Research Article

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The Impact of Receiving Predictive Genetic Information about Lynch Syndrome on Individual Colonoscopy and Smoking Behaviors

Joanne Soo-Min Kim[1,2], Peter C. Coyte[1,2], Michelle Cotterchio[3], Louise A. Keogh[4], Louisa B. Flander[5], Clara Gaff[6,7], and Audrey Laporte[1,2]

Abstract

Background: This study investigated whether receiving the results of predictive genetic testing for Lynch syndrome, indicating the presence or absence of an inherited predisposition to various cancers, including colorectal cancer, was associated with change in individual colonoscopy and smoking behaviors, which could prevent colorectal cancer.

Methods: The study population included individuals with no previous diagnosis of colorectal cancer, whose families had already identified deleterious mutations in the mismatch repair or *EPCAM* genes. Hypotheses were generated from a simple health economics model and tested against individual-level panel data from the Australasian Colorectal Cancer Family Registry.

Results: The empirical analysis revealed evidence consistent with some of the hypotheses, with a higher likelihood of undergoing colonoscopy in those who discovered their genetic predisposition to colorectal cancer and a lower likelihood of quitting smoking in those who discovered their lack thereof.

Conclusions: Predictive genetic information about Lynch syndrome was associated with change in individual colonoscopy and smoking behaviors but not necessarily in ways to improve population health.

Impact: The study findings suggest that the impact of personalized medicine on disease prevention is intricate, warranting further analyses to determine the net benefits and costs. *Cancer Epidemiol Biomarkers Prev; 25(11); 1524–33. ©2016 AACR.*

Introduction

Personalized medicine refers to the tailoring of preventive, diagnostic, and therapeutic interventions to the characteristics of individuals, using advanced biomedical technologies (1). Its ability to identify genetic susceptibilities to preventable diseases, obtain unequivocal diagnostic results, and tailor drug therapies on an individual basis promises to revolutionize health care and improve population health (2, 3).

Many promises of personalized medicine have been realized, especially in cancer treatment (4). Its impact in cancer prevention, such as predictive genetic testing—assessing whether individuals with a family history, but no previous diagnosis, of a genetic disorder carry their family's deleterious genetic mutation and are at elevated risk of developing the disease in the future—has also been demonstrated. For example, positive results from predictive genetic testing for hereditary breast cancer or Lynch syndrome are associated with increased adherence to risk-reducing strategies, such as prophylactic surgery or surveillance (5), although behavioral change from predictive genetic information has generally been deemed less than expected (6, 7).

Building on this literature, this study investigated whether receiving a positive or negative result from predictive genetic testing for Lynch syndrome was associated with change in individual health behaviors in Australasians. The lifetime probability of developing colorectal cancer is estimated to be 54% to 74% for men and 30% to 52% for women with Lynch syndrome, compared with 5% to 6% for the general population (8–10). Various health behaviors have been demonstrated to reduce the risk of hereditary colorectal cancer in Lynch syndrome families, such as colonoscopy use (11, 12), smoking (13, 14), and other lifestyle behaviors, including diet (15). On the basis of data availability, this study focused on colonoscopy and smoking behaviors. Colonoscopy is recommended for the prevention and early detection of colorectal cancer for individuals at elevated risk (11), and its use has been shown to change upon genetic testing for Lynch syndrome (16–23). Smoking represents a broader array of health behaviors that also affect the incidence of colorectal cancer, but the impact of genetic testing for Lynch syndrome on smoking, or any other lifestyle behaviors, is yet to be assessed.

From a simple health economics model, we generated hypotheses on the impact of the new information that the advanced biomedical technology provides. We then tested the hypotheses

[1]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. [2]Canadian Centre for Health Economics, Toronto, Canada. [3]Prevention and Cancer Control, Cancer Care Ontario, Toronto, Canada. [4]Centre for Health Equity, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia. [5]Centre for Epidemiology and Biostatistics, University of Melbourne, Melbourne, Australia. [6]Department of Paediatrics, University of Melbourne, Melbourne, Australia. [7]Department of Medicine, University of Melbourne, Melbourne, Australia.

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Corresponding Author: Joanne Soo-Min Kim, Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street Suite 425, Toronto, Ontario, M5T 3M6, Canada. Phone: 1-416-985-8302; Fax: 1-416-978-7350; E-mail: joanne.kim@mail.utoronto.ca

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against individual-level panel data. Our study distinguished individuals with a positive genetic predisposition ("carriers") from those without ("noncarriers"), as well as individuals who received their genetic testing results ("receivers") from those who did not ("nonreceivers").

In what follows, we present our hypotheses, data, and empirical strategy. We then describe our results. The final section discusses and concludes.

Materials and Methods

Hypotheses

We developed a model of utility maximization under uncertainty that incorporated Ehrlich and Becker's concepts of self-insurance and self-protection (24). The full model is presented in Supplementary Materials and Methods. Briefly, our model characterized the occurrence of colorectal cancer as a probabilistic event, in which carriers have a higher probability of developing colorectal cancer, compared with noncarriers (8, 9). The probability of developing colorectal cancer was defined as a combination of exogenously determined genetics and endogenously determined health behaviors, namely, colonoscopy use and smoking. Receivers, unlike nonreceivers, have an opportunity to change their behaviors, based on the results that are returned to them. Our model predicts that carriers who receive their genetic information are more likely to undergo colonoscopy but less likely to smoke, compared with carriers who do not receive their genetic information, as the opportunity cost of foregoing healthy behaviors rises with increasing risk. Our model also predicts that noncarriers who receive their genetic information are less likely to undergo colonoscopy but more likely to smoke, compared with noncarriers who do not receive their genetic information, as the opportunity cost of investing in healthy behaviors rises with decreasing risk. The predictions were tested empirically.

Data source

We used data from the Australasian Colorectal Cancer Family Registry (ACCFR) for the statistical analysis. Ethics approval for the analysis was obtained from the Office of Research Ethics at the University of Toronto (Toronto, Canada). Detailed descriptions of the ACCFR were provided by Newcomb and colleagues (25) and Jenkins and colleagues (26). Here, we provide an overview of the ACCFR registrant recruitment, data collection, and genetic testing.

ACCFR registrant recruitment. Between 1997 and 2007, the ACCFR used several recruitment strategies. Individuals who were diagnosed with their first colorectal cancer between the ages of 18 and 59 years (1997–2001) or 18 and 49 years (2001–2006) were identified from the population-based Victorian Cancer Registry. Cases of colorectal cancer or other Lynch syndrome–related cancers (i.e., of the endometrium, stomach, small intestine, urinary tract, or central nervous system) were also identified from seven family cancer clinics across Australia and New Zealand. From these clinics, individuals at high risk of Lynch syndrome were also identified, using the Amsterdam criteria (27). All identified individuals, known as probands, were invited to register with the ACCFR. The probands' first- and second-degree relatives, as well as other relatives with previous diagnosis of any cancer, were also invited to register with the ACCFR (25). Therefore, the ACCFR registrants comprised individuals with previous diagnosis of colorectal cancer or other Lynch syndrome–related cancers and their first-degree, second-degree, and more distant relatives with or without any cancer.

ACCFR data collection. The ACCFR registrants were asked to complete an interviewer-administered questionnaire at enrollment ("baseline") and after 5 years ("follow-up"). The baseline questionnaire asked about the registrants' socio-demographic factors (e.g., age, sex, marital status, and education), health behaviors (e.g., colonoscopy use and smoking), and medical conditions (e.g., previous cancer diagnosis). The follow-up questionnaire obtained updates on the registrants' health behaviors and medical conditions. All reported incidents of Lynch syndrome–related cancers were verified against medical records (25, 26).

ACCFR genetic testing. The ACCFR registrants were asked to provide a blood sample for the purpose of conducting research and not for the purpose of genetic testing *per se*. Instead, blood samples of the registrants whose families had previously identified deleterious mutations in the mismatch repair (MMR) or *EPCAM* genes were tested for their families' genetic mutations by the ACCFR. Therefore, the registrants did not choose to undergo genetic testing, and the availability of their results at the ACCFR was free of potential selection bias associated with the choice to undergo genetic testing. The registrants were informed of the availability of their results and referred to a genetic counseling clinic to receive formal retesting and their results free of charge (28–30).

Study participant selection

The study population for the analysis included all registrants of the ACCFR that would have been eligible for predictive genetic testing for Lynch syndrome, having (i) no previous diagnosis of colorectal cancer at follow-up so that the testing would be truly predictive; and (ii) a family with a previously identified deleterious mutation in the MMR or *EPCAM* genes so that testing for that mutation would conclusively distinguish carriers from noncarriers. A total of 1,753 registrants of the ACCFR satisfied the conditions and had been tested and identified as either carriers or noncarriers of their families' deleterious mutations in the MMR or *EPCAM* genes. However, 1,246 of the 1,753 individuals had insufficient information on whether or when their genetic testing results had been disclosed to them and were excluded from the analysis. Therefore, the study sample for the analysis comprised 507 individuals who had sufficient information on whether or when their results had been disclosed to them.

Measures and statistical analysis

We used logit regression to estimate the probability that an individual underwent colonoscopy or smoked between baseline and follow-up (i.e., yes/no), $I_{B\text{-}F}$ or $S_{B\text{-}F}$, respectively, as a function of the carrier status (i.e., carrier/noncarrier), G; the receiver status at follow-up (i.e., receiver/nonreceiver), R_F; previous cancer diagnosis at follow-up (i.e., yes/no), H_F; the interaction of the carrier and receiver statuses and previous cancer diagnosis at follow-up, $G \times R_F$, $G \times H_F$, $R_F \times H_F$, and $G \times R_F \times H_F$; a vector of the socio-demographic (i.e., age at follow-up, sex, marital status, and education) and colorectal cancer awareness (i.e., degree of

relatedness to family probands) factors, D_F; and colonoscopy use or smoking at baseline (i.e., yes/no), I_B or S_B, respectively. In other words:

$$logit(P(I_{B-F})) = \alpha_0 + \alpha_1 G + \alpha_2 R_F + \alpha_3 H_F + \alpha_4 GxR_F + \alpha_5 GxH_F + \alpha_6 R_F xH_F + \alpha_7 GxR_F xH_F + \alpha_8 D_F + \alpha_9 I_B + \varepsilon_I$$

$$logit(P(S_{B-F})) = \beta_0 + \beta_1 G + \beta_2 R_F + \beta_3 H_F + \beta_4 GxR_F + \beta_5 GxH_F + \beta_6 R_F xH_F + \beta_7 GxR_F xH_F + \beta_8 D_F + \beta_9 S_B + \varepsilon_S$$

Table 1 provides the full variable list, including the scales and sources of the variables.

Colonoscopy use and smoking between baseline and follow-up (i.e., $I_{B\text{-}F}$ and $S_{B\text{-}F}$), as well as before baseline (i.e., I_B and S_B), were defined in terms of propensity (i.e., yes/no) to undertake the behaviors. We adjusted for the respective behaviors at baseline (i.e., I_B or S_B), following suggestions by others to account for any baseline imbalance in the outcome variables (31). We repeated the analysis on colonoscopy use within 2 years of follow-up and smoking at follow-up, adjusting for colonoscopy use within 2 years of baseline and smoking at baseline, respectively, to ensure the relevance of the behaviors at those time points. We also

Table 1. Variable list

Variable	Scale	Source (question asked)
Outcomes		
Colonoscopy use between baseline and follow-up	Binomial: Yes/no	Follow-up ACCFR questionnaire ["Since the date of your last interview (baseline), have you had a colonoscopy?"]
Colonoscopy use within 2 years of follow-up	Binomial: Yes/no	Follow-up ACCFR questionnaire ["Since the date of your last interview (baseline), have you had a colonoscopy?" and "What was your age when you had your most recent (colonoscopy) test?"]
Smoking between baseline and follow-up	Binomial: Yes/no	Follow-up ACCFR questionnaire ["Since the date of your last interview (baseline), have you ever smoked a cigarette a day for 3 months or longer?"]
Smoking at follow-up	Binomial: Yes/no	Follow-up ACCFR questionnaire ("Do you currently smoke at least one cigarette a day?")
Exposures		
Carrier status	Binomial: Carrier/noncarrier	Genetic testing results available at the ACCFR
Receiver status at follow-up	Binomial: Receiver/nonreceiver	Dates of genetic counseling sessions provided from the ACCFR-referred clinics and available at the ACCFR against dates of the ACCFR questionnaire administration Records of previous receipts of genetic testing results from elsewhere before follow-up or refusals to receive genetic testing results from the ACCFR-referred clinics
Previous cancer diagnosis at follow-up	Binomial: Yes/no	Baseline ACCFR questionnaire ("Has a doctor ever told you that you had cancer, leukemia, or a malignant tumor?") Follow-up ACCFR questionnaire ["Since the date of your last interview (baseline), has a doctor told you that you had any type of cancer, leukemia, or a malignant tumor?"] Pathology reports, hospital records, and cancer registries accessed by the ACCFR
Controls		
Age	Continuous: Years	Baseline and follow-up ACCFR questionnaires ("What is your age?")
Sex	Binomial: Female/male	Baseline ACCFR questionnaire ("Are you male or female?")
Marital status	Binomial: Married or common-law/single	Baseline ACCFR questionnaire ("Marital status?")
Education	Categorical: Less than high school/ high, vocational, or training school/college, university, or more	Baseline ACCFR questionnaire: ("What is the highest level of education that you have completed?")
Degree of relatedness to family probands	Categorical: Self or identical twin/1st/2nd/3rd/ higher degree	Family information collected at enrollment into the ACCFR
Colonoscopy use before baseline	Binomial: Yes/no	Baseline ACCFR questionnaire ("Have you ever had a colonoscopy?")
Colonoscopy use within 2 years of baseline	Binomial: Yes/no	Baseline ACCFR questionnaire ["Have you ever had a colonoscopy?" and "What was your age when you last had this (colonoscopy) test?"]
Smoking before baseline	Binomial: Yes/no	Baseline ACCFR questionnaire ("Have you ever smoked at least one cigarette a day for 3 months or longer?")
Smoking at baseline	Binomial: Yes/no	Baseline ACCFR questionnaire ("Do you currently smoke at least one cigarette a day?")

conducted subgroup analyses only on the study participants who had undergone colonoscopy or smoked before baseline (i.e., $I_B =$ yes or $S_B =$ yes) to eliminate any baseline imbalance.

The carrier status (i.e., G) distinguished carriers, who carried any deleterious mutations in the MMR or *EPCAM* genes, from noncarriers, who did not carry their families' deleterious mutations in the MMR or *EPCAM* genes.

The receiver status at follow-up (i.e., R_F) distinguished 392 receivers, who had received their genetic testing results before follow-up, from 115 nonreceivers, who had either received their results after follow-up ($n = 80$) or never received them ($n = 35$), among the 507 study participants.

The receiver status at follow-up (i.e., receiver/nonreceiver) only allowed for the comparison of those who had received their results versus those who had not, which was not a pre- and postintervention study design. To address this shortcoming, we conducted a subgroup analysis that directly compared 43 receivers, who had received their results between baseline and follow-up, and 80 nonreceivers at follow-up, who had received their results after follow-up, in a pre- and postintervention study design.

Previous cancer diagnosis at follow-up (i.e., H_F) distinguished those who had been diagnosed with some non-colorectal cancer before follow-up from those who had not. We adjusted for this factor and interacted it with the carrier and receiver statuses at follow-up, following the observations of another study reporting that previous cancer diagnosis affected individual health behaviors differentially among receiver/nonreceiver carrier/noncarrier subgroups (32). None of the study participants had had colorectal cancer at follow-up, as we selected for individuals with no previous diagnosis of colorectal cancer at follow-up. We also conducted subgroup analyses only on the study participants with no previous cancer diagnosis at follow-up (i.e., $H_F =$ no) to eliminate any endogeneity associated with the variable.

We controlled for the study participants' age at follow-up (i.e., years), sex (i.e., female/male), marital status (i.e., married or common-law/single), education (i.e., less than high school/vocational, training, or high school/college, university, or more), and degree of relatedness to their family probands (i.e., self or identical twin/first/second/third/higher degree, factors previously identified to affect individual health behaviors that modulate the risk of cancer (32–35). The degree of relatedness to family probands also addressed potential heterogeneity in the study participants' awareness of colorectal cancer from their family relationships.

All statistical tasks were performed with the Stata (version 12.1) software (36). The estimation results on the carrier and receiver statuses and previous cancer diagnosis at follow-up and their interaction terms were linearly combined to compare the receivers and nonreceivers in the various carrier/noncarrier cancer/no-cancer subgroups to test the hypotheses from the previous section.

Results

Descriptive statistics

Table 2 reports the descriptive statistics on the study participants and nonparticipants. The study participants were, on average, in their mid-40s at baseline, more often female, and predominantly married or in a common-law relationship and had high-school education or more. Before baseline, 71% and 47% of the study participants had ever undergone colonoscopy or smoked, respectively, whereas 47% and 17% had undergone colonoscopy within 2 years or were currently smoking, respectively. By baseline, 13% had been diagnosed with some non-colorectal cancer. Compared with the 507 study participants, the 1,246 nonparticipants were significantly older, more often male, more often single, with lower levels of education, more distant relatives to their family probands, and less likely to have undergone colonoscopy.

The study participants were stratified by the carrier and receiver statuses. The receivers were older than the nonreceivers, suggesting that the receivers enrolled in the ACCFR earlier than the nonreceivers. The carriers were younger than the noncarriers, which was expected, as identifying individuals with no previous diagnosis of colorectal cancer leads to selection for carriers who are younger than noncarriers. At baseline, the receivers had higher rates of colonoscopy use, compared with the nonreceivers, likely because the receivers were older than the nonreceivers and already under colon screening. Indeed, aging is a good predictor of colonoscopy use (37). The carriers had higher rates of previous diagnosis of non-colorectal cancer, compared with the noncarriers, which was expected, as the carriers' genetic mutations predisposed them to colorectal cancer, as well as other cancers (8). No other significant differences or indications of systemic differences were observed among the receiver/nonreceiver carrier/noncarrier subgroups.

Estimation results

Table 3 reports the estimation results of the logit regression models on the likelihood of undergoing colonoscopy or smoking between baseline and follow-up. Odds ratios (ORs) greater (or less) than one indicate higher (or lower) probabilities for undergoing colonoscopy or smoking versus not undergoing colonoscopy or smoking, respectively, between baseline and follow-up.

There were significant associations between the likelihood of undergoing colonoscopy between baseline and follow-up and the single and interaction terms of the carrier and receiver statuses and previous cancer diagnosis at follow-up. The study participants who discovered that they carried a genetic mutation predisposing to colorectal cancer (i.e., receiver carriers) were more likely to undergo colonoscopy compared with those who were also carriers but had not received their results (i.e., nonreceiver carriers). However, this was only true for the study participants with no previous cancer diagnosis (OR = 13.124, $P < 0.001$) and not for those with previous cancer diagnosis (OR = 1.502, $P = 0.698$). The study participants who discovered that they did not carry a genetic mutation predisposing to colorectal cancer (i.e., receiver noncarriers) were not different from those who were also noncarriers but had not received their results (i.e., nonreceiver noncarriers) in their colonoscopy use (OR = 1.213, $P = 0.587$ for no previous cancer diagnosis; OR = 0.702, $P = 0.717$ for previous cancer diagnosis).

There were also significant associations between the likelihood of smoking between baseline and follow-up and the single and interaction terms of the carrier and receiver statuses and previous cancer diagnosis at follow-up. The study participants who discovered that they did not carry a genetic mutation predisposing to colorectal cancer (i.e., receiver noncarriers) were more likely to smoke compared with those who were also noncarriers but had not received their results (i.e., nonreceiver noncarriers). This was because the receiver noncarriers were less likely to quit smoking,

Table 2. Descriptive statistics

	Study participants		Study nonparticipants		Participants vs. nonparticipants	Receivers at follow-up				Nonreceivers at follow-up				Non-/receivers vs. non-/carriers
						Carriers		Noncarriers		Carriers		Noncarriers		
	n	%/M (SD)	*n*	%/M (SD)	*P*	*n*	%/M (SD)	*n*	%/M (SD)	*n*	%/M (SD)	*n*	%/M (SD)	*P*
Total *n*	507	100%	1,246	100%		171	44%	221	56%	45	39%	70	61%	
Socio-demographic factors														
Age (years)														
At baseline	507	43.7 (14.5)	1,232	48.0 (16.3)	<0.001[a]	171	41.5 (14.1)	221	46.8 (14.3)	45	37.8 (13.3)	70	43.0 (15.2)	<0.001[a]
At follow-up	500	48.9 (14.5)	925	52.6 (15.6)	<0.001[a]	165	46.9 (14.0)	220	52.1 (14.2)	45	42.9 (13.2)	70	47.7 (15.5)	<0.001[a]
Sex														
Female (vs. male)	507	61%	1,246	56%	0.049[b]	171	66%	221	60%	45	51%	70	56%	0.206
Marital status														
Married or common-law (vs. single)	505	74%	1,240	69%	0.043[b]	170	70%	220	77%	45	73%	70	76%	0.486
Education														
Less than high school	497	31%	1,224	37%	0.046[b]	168	26%	215	34%	45	31%	69	33%	0.421
High, vocational, or training school		43%		39%			45%		43%		49%		36%	
College, university, or more		26%		24%			29%		23%		20%		30%	
Colorectal cancer awareness														
Degree of relatedness to family probands														
Self or identical twin	499	4%	1,053	3%	0.005[b]	171	8%	217	4%	45	0%	66	0%	0.330
1st degree		23%		25%			20%		24%		29%		23%	
2nd degree		27%		33%			27%		28%		22%		29%	
3rd degree		16%		17%			16%		15%		16%		18%	
Higher degree		29%		22%			28%		29%		33%		30%	
Health behaviors														
Colonoscopy use (vs. no use)														
Before baseline	507	71%	1,229	59%	<0.001[a]	171	77%	221	76%	45	53%	70	53%	<0.001[a]
Within two years of baseline	367	47%	908	35%	<0.001[a]	129	60%	157	46%	34	35%	47	21%	<0.001[a]
Between baseline & follow-up	491	68%	832	52%	<0.001[a]	161	94%	217	58%	45	62%	68	43%	<0.001[a]
Within two years of follow-up	449	54%	779	40%	<0.001[a]	156	91%	197	35%	35	37%	61	30%	<0.001[a]
Smoking (vs. no smoking)														
Before baseline	506	47%	1,240	47%	0.507	170	49%	221	49%	45	53%	70	34%	0.115
At baseline	506	17%	1,232	16%	0.354	170	18%	221	17%	45	20%	70	9%	0.259
Between baseline & follow-up	454	21%	385	21%	0.483	144	23%	200	22%	44	25%	66	12%	0.264
At follow-up	454	17%	384	17%	0.474	144	19%	200	18%	44	20%	66	5%	0.042[b]
Health outcome														
Previous cancer diagnosis (vs. no diagnosis)														
At baseline	507	13%	1,246	12%	0.379	171	19%	221	12%	45	9%	70	7%	0.032[b]
At follow-up	507	19%	1,246	17%	0.329	171	26%	221	15%	45	20%	70	11%	0.022[b]

NOTE: Statistical comparisons between the study participants and nonparticipants were made, using the Fisher exact test for binomial variables, χ^2 test for categorical variables, and Mann–Whitney U test for continuous variables. Statistical comparisons among the four receiver/nonreceiver carrier/noncarrier subgroups were made, using χ^2 test for binomial and categorical variables and Mann–Whitney U test for continuous variables.
Abbreviations: M, mean; *n*, sample size.
[a]Statistically significant at $P = 0.001$.
[b]Statistically significant at $P = 0.05$.

Table 3. Estimation results of the logit regression models on colonoscopy use and smoking between baseline and follow-up

	Colonoscopy use between baseline and follow-up (vs. no use)			Smoking between baseline and follow-up (vs. no smoking)		
Observations	473			442		
Pseudo R^2	0.288			0.449		
Area under ROC curve	0.842			0.917		
Somers D	0.566			0.794		
Brier score	0.157			0.108		
	OR	***P***	**lrtest**	**OR**	***P***	**lrtest**
Carrier status × receiver status at follow-up × previous cancer diagnosis at follow-up						
Carrier (vs. noncarrier)	2.358	0.089		2.226	0.302	
Receiver (vs. nonreceiver)	1.213	0.587		4.147	0.037[b]	
Previous cancer diagnosis (vs. no diagnosis)	0.640	0.638		27.499	0.120	
Carrier receiver (vs. noncarrier nonreceiver)	10.822	0.001[a]	<0.001[a]	0.193	0.067	0.031[b]
Carrier with previous cancer diagnosis (vs. noncarrier with no diagnosis)	2.001	0.604		0.084	0.344	
Receiver with previous cancer diagnosis (vs. nonreceiver with no diagnosis)	0.579	0.600		0.006	0.026[b]	
Carrier receiver with previous cancer diagnosis (vs. noncarrier nonreceiver with no diagnosis)	0.198	0.309		314.316	0.043[b]	
Linear combination						
Receiver carrier (vs. nonreceiver carrier) with no previous cancer diagnosis	13.124	<0.001[a]		0.802	0.702	
Receiver carrier (vs. nonreceiver carrier) with previous cancer diagnosis	1.502	0.698		1.511	0.800	
Receiver non-carrier (vs. nonreceiver noncarrier) with no previous cancer diagnosis	1.213	0.587		4.147	0.037[b]	
Receiver non-carrier (vs. nonreceiver noncarrier) with previous cancer diagnosis	0.702	0.717		0.025	0.089	
Socio-demographic factors						
Age at follow-up						
Age (years)	1.132	0.034[b]	0.079	0.852	0.060	<0.001[a]
Age squared	0.999	0.049[b]		1.001	0.262	
Female (vs. male)	2.489	<0.001[a]		1.213	0.563	
Married or common-law (vs. single)	1.100	0.759		0.397	0.020[b]	
Education (vs. less than high school)						
High, vocational, or training school	1.503	0.176	0.380	1.118	0.764	0.010[c]
College, university, or more	1.160	0.655		0.321	0.019[b]	
Colorectal cancer awareness						
Degree of relatedness to family probands (vs. self or identical twin)						
1st degree	0.721	0.700	0.020[b]	0.808	0.820	0.776
2nd degree	0.460	0.356		0.753	0.754	
3rd degree	0.400	0.286		0.438	0.389	
Higher degree	0.245	0.091		0.788	0.794	
Baseline health behaviors						
Colonoscopy use before baseline (vs. no use)	4.414	<0.001[a]				
Smoking before baseline (vs. no smoking)				210.723	<0.001[a]	
Constant	0.015	0.014[b]		0.866	0.948	

Abbreviation: lrtest, likelihood ratio test, using χ^2 statistics.
[a]Statistically significant at $P = 0.001$.
[b]Statistically significant at $P = 0.05$.
[c]Statistically significant at $P = 0.01$.

and not because the receiver noncarriers were more likely to take up smoking, compared with the nonreceiver noncarriers (see Supplementary Table S1). However, this was only true for the study participants with no previous cancer diagnosis (OR = 4.147, $P = 0.037$) and not for those with previous cancer diagnosis (OR = 0.025, $P = 0.089$). The study participants who discovered that they carried a genetic mutation predisposing to colorectal cancer (i.e., receiver carriers) were not different from those who were also carriers but had not received their results (i.e., nonreceiver carriers) in their smoking behavior (OR = 0.802, $P = 0.702$ for no previous cancer diagnosis; OR = 1.511, $P = 0.800$ for previous cancer diagnosis).

The ORs on the other explanatory variables were consistent with expectations. For colonoscopy, the age terms suggested increasing colonoscopy use until 57 years of age and decreasing colonoscopy use thereafter. Being female versus male was associated with a higher likelihood of undergoing colonoscopy. Closer relatives to family probands had a higher likelihood of undergoing colonoscopy, compared with more distant relatives. For smoking, the age terms suggested decreasing smoking with age. Being married or in a common-law relationship versus being single was associated with a lower likelihood of smoking. Higher education was associated with a lower likelihood of smoking. For both colonoscopy and smoking, each behavior at baseline was a significant and positive predictor of itself between baseline and follow-up. The area under the receiver operating characteristic (ROC) curve, Somers D_{xy} rank correlation, and Brier score indicated good predictive abilities of the models.

Supplementary Tables S2 and S3 report the results of the subgroup analyses, estimated only on the study participants who had undergone colonoscopy or smoked before baseline, respectively. Supplementary Table S4 reports the results of the subgroup analyses, estimated only on the study participants with no previous cancer diagnosis at follow-up. The results presented in Supplementary Tables S2–S4 were in agreement with those presented in Table 3, although the results in Supplementary Tables S2–S4 were lacking power, due to the smaller sample sizes.

Table 4. Estimation results of the logit regression models on recent colonoscopy and current smoking

	Colonoscopy use within 2 years of follow-up (vs. no use)			Smoking at follow-up (vs. no smoking)		
Observations	248			362		
Pseudo R^2	0.363			0.569		
Area under ROC curve	0.872			0.943		
Somers D	0.567			0.832		
Brier score	0.185			0.0618		
	OR	***P***	**lrtest**	**OR**	***P***	**lrtest**
Carrier status × receiver status at follow-up						
Carrier (vs. noncarrier)	0.749	0.706		5.450	0.135	
Receiver (vs. nonreceiver)	0.903	0.847	<0.001[a]	8.549	0.030[b]	0.120
Receiver carrier (vs. nonreceiver noncarrier)	59.740	<0.001[a]		0.117	0.365	
Linear combination						
Receiver carrier (vs. nonreceiver carrier)	53.928	<0.001[a]		1.002	0.998	
Receiver non-carrier (vs. nonreceiver noncarrier)	0.903	0.847		8.549	0.030[b]	
Socio-demographic factors						
Age at follow-up						
Age (years)	1.156	0.117	0.002[c]	1.130	0.365	0.102
Age squared	0.999	0.301		0.998	0.225	
Female (vs. male)	1.676	0.139		1.028	0.954	
Married or common-law (vs. single)	0.857	0.747		0.756	0.603	
Education (vs. less than high school)						
High, vocational, or training school	2.152	0.066	0.105	0.463	0.189	0.183
College, university, or more	1.038	0.938		0.280	0.078	
Colorectal cancer awareness						
Degree of relatedness to family probands (vs. self or identical twin)						
1st degree	1.103	0.915		2.066	0.699	
2nd degree	1.092	0.922	0.740	2.321	0.648	0.852
3rd degree	0.597	0.601		1.294	0.893	
Higher degree	0.709	0.704		1.342	0.874	
Baseline health behaviors						
Colonoscopy use within 2 years of baseline (vs. no use)	1.624	0.202				
Smoking at baseline (vs. no smoking)				97.021	<0.001[a]	
Constant	0.002	0.007[c]		0.001	0.076	

Abbreviation: lrtest, likelihood ratio test, using χ^2 statistics.
[a]Statistically significant at $P = 0.001$.
[b]Statistically significant at $P = 0.05$.
[c]Statistically significant at $P = 0.01$.

Table 4 reports the estimation results of the logit regression models on the likelihood of undergoing colonoscopy within 2 years of follow-up or smoking at follow-up. Because some of the interaction terms involving previous cancer diagnosis at follow-up did not have any observations and could not be estimated, these models were estimated on the study participants with no previous cancer diagnosis at follow-up.

The results presented in Table 4 were in agreement with those presented in Table 3, although the results in Table 4 were lacking power, due to the smaller sample sizes.

Table 5 reports the estimation results of the logit regression model on the likelihood of undergoing colonoscopy between baseline and follow-up, in a subgroup analysis that directly compared the 43 receivers, who had received their results between baseline and follow-up, and the 80 nonreceivers at follow-up, who had received their results after follow-up, in a pre- and postintervention study design. Because some of the interaction terms involving previous cancer diagnosis at follow-up did not have any observations and could not be estimated, this model was estimated on the study participants with no previous cancer diagnosis at follow-up. Because none of the 43 and 80 study participants were first-degree relatives to their family probands, the degree of relatedness to family probands variable had four, instead of five, categories. For smoking, because the 43 receivers, who had received their results between baseline and follow-up, were lacking information on smoking at follow-up and automatically omitted from the estimation, the model could not be estimated.

The results presented in Table 5 were in agreement with those presented in Table 3, although the results in Table 5 were lacking power, due to the smaller sample size. For example, the carriers who had received their results between baseline and follow-up (i.e., receiver carriers) were more likely to undergo colonoscopy compared with the carriers who had not received their results until after follow-up (i.e., nonreceiver carriers; OR = 6.121, $P = 0.088$).

Discussion

We found strong evidence of a higher likelihood of undergoing colonoscopy for individuals with a family history of Lynch syndrome, but no previous cancer diagnosis, upon learning that they were carriers of a genetic mutation predisposing to colorectal cancer. There was also strong evidence of a lower likelihood of quitting smoking for individuals with a family history of Lynch syndrome, but no previous cancer diagnosis, upon learning that they were noncarriers of a genetic mutation predisposing to colorectal cancer. These empirical findings were consistent with the hypotheses generated from our simple health economics

Table 5. Estimation results of the logit regression model on colonoscopy use between baseline and follow-up on the pre- and postintervention study design subgroup

	Colonoscopy use between baseline and follow-up (vs. no use)		
Observations	94		
Pseudo R^2	0.275		
Area under ROC curve	0.829		
Somers D	0.653		
Brier score	0.156		
	OR	***P***	**lrtest**
Carrier status × receiver status at follow-up			
Carrier (vs. noncarrier)	2.708	0.121	
Receiver (vs. nonreceiver)	0.849	0.835	0.011[a]
Carrier receiver (vs. noncarrier nonreceiver)	7.208	0.136	
Linear combination			
Receiver carrier (vs. nonreceiver carrier)	6.121	0.088	
Receiver non-carrier (vs. nonreceiver noncarrier)	0.849	0.835	
Socio-demographic factors			
Age at follow-up			
Age (years)	1.078	0.533	0.482
Age squared	0.999	0.684	
Female (vs. male)	3.577	0.035[a]	
Married or common-law (vs. single)	1.556	0.556	
Education (vs. less than high school)			
High, vocational, or training school	1.450	0.589	0.571
College, university, or more	2.200	0.297	
Colorectal cancer awareness			
Degree of relatedness to family probands (vs. self or identical twin)			
2nd degree	0.581	0.465	
3rd degree	0.429	0.304	0.096
Higher degree	0.153	0.021[a]	
Baseline health behaviors			
Colonoscopy use before baseline (vs. no use)	5.070	0.007[b]	
Constant	0.020	0.209	

Abbreviation: lrtest, likelihood ratio test, using χ^2 statistics.
[a]Statistically significant at $P = 0.05$.
[b]Statistically significant at $P = 0.01$.

model. They also agreed well with previous studies that reported substitutive effects between genetic endowments and personal health behaviors in economic (38–40) and clinical (16–23) literature. They were also congruent with a previous study that reported modulating effects of previous cancer diagnosis (32). The empirical findings were robust to factors analyzed in subsequent and subgroup analyses, involving the recent colonoscopy use and current smoking measures and the pre- and postintervention study design.

However, no empirical evidence was found to support the hypotheses that individuals with a family history of colorectal cancer are less likely to undergo colonoscopy upon learning their noncarrier status and also more likely to quit smoking upon learning their carrier status. These discrepancies may imply the receivers' misunderstanding of their genetic status and/or difficulty in accepting the new information. Indeed, some of the previous studies also found noncarriers who continued to undergo colonoscopy (18) and identified the family history of colorectal cancer, as opposed to new information obtained through predictive genetic testing, as the most significant attribute to one's perceived risk (41). Furthermore, a recent study using the ACCFR data identified individuals from colorectal cancer-causing mutation-carrying families who perceived their risk of having colorectal cancer as high and did not receive or refused genetic testing results (28). A lack of guidance on appropriate colon screening behaviors may have been another factor, and further research on the screening advice given to receivers by their physicians is required. The discrepancies may also imply the receivers' difficulty in overcoming an addiction and/or understanding that smoking is associated with high risk of colorectal cancer (13, 14). Alternatively, the lack of significant evidence may reflect the fact that the predicted change from "use" to "no-use" would not be captured in our data if the study participants who received their genetic testing results between baseline and follow-up had undergone colonoscopy or smoked after baseline but before receiving their results.

Our study had many strengths. To the best of our knowledge, it was the first to investigate the impact of receiving predictive colorectal cancer genetic information on individual smoking behavior and offered the longest follow-up duration of 5 years among the studies of its kind on colorectal cancer (16–23). However, there were several limitations.

Of the 1,753 individuals in the ACCFR who were potentially eligible for inclusion in our study, 1,246 had insufficient information on whether or when their genetic testing results had been disclosed to them and were excluded from the analysis. Our descriptive statistics identified significant differences in age, sex, marital status, education, degree of relatedness to family probands, and colonoscopy use between the study participants and nonparticipants. Being female and receiving family support have been shown to be positively associated with individual health behaviors that modulate the risk of colorectal cancer (32, 37). Consistent with these observations, the study nonparticipants, who were more often male and more distant relatives to their probands, compared with the study participants, were less likely to have undergone colonoscopy. Therefore, the findings of our study might have been biased toward predicting healthier behaviors than it would have, had it included the study nonparticipants from the study population. In other words, the higher likelihood of undergoing colonoscopy for individuals upon learning that they were carriers and the lower likelihood of quitting smoking for individuals upon learning that they were noncarriers might in fact be lower in a broader population.

Because the ACCFR registrants did not choose to obtain genetic testing, the availability of their results was free of potential selection bias associated with the choice to undergo genetic testing. Although there was potential selection bias associated with the choice to receive genetic testing results, our descriptive statistics found no indications of systemic differences between the receivers and nonreceivers other than age, which was adjusted for in all our regression models. Furthermore, the majority of the nonreceivers at follow-up (i.e., 80/115) did receive their results after follow-up, suggesting against inherent differences between the receivers and nonreceivers in their choice to receive genetic testing results. Rather, the receiver status at follow-up was an artificial distinction, made to take advantage of the differential timing in the receipt of the results. Nevertheless, this being an observational study, there remain concerns that the receiver/nonreceiver carrier/

noncarrier subgroups were inherently different from each other on some unmeasured characteristics. Specifically, the lower likelihood of quitting smoking for individuals upon learning that they were noncarriers was driven by the particularly low rate of smoking in the nonreceiver noncarriers. Our study must be replicated on different populations, to test not only the generalizability of our study findings but also their robustness.

For the majority of the receivers (i.e., 343/392), the exact dates of their receipt were unavailable. As some of these receivers had likely received their results before baseline, baseline for the receivers did not necessarily represent "preintervention." Therefore, the receiver status at follow-up only allowed for the comparison of those who had received their results versus those who had not, which was not a pre- and postintervention study design. Assuming that behavioral change from this new information generally occurs shortly after its receipt, we took a conservative approach by including these individuals in our empirical analysis and still discovered significant effects. Furthermore, our analysis on a pre- and postintervention study design subgroup found consistent results, although the results were lacking power, due to the smaller sample sizes. Future studies may benefit from larger sample sizes.

In conclusion, our empirical analysis identified intended and unintended consequences of predictive genetic testing for colorectal cancer, suggesting that the impact of personalized medicine on disease prevention is more intricate than generally expected. The exact consequences of providing individuals with new information about their genetic disease risk will likely differ from one disease to another, with variations in the efficacy of the intervention, penetrance of the genetics, effectiveness of the preventive measures, and individual attitudes toward risk. Therefore, our research findings highlight the need for a fulsome assessment on the benefits and costs of personalized preventive interventions from both the clinical and societal perspectives that take account of individual responses to the resulting new information.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.S.-M. Kim, P.C. Coyte, M. Cotterchio, L.A. Keogh, A. Laporte
Development of methodology: J.S.-M. Kim, P.C. Coyte, L.A. Keogh, A. Laporte
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Gaff
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S.-M. Kim, P.C. Coyte, A. Laporte
Writing, review, and/or revision of the manuscript: J.S.-M. Kim, P.C. Coyte, M. Cotterchio, L.A. Keogh, L.B. Flander, C. Gaff, A. Laporte
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S.-M. Kim
Study supervision: J.S.-M. Kim, P.C. Coyte

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