAIDs and other promising pharmacological chemoprevention agents for CRC recurrence risk management continue to evolve. (Zhang et al. 2018) NSAIDs, specifically aspirin, are currently in clinical use for primary CRC prevention and under investigation for effectiveness in preventing cancer recurrence. (Zhang et al. 2018; Umezawa et al. 2019; Chan 2016) Although research investigating clinical applications of NSAIDs and the mechanisms that promote cancer prevention are on the rise, its definitive role in the management of CRC recurrence reduction has not yet been determined. (Zhang et al. 2018).

In 2016, the US Preventive Service Task Force (USPSTF) recommended the initiation of low-dose daily aspirin (ASA) for primary prevention of cardiovascular disease (CVD) and CRC based on age (starting daily use in patients between 50–59 years old), CVD risk (< 10% risk over 10 years), willingness to take ASA for 10 years, and bleeding complication risks. (Bibbins-Domingo 2016) Targeted long-term use of ASA may have the potential to reduce CVD risk and reduce cancer recurrence in patients with a CRC history. (Umezawa et al. 2019; Chan et al. 2012; Garcia-Albeniz and Chan 2011; Rothwell et al. 2010; Ishikawa et al. 2014; Baron et al. 2003; Benamouzig et al. 2012; Logan et al. 2008; Sandler et al. 2003) Genomic information, ascertained from testing, has been proposed as a strategy to guide the use of ASA among CRC survivors who have gene polymorphisms with known sensitivity to aspirin. (Umezawa et al. 2019; Oijen et al. 2006; Zumwalt et al. 2017) As more precise evidence about the mechanisms of ASA/NSAIDs are identified, the potential for drug therapies to optimize clinical outcome and reduce harms using genomic testing becomes closer to being realized. (El-Shami et al. 2015; Perk et al. 2012; Vandvik et al. 2012; Goldstein et al. 2011; USPSTF 2009; Weaver et al. 2013).

Research discerning patient knowledge, attitudes, and preferences about genomic testing and targeted pharmacological interventions provide insights on how to support the implementation of these strategies in cancer care delivery. (McBride et al. 2015) In a study of cancer survivors (across cancer types) recommended to receive chemotherapy, the majority expressed interest in genomic testing to inform treatment and detect the risks of toxicity. (Cuffe et al. 2014) A recent study (Hunter et al. 2015) assessing CRC patients' attitudes about universal Lynch syndrome testing found that the majority of CRC survivors endorsed the potential personal benefits (e.g., better understanding of why they developed cancer, potential relief of not having a genetic condition) as well as benefits for their relatives of receiving testing; the major reservation cited were cost concerns. Another cross-sectional survey (Hamilton et al. 2017) of survivors with metastatic disease (inclusive but not limited to CRC) found that the majority of respondents were interested in germline testing (57%); however, they expressed concerns about potential harms of this information to their families and other patients.

Interest in genomic testing and targeted pharmacological interventions among cancer survivors, including but not limited to ASA use, is needed to support transformations in care delivery. In the Hispanic population, there have been

care delivery disparities related to referral to and receipt of genomic testing, which exacerbate known CRC disparities (earlier age at diagnosis, more advanced disease at diagnosis, and poorer outcomes). (Stefanidis et al. 2006; Miller et al. 2018) Research suggests that institutional practices in care delivery need to be addressed to promote equitable uptake of genomic testing in the Hispanic population. (Muller et al. 2018) The identification of patient-level determinants may help guide the development of multi-level strategies to foster equitable uptake and ultimately improve health outcomes. Recently, Wang et al. (Wang et al. 2020) described unique genomic profiles among the Hispanic population that may partially explain more aggressive clinical phenotypes, which suggests the benefits of individualized prevention and screening, genomic testing and treatments that take ethnicity into consideration may be needed in the future.

More information is needed about perceptions regarding genomic testing to guide CRC recurrence and secondary cancer risk reduction among ethnically and other underserved populations. New Mexico is a minority–majority state (< 50% non-Hispanic White). (Census 2019) Majority of the counties in New Mexico are medically underserved (32 of 33 counties), and the rates of low socioeconomic status (18.2% poverty rate) are the among the highest (ranked 3rd) in the USA. (U.S. Department of Health and Human Services 2015) New Mexico is also geographically disperse (5th among the largest and 6th among the lowest population density states). (World Population Review 2021) Therefore, a survey of New Mexico's cancer survivor population provides insights about the acceptability of genomic testing and targeted use of ASA/NSAIDs in a sample representative of rural, low-income and Hispanics in our cancer center's catchment area, the state of New Mexico. The aim of this study was to examine correlates to CRC survivors' interest in genomic testing, current ASA use, and receptivity toward future ASA/NSAID use to manage CRC recurrence and secondary cancer risks. Findings from our study may inform translational efforts to reduce the risk of recurrence with genomic testing guided interventions and promote health equity.

MATERIALS AND METHODS

Study Design and Source of Participants

The New Mexico Colorectal Cancer Survivor Project is a cross-sectional population-based study, designed to assess survivorship issues among a diverse sample of CRC survivors in New Mexico. The study design and methods have been previously reported (McDougall et al. 2018, 2019; Blair et al. 2019). The study was reviewed and approved by the Human Research Protections Office of the University of New Mexico Health Sciences Center (Federal Wide Assurance #00003255).

Study Population

CRC survivors diagnosed with stage I-III, pathologically confirmed, non-hereditary cancers of the colon or rectum between 2004 and 2012 were identified through the New Mexico Tumor Registry (NMTR), a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of cancer registries. Patients with known hereditary cancers were excluded, based on their self-reported response to a question assessing if they or any member of their family have any hereditary cancer syndromes (e.g., familial adenomatous polyposis (FAP), Gardner's syndrome, attenuated familial adenomatous polyposis, Lynch syndrome, Turcot syndrome, MutYH-associated polyposis, serrated polyposis, Peutz-Jeghers syndrome, and Hamartomatous polyposis syndrome). Inclusion criteria were being between 30–74 years of age and New Mexico residency at time of CRC diagnosis. Exclusion criteria included missing information on questions regarding type of aspirin or other NSAID used regularly (n = 23) and for missing data for the dependent variables regarding interest in genomic testing (n = 5).

Study Procedures and Measures

The NMTR contacted potentially eligible participants via a mailed packet containing a self-administered questionnaire (English or Spanish), a postage paid return envelope, and a $2 bill as an incentive to participate. The questionnaire was designed to provide an assessment of the survivors' psychosocial experiences, health behaviors, symptoms, and medical history. We contacted survivors who did not return a completed survey within three weeks by telephone and asked respondents to complete the survey with a bilingual interviewer. Participants received a $25 merchandise card following completion of the survey.

The main outcomes for this analysis were: 1) genomic testing interest to guide targeted drug therapy for recurrence and secondary cancer risks; 2) ASA use; and 3) likelihood of ASA/NSAID use in those not currently using them (See supplementary Fig. 1 for main outcome survey questions). To assess interest in genomic testing, participants were asked, "How interested would you be in taking a genetic test if this test could help determine a way to prevent cancer from coming back or prevent getting cancer of another type?" Response options were not interested and interested (somewhat/very interested). For our second main outcome, we opted to focus on ASA use rather than the broader category of ASA/NSAIDs. At the time of this analysis, the USPSTF recommended ASA specifically for primary cancer

prevention, and the evidence base for ASA use was stronger for CRC recurrence prevention. (Zhang et al. 2018; Bibbins-Domingo 2016) We assessed daily ASA/NSAID use with the following question: "Do you take aspirin or another non-steroidal anti-inflammatory drug daily for any reason?" We provided participants with a list of aspirin and non-aspirin NSAIDs to select from to reduce misclassification. The next question prompted participants who were taking an ASA or an NSAID to write in the name, frequency, and indication for each medication. We coded individuals as an ASA user, ASA/NSAID user (inclusive of ASA users), and non-ASA/NSAID user based on participant responses. We assessed likelihood of ASA/NSAIDs use for cancer risk management with a single question, "If aspirin or another non-steroidal anti-inflammatory drug could reduce your risk of getting cancer again how likely would you be to take it on a regular basis?" Response options were "not interested (e.g., definitely/probably not want to take it) and interested (e.g., definitely/probably want to take it)." With these responses, we conducted an exploratory analysis (restricted to non-ASA/NSAID users) regarding participant likelihood of taking ASA/NSAIDs to manage cancer risks. We restricted this analysis to non-ASA/NSAID users to identify the group of CRC survivors who maybe in need of educational intervention to guide decision-making about the potential role of ASA/NSAIDs in cancer risk management.

The survey assessed race and ethnicity, marital status, education, and household income. Marital status was categorized as uncoupled (e.g., single, separated, divorced, widowed, or never married) vs. coupled (e.g., married, unmarried couple). Education was dichotomized as "≤high school or GED" and "high school and beyond" (e.g., vocational school or college). We used the 2015 poverty guidelines to calculate 200% above the poverty level using the median value of each household and the number of household members. (U.S. Department of Health and Human Services 2015) Residence was classified using Rural–Urban Commuting Area (RUCA) codes based on the county of residence (at time of diagnosis which were the same addresses used to send the mailed surveys). (Hart et al. 2005) NMTR abstractors collected demographic data (e.g., age, sex, and zip code of residence at the time of diagnosis) and cancer-related variables (e.g., date of diagnosis and tumor stage).

All remaining cancer, health, and psychosocial variables were based on self-report. Survivors' indicated if they had a first-degree relative with a CRC diagnosis (yes/no) and if they had experienced a CRC recurrence (yes/no). Health literacy was assessed using a single-validated measure that asked, "How confident are you filling out forms yourself?" with a five-item response scale. (Chew et al. 2008, 2004) Health literacy responses were classified as "low" (not at all/a little bit), "medium" (somewhat/quite a bit), and "high" (extremely). Global self-reported health was assessed with a single-item. Responses for the 5-point Likert scale were recoded as "positive" (excellent/very good/good) and "negative" (fair/poor). Smoking history was coded into current/former smoker vs. no smoking history. Participants indicated if a health professional diagnosed medical conditions that are associated with an increased risk of CRC or that are common among CRC survivors. CVD history included diagnoses of hypertension, myocardial infarction, or congestive heart failure. Diabetes history was reported separately. Body mass index (BMI) was calculated based on self-reported height and weight. We dichotomized BMI by obesity (BMI ≥ 30 kg/m^2) vs. non-obese (BMI = 18.5–29.9 kg/m^2), consistent with earlier studies from this data set (Blair et al. 2019) and the literature. (Schlesinger et al. 2014; Centers for Disease Control and Prevention 2015).

Psychosocial variables included the frequency and intensity of worry about personal "CRC risk" and personal risk of "getting another type of cancer" and were each assessed separately using a 3-item scale. (McCaul KD & Goetz PW 2020; Glanz et al. 1999) Cronbach's alphas for these items (ranged from 0.77–0.94) were consistent with previous studies demonstrating the reliability of these constructs. (Mullens et al. 2004) Concern about risk for CRC among biological relatives was assessed with a single item with a 4-point Likert style response scale ranging from very concerned to not concerned at all. Distress was measured using the National Comprehensive Cancer Network (NCCN) distress thermometer with the cut point of ≤ 4 classified as "low/no distress" and those scoring 5 + categorized as "mid to high distress." (Holland et al. 2013).

Statistical Analysis

Univariate logistic regression models were used to examine associations between socio-demographics, cancer, general health, and psychosocial factors in relation to: (1) interest in genomic testing; (2) current aspirin use; and (3) likelihood of use of aspirin or other NSAIDs for chemoprevention (restricted to non-ASA/NSAID users). Survivors who were "not interested" in genomic testing, non-ASA, and non-ASA/NSAID users served as the reference groups for these analyses, respectively. In our multivariable logistic models, factors were identified for inclusion using forward stepwise logistic regression with the following parameters: $p < 0.20$ to enter the model and $p < 0.05$ to remain in the model. Variables with the highest p-values were removed one by one until only significant predictors remained ($p < 0.05$). All analyses were conducted using SAS (9.4) (SAS Institute, Inc.)

RESULTS

Characteristics of the Sample

Among the three hundred and one CRC survivors who completed the survey, 91% (n = 273) met the overall eligibility criteria and were included in this analysis. The contact rate was 57.5% (i.e., percentage contacted by mail or telephone) and the cooperation rate was 62% (i.e., those enrolled based on number contacted).

The mean age was 62.6 (SD = 7.7) years; 51% were male, 38% resided in a rural area, and 42% self-identified as Hispanic, 35% had a household income that was 200% below the federal poverty level. Majority of the sample identified as White/Caucasian (96.0%), with 2.2% American Indian/Alaskan Native, 0.4% Asian, and 1.5% multiple races (see Table 1). The majority of respondents had stage I-II CRC (67%), and nearly half (48%) were diagnosed within the prior 5 years of the study period. More than half of survivors had a history of CVD (53%), one quarter (26%) reported negative (e.g., fair-poor) health overall, and one-fifth (22%) had a previous diagnosis of diabetes. The mean level of worry about CRC recurrence or risk of other cancer was low (mean 2.0–2.1; SD = 0.9–1.0). Approximately, half (52%) of survivors reported higher levels of concerns about CRC risk for family members and nearly one-third (31%) of survivors reported moderate to severe levels of cancer-specific distress.

Correlates Associated with Interest in Genomic Testing

The majority of participating cancer survivors (83%) were interested in genomic testing to guide recurrence management strategies (Table 1). Survivors who were uncoupled had 2.56 times the odds of interest in genomic testing compared to those who were coupled (Table 2). Current and former smoking history (OR: 0.36, 95% CI: 0.16–0.8) was associated with decreased likelihood of testing interest compared to survivors with no smoking history. Survivors with low or moderate health literacy had 61% and 77% lower odds of interest compared to those with high literacy (OR = 0.39; 95% CI: 0.11–1.37 and OR = 0.23; 95% CI = 0.11–0.49, respectively; p = 0.0006).

In the adjusted model, factors associated with interest in genomic testing included: marital status; household income, smoking status, health literacy, and worry about CRC recurrence (Table 3). Survivors who were uncoupled had a 4.11 greater odds (95% CI: 1.49–11.35, p = 0.006) of expressing interest in genomic testing compared to coupled survivors. Survivors residing in low income households

Table 1 Characteristics of the sample (n = 273)

Demographic factors	
Age, mean	62.6 ± 7.7
Sex	
Male	140 (51.3%)
Female	133 (48.7%)
Residence	
Urban	169 (61.9%)
Rural	104 (38.1%)
Race	
American Indian/Alaskan Native	6 (2.2%)
Asian	1 (0.4%)
more than one	4 (1.5%)
White/Caucasian	262 (96.0%)
Ethnicity*	
Non-Hispanic	158 (58.1%)
Hispanic	114 (41.9%)
Marital Status	
Coupled	177 (64.8%)
Uncoupled	96 (35.2%)
Education	
≤ High school or GED	74 (27.1%)
Beyond High School	199 (72.9%)
Income	
Low	90 (35.2%)
Moderate–High	166 (64.8%)
Cancer related factors	
Stage	
Stage I-II	182 (66.7%)
Stage III	91 (33.3%)
Time since Diagnosis	
≤ 5 years (inclusive)	130 (47.8%)
> 5 years	142 (52.2%)
CRC in first degree relative	
Yes	38 (13.9%)
No	235 (86.1%)
Recurrent CRC	
Yes	17 (6.2%)
No	256 (93.8%)
Health-related Factors	
Health literacy	
Low	23 (8.5%)
Medium	116 (42.8%)
High	132 (48.7%)
General health	
Positive	200 (73.8%)
Negative	71 (26.2%)
Smoking History	
Current/former smoker	180 (66.2%)
No history	92 (33.8%)
History of CVD	
Yes	141 (53.2%)

Table 1 (continued)

Demographic factors	
No	124 (46.8%)
History of Diabetes	
Yes	58 (21.6%)
No	211 (78.4%)
BMI	
Normal/Overweight	168 (62.7%)
Obese	100 (37.3%)
Psychosocial Factors	
Worry/Bother about personal CRC risk	2.1 ± 0.96
Worry/Bother personal risk of non-CRC cancers	2.0 ± 0.89
Concern about CRC risk for family members	
High concern	141 (52.2%)
Low/No concern	129 (47.8%)
Distress	
Low/No distress	181 (68.8%)
Mid/High Distress	82 (31.2%)

Abbreviations ASA: daily aspirin use, BMI: Body Mass Index, CRC: colorectal cancer, CVD: cardiovascular disease, GED: general education diploma, NHW: non-Hispanic White, NSAID: non-steroidal anti-inflammatory drug

had a 0.35 lower odds (95% CI: 0.14–0.88, p = 0.03) of expressing interest compared to those with middle to high-income households. Survivors with positive smoking histories had a decreased likelihood (OR: 0.35, 95% CI: 0.14–0.9, p = 0.03) of expressing interest in genomic testing compared to survivors who never smoked. Survivors with low or moderate health literacy had 67% and 74% lower odds of interest compared to those with high literacy (OR = 0.33; 95% CI: 0.07–1.43 and OR = 0.26; 95% CI = 0.11–0.61, respectively; p = 0.009). For every unit increase in self-reported worry/bother about personal CRC risk, the odds of reporting interest in genomic testing increased by a factor of 2.86 (95% CI: 1.63–5.02, p = 0.0002).

Current Daily Aspirin Use

Twenty-five percent of CRC survivors reported taking ASA daily. Age, CVD history, and diabetes history were significant correlates of ASA use (Table 2). Each additional year of age was associated with 1.06 greater odds (95% CI: 1.02–1.10, p = 0.006) of ASA use. Survivors with a history of CVD had 3.46 greater odds of ASA use (95% CI: 1.87–6.41, = < 0.0001) compared to survivors with no CVD history. Survivors diagnosed with diabetes had 2.49 greater odds (95% CI: 1.34–4.65, p = 0.004) of ASA use compared to survivors with no diabetes history. A multivariable model found that the only variables associated with current ASA use were age and CVD history. In the adjusted model, each additional year of age was associated with 1.05 greater odds (95% CI: 1.01–1.10, p = 0.03) of ASA use. In this model, survivors with CVD history had 2.42 greater odds (95% CI: 1.23–4.37, p = 0.01) of daily ASA use compared to survivors with no CVD history (data not shown).

Likelihood of Future ASA/NSAID Use for Cancer Risk Management among non ASA/NSAIDs users

About one-half (53%) of CRC survivors reported not taking either ASA or NSAIDs daily. Among non-ASA/NSAID users, the majority of CRC survivors were receptive to taking ASA or NSAIDs to manage cancer risk (83.3%). There were no significant correlates for interest in taking ASA/NSAIDs for recurrence risk reduction in univariate analyses.

There were no significant differences between Hispanics and non-Hispanics and rural and non-rural populations for the three main outcomes of this study.

DISCUSSION

This study is among the first to examine CRC survivors' interest in genomic testing for recurrence risk, current ASA/NSAIDs use, and receptivity for future use of ASA and other NSAIDS to manage cancer risks. Overall, survivors' reported high levels of interest in genomic testing and future use of ASA/NSAIDs to manage cancer risks. This study provides insights into the perceptions of genomic testing and targeted NSAID use in a socioeconomically, ethnically (42% identified as Hispanic), and geographically (38% rural) diverse population. Factors associated with receptivity can inform the development of tailored communications to guide genomic testing and NSAID decision making for individuals with low–moderate health literacy and managing substantial CVD comorbidity (53%). Worry about cancer recurrence or secondary cancers was independently associated with interest in genomic testing. In our sample, (e.g., CRC survivors who do not have known hereditary cancer syndromes) the factors associated with interest in genomic testing (i.e., marital status and cancer worry) are consistent with prior findings of similar studies that surveyed survivors with intermediate familial risks. (Anderson et al. 2001) Interest in genomic testing appears to be associated with both social (i.e., being uncoupled, income, health literacy) and behavioral (i.e., smoking, personal risk worries) factors.

Despite known general and cancer-related benefits of ASA, (Rothwell et al. 2010, 2012; Chan et al. 2009; Liao et al. 2012) only one-quarter of CRC survivors reported daily ASA use. Further, although more than half of the sample of CRC survivors reported a CVD history, ASA use remained relatively low. Among non-users of ASA and NSAIDs, over three quarters expressed interest in using ASA/NSAIDs

Table 2 Univariate analysis of correlates of genomic testing interest, daily aspirin use, and receptivity to taking ASA/NSAID for cancer risk among CRC survivors (n = 273)

	Interest in Genomic Testing		**Current ASA Use**		**Receptivity to ASA or NSAID Use$_1$**	
Demographics	OR (CI 95%)	P-Value	OR (CI 95%)	P Value	OR (CI 95%)	P Value
Age	0.98 (0.94–1.02)	0.35	1.06 (1.02–1.10)	.006	0.96 (0.90–1.02)	0.14
Sex						
Male	Ref	0.32	Ref	0.86	Ref	0.24
Female	1.16 (0.61–2.19)		0.95 (0.55–1.65)		1.72 (0.70–4.24)	
Residence						
Urban	Ref	0.41	Ref	0.13	Ref	0.88
Rural	0.76 (0.40–1.45		0.64 (0.36–1.14)		1.08 (0.43–2.72)	
Race						
Ethnicity						
Hispanic	Ref	0.71	Ref	0.98	Ref	0.71
Non-Hispanic	1.13 (0.59–2.16)		0.99 (0.57–1.73)		0.84 (0.34–2.07)	
Marital Status						
Coupled	Ref	0.02	Ref	0.94	Ref	0.69
Uncoupled	2.56 (1.18–5.55)		0.98 (0.55–1.73)		1.21 (0.47–3.17)	
Education						
≤ High school or GED	0.57 (0.29–1.12		0.84 (0.45–1.58)		0.92 (0.35–2.42)	
Beyond High School	Ref	0.10	Ref	0.59	Ref	0.87
Income						
Low	Ref	0.08	Ref	0.45	Ref	0.57
Moderate–High	1.85(0.93–3.66)		1.26 (0.69–2.31)		1.31 (0.52–3.34)	
Time since Dx						
≤ 5 years	Ref	0.33	Ref	0.99	Ref	0.17
> 5 years	1.37 (0.73–2.59		1.00 (0.58–1.73)		0.53 (0.21–1.32)	
Cancer Stage						
Stage I-II	Ref	0.57	Ref	0.77	Ref	0.64
Stage III	0.83 (0.43–1.60)		0.92 (0.51–1.64)		1.26 (0.48–3.28)	
CRC in 1st degree relative						
Yes	1.09 (0.43–2.79)		1.91 (0.93–3.94)		0.51 (0.15–1.74)	
No	Ref	0.85	Ref	0.08	Ref	0.28
Recurrent CRC						
Yes	0.94 (0.26–3.42)		1.67 (0.59–4.70)		0.68 (0.13–3.50)	
No	Ref	0.93	Ref	0.33	Ref	0.65
Health related Factors						
Health literacy						
Low	0.39 (0.11–1.37)		1.03 (0.35–3.02)		0.43 (0.10–1.90)	
Medium	0.23 (0.11–0.48)		1.67 (0.94–2.97)		0.96 (0.38–2.47)	
High	Ref	0.0006	Ref	0.14	Ref	0.53
General health						
Positive	Ref	0.98	Ref	0.95	Ref	0.94
Negative	1.01 (0.49–2.07)		1.02 (0.55–1.90)		0.96 (0.33–2.83)	
Smoking History						
No history	Ref	0.01	Ref	0.33	Ref	0.38
Current or former smoker	0.36 (0.16–0.8)		1.35 (0.74–2.44)		0.65 (0.25–1.70)	
History of CVD						
Yes	0.80 (0.42–1.53)		3.46 (1.87, 6.41)		1.43 (0.58–3.52)	
No	Ref	0.5	Ref	< 0.0001	Ref	0.44
History of Diabetes						

Table 2 (continued)

	Interest in Genomic Testing		Current ASA Use		Receptivity to ASA or NSAID Use$_1$	
Yes	0.54 (0.27–1.10)		2.49 (1.34–4.65)		1.07 (0.33–3.46)	
No	Ref	0.09	Ref	0.004	Ref	0.91
BMI						
Normal/Overweight	Ref	0.35	Ref	0.38	Ref	0.25
Obese	1.39 (0.70–2.76)		1.29 (0.73–2.26)		1.87 (0.65–5.39)	
Psychosocial Factors						
Worry/Bother about personal CRC risk	2.45 (1.53–3.92)	0.0002	0.89 (0.66–1.19)	0.43	0.93 (0.57–1.54)	0.79
Worry/Bother personal risk of non-CRC cancers	2.36 (1.46–3.82)	0.0005	1.06 (0.78–1.44)	0.72	1.07 (0.62–1.87)	0.80
Concern about CRC risk for family members						
High concern	Ref	0.87	Ref	0.12	Ref	0.20
Low/no concern	1.06 (0.56–2.00)		1.55 (0.89–2.69)		0.55 (0.22–1.36)	
Distress						
Low/no distress	Ref	0.88	Ref	0.86	Ref	0.16
Mid/high distress	1.06 (0.52–2.15)		0.95 (0.52–1.73)		2.49 (0.69–8.97)	

Abbreviations ASA: daily aspirin use, BMI: Body Mass Index, CI: confidence interval, CRC: colorectal cancer, CVD: cardiovascular disease, GED: general education diploma, NHW: non-Hispanic White, NSAID: non-steroidal anti-inflammatory

Notes: 1-Only CRC survivors currently not using ASA or any NSAIDs were included in this analysis (n = 144)

Table 3 Multivariate patient factors associated with interest in genomic testing

	Final Multivariable Model
Variable	*OR[a] (95% CI)[b]*
Marital Status	
Coupled	1.00 (ref)
Uncoupled	4.11 (1.49–11.35), p = 0.006
Household Income	
Low	0.35 (0.14–0.88), p = 0.03
Moderate to High	1.00 (ref)
Smoking History	
No History	1.00 (ref)
Current or Former	0.35 (0.14–0.90), p = 0.03
Health Literacy	p = 0.009
Low	0.33 (0.07–1.43)
Moderate	0.26 (0.11–0.61)
High	1.00 (ref)
Worry/bother about personal CRC risk	2.86 (1.63–5.02), p = 0.0002

a = OR: odds ratio, b = CI: confidence interval

for cancer risk management. Hawkins and colleagues have reported that cancer survivors are less likely to use adult (325 mg) or baby strength (81 mg) aspirin compared to non-cancer controls. (Hawkins et al. 2017) In contrast, another study found that 51% of cancer survivors reported taking daily ASA compared to 46% among non-cancer matched controls. (Gupta et al. 2018) Nevertheless, the prevalence of ASA use among our sample (25%) was appreciably lower than previously reported in other studies (42–58%). (Gupta et al. 2018; Zanders et al. 2015; Hua et al. 2017) Rates reported by Hua et al. (2017) illustrated wide variations in use of ASA and NSAIDs post-CRC, with prevalence rates ranging from 5–58% based on the geographic location.

Notably, interest in genomic testing, ASA use and receptivity to NSAIDs/ASA for recurrence risk management were not significantly associated with Hispanic ethnicity. This finding suggests that interest may not be a barrier to equitable uptake to genetic testing among Hispanics, and translational efforts to address ethnic disparities should focus on increasing awareness, patient education, and addressing individual, interpersonal, as well as systemic barriers at clinical sites (e.g., risk assessment and communication and referral patterns). (Muller et al. 2018) Previous studies have reported suboptimal use of ASA among Hispanics for primary and secondary CVD prevention, despite greater prevalence of diabetes. (Sanchez et al. 2011; Brown et al. 2005; Ajani et al. 2005; Qato et al. 2010). The prevalence of ASA for CVD prevention among an urban Hispanic population (22%) was found to be associated with discussions with and recommendations from a health care provider. (Misialek and Van't Hof JR, Oldenburg NC, Jones C, Eder M, 2020). In our study, the rates of ASA use were similar for non-Hispanics and Hispanics, with 25% of each subpopulations reporting daily use. These rates may be due to secular trends and ongoing controversies about the safety and efficacy of ASA use for cancer and CVD prevention. (Raber et al. 2019).

The strongest association with interest in genomic testing was being uncoupled. This finding was consistent with a study that assessed genomic testing interest among individuals with intermediate risk based on family history that found unmarried individuals had more interest in testing (Anderson et al. 2014). However, this finding contradicts patterns found in screening for the early detection of CRC among average risk individuals. (El-Haddad et al. 2015) Among average risk individuals without a personal history of cancer, being unmarried has been shown to be positively associated with non-adherence to CRC screening recommendations. (El-Haddad et al. 2015) Previous research focused on interests in genomic testing, surveyed women with breast cancer and individuals at average risk for CRC, and found relationship status was not associated with interest in testing. (Anderson et al. 2014; Leventhal et al. 2013) Our analysis may overestimate the association of being "uncoupled" with interest in genomic testing. In this analysis, we included those who were separated, divorced, widowed, and never married in the "uncoupled" category due to smaller numbers for each discrete grouping, which would limit analytical precision. This limitation was also noted in the Anderson et al. (Anderson et al. 2014) study which also found a positive association between unmarried status with increased interest in genomic testing among individuals with a family history of colorectal cancer. Similarly, we did not measure parental status, and this may confound patient interest levels in genomic testing. Previous studies have shown that being able to share information with family members to mitigate risk is a significant predictor of interest in genomic testing. (Hunter et al. 2015; Hamilton et al. 2017; Anderson et al. 2014) Future research is needed to parse out the differences in CRC survivors' motivations (their own health vs. their relatives) for genomic testing, both germline and somatic, to provide more clarity regarding the social context of these decisions.

Our study found that cancer worry was associated with interest in genomic testing, which is consistent with studies investigating interest in germline testing for hereditary cancer (Bartley et al. 2021) and genomic testing among individuals with a family history CRC. (Anderson et al. 2014) It is noteworthy that this study's primary outcome, genomic testing interest, assessed a theoretical laboratory test that would help guide interventions that might mitigate the risk of cancer recurrence or secondary cancers. A qualitative study (Leventhal et al. 2013) explored interest in germline testing for CRC susceptibility to guide screening recommendations among average risk individuals and found that the potential of providing information that was clinically actionable to manage health and risks were associated with greater patient interest. (Leventhal et al. 2013) Cancer-related fears about recurrence are common in the CRC population, and this may be a main driver of interest in testing given that interest was predicated on this information being actionable. (Fisher et al. 2016) A study investigating the impact of receiving genomic recurrence risk analysis estimates among women with early-stage, estrogen receptor-positive breast cancers demonstrated that patients were responsive to these results. (Evans et al. 2016) found that after receiving a genomic recurrence risk score, women with early stage breast cancers perception of recurrence risk decreased but distress levels remained unchanged. This study also demonstrated that although patients with higher recurrence risk scores were more likely to opt for adjuvant chemotherapy their perception of the pros/cons of chemotherapy were significant in that process. (Evans et al. 2016) Therefore, it is important to assess both recurrence risk and the acceptability of possible therapeutic options that may be offered. Our study found that both the unspecified drug to reduce recurrence risks and secondary cancers posed in the genomic testing interest question and ASA/NSAIDs were acceptable to majority of the CRC survivors surveyed.

Decreased interest in genomic testing was associated with former and/or current smoking and low-income status. This is consistent with previous research, which demonstrated that higher-income levels are associated with greater awareness and knowledge of genetic testing for cancer susceptibility and treatment-focused genomic testing. (Mai et al. 2014; Wolyniec et al. 2020) Low-income survivors (across cancer sites) are 2.7 times more likely to be smokers compared to high-income survivors. (Naik et al. 2016) Smokers and former smokers' engagement with various cancer-related testing is situation-specific. Olfson et al. (Olfson et al. 2016) found that current smokers were much more interested in their genetic risk results for lung cancer susceptibility (65%) compared to former smokers (50%) and those who never smoked (37%). Prior research indicates that fatalistic beliefs about cancer and treatment expectancies influence cancer prevention health decisions; thus, these factors may require further exploration related to genomic testing. (Smits et al. 2018).

The USPSTF updated their recommendations for primary CVD prevention in 2016 to include ASA use for primary CRC prevention. (Bibbins-Domingo et al. 2016) Since that time, evidence has emerged from three trials in 2018 (Bowman et al. 2018; Gaziano et al. 2018; McNeil et al. 2018) indicating that the bleeding risks may outweigh the benefit of ASA use for primary CVD prevention (Mahmoud et al. 2018). As the CVD clinical community determines the best path forward for risk stratification, clinical trials are underway to identify the mechanisms of aspirin and NSAIDs in CRC cancer risk management. The randomized phase III Alliance 80,702 trial failed to demonstrate a significant 3-year disease free survival or 5-year overall survival benefit with the addition of the non-steroidal anti-inflammatory agent, celecoxib, in stage III CRC. However, the aspirin for Dukes C and High Risk Dukes B Colorectal Cancers study

(ASCOLT) trial will more directly clarify the role of ASA in resected CRC. (Shi et al. 2017; Ali et al. 2011) These findings have the potential to inform clinical decision making for ASA and NSAIDs use in recurrence risk reduction. (Sankaranarayanan et al. 2020; Aimo and Caterina 2019).

Given the new evidence challenging the utility of ASAs role in CVD prevention due to bleeding risks, (El-Shami et al. 2015; Perk et al. 2012; Vandvik et al. 2012; Goldstein et al. 2011; Bibbins-Domingo 2016) there is a greater need to discern CRC survivors' behavioral intentions of daily ASA use. In our sample, the prevalence of ASA use among survivors with CVD (75%) was high. Despite risks associated with diabetes comorbidity during CRC survivorship (e.g., decreased likelihood of progression-free survival, higher morbidity, all-cause, and cancer specific mortality), ASA use among CRC survivors with diabetes (34%) in our sample was suboptimal. (Boakye et al. 2018; Jiang et al. 2011; Mills et al. 2013; Croft et al. 2019) In our study, the motivating clinical indication for ASA use was unknown; however, if it were CRC recurrence risk management, we would expect to observe higher rates of ASA among survivors less than five years from diagnosis when the risk for recurrence is greater. However, rates of ASA use in our sample were equally distributed between early phase survivors and those five-year post-diagnosis. Current CRC survivorship guidelines do not specifically recommend ASA use to prevent CRC recurrence; however, risk stratified approaches of ASA recommendation for CVD are on the horizon and will likely factor into clinical decision making (El-Shami et al. 2015; Perk et al. 2012; Vandvik et al. 2012; Goldstein et al. 2011; Bibbins-Domingo 2016) underscoring the significance of our study in planning to implement targeted NSAID use to reduce cancer recurrence.

Our study includes a few notable limitations. First, the generalizability of our findings is limited as we utilized a regional sampling strategy. While we cannot generalize nationally, the sample includes subpopulations (e.g., Hispanics, individuals with lower income, and rural dwellers) underrepresented in cancer survivorship and genomic research. Our research team employed evidence-based survey methods to improve response rates; (Dillman 2011) however, only 56% of eligible potential subjects completed the questionnaire. This response rate is higher than many current national surveys. (Chawla et al. 2016) Respondents were more likely to be non-Hispanic and reside in urban areas compared to non-respondents, which may have inflated the level of interest for testing and underestimated the prevalence of ASA/NSAID use. The ASA/NSAID use measure was based on a multi-step, self-report question series that required participants to accurately recall and report the drug and frequency of administration, subjecting the variable to potential recall bias. Information regarding dosage or duration of ASA/NSAID use was not available, which are important considerations in examining the associations between ASA/NSAID use and CRC recurrence risk management strategies.

In conclusion, this study is an important initial step toward understanding the potential implementation of genomic testing and targeted NSAID use for CRC recurrence reduction. The majority of CRC cancer survivors cited interest in genomic testing to guide cancer-risk management strategies. Future research is warranted to better understand the motivational impact of genomic risk communication related to chemoprevention that is tailored to cancer patients' genomic profiles. (McBride et al. 2015).

Further research is needed to ensure that low-income survivors, survivors with low health literacy, and present and former smokers have the necessary knowledge about recurrence prevention. Previous research highlights the importance of patient education and healthcare provider interactions in decision making about ASA/NSAID use. (Misialek JR et al. 2020) Additional research is needed to explore whether and how oncology and primary care providers recommend ASA/NSAIDs for CRC/CVD prevention and recurrence risk reduction and the management of other chronic diseases in cancer survivors. The need for educational and decision support resources will be particularly important if future translational research demonstrates the clinical utility of genomic testing and beneficial effects of ASA/NSAIDs to reduce the risk of recurrence.

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Declarations

Conflict of Interest Drs. Denalee O'Malley, Cindy Blair, Alissa Greenbaum, Charles Wiggins, Ashwani Rajput, Vi Chiu, and Anita Kinney declare that they have no conflict of interest.

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