Colorectal Carcinoma Symptoms and Risk Factors

by

Dr. Anthony Morham, MD, CCFP

A thesis submitted to the Faculty of Graduate Studies

in partial fulfillment of the requirements for the degree of

Master of Science

Community Health Sciences
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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

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I) Abstract

Colorectal cancer affects many Canadians. Six and a half percent (1 in 16) of Canadians will be diagnosed with colorectal cancer in their lifetime, while 2.8% (1 in 36) of Canadians will die of colorectal cancer. Therefore, most Canadians will know someone who has or will get colorectal cancer at some point in their lives, even if it does not affect them personally.

Many symptoms, signs, and other risk factors have historically been associated with colorectal cancer, but few of these have been proven. Studies that have investigated risk factors for colorectal carcinoma have tended to examine the relationship between the cancer and a single category of risk factor (e.g. diet or symptoms or family history), which makes independence of the associations of the risk factors difficult to determine. For these reasons, and others outlined in this paper, it is difficult for physicians to assess patients' colorectal carcinoma risk based on clinical grounds alone.

This study attempted to determine the significant independent colorectal cancer symptoms, signs, and other risk factors by combining several categories of risk factors in one questionnaire. With this information, physicians will be able to calculate the actual likelihood of colorectal cancer in their patient(s), before the definitive test of colonoscopy. This might aide both the physician and patient in decision-making with regard to when to investigation further for colorectal cancer.

The objectives of the study were as follows:

1. To describe the patient population undergoing colonoscopies in participating colonoscopy suites in Winnipeg, MB

2. To determine the self reported risk factors and symptoms associated with a diagnosis of colorectal carcinoma in a group of patients undergoing colonoscopies in Winnipeg MB.

3. To develop a statistical model that calculates the probability of colorectal carcinoma.

To realize these objectives, a written self-administered questionnaire was given to consecutive patients who were to undergo colonoscopy in three colonoscopy suites in Winnipeg, MB, Canada. The reasons for the colonoscopies varied but included primary physician referral for symptoms and follow-up examinations from previous colonoscopies. Excluded were patients who could not complete the survey independently. The ICD-9 coding from the colonoscopy was the basis for the diagnosis of colorectal carcinoma. Descriptive, univariate and multiple logistic regression calculations were made. Finally, odds ratios and likelihood ratios for significant variables were calculated.

Six hundred and forty two were included in the study, of a potential 1504. There were 11 colorectal cancers found and 1 carcinoma-in-situ. Eighty three percent were

over 40 years of age, with a mean age of 56.5 years. In the univariate analysis, age (OR = 1.08/year, p=0.004), bleeding (OR 5.77, p=0.0257), and weight loss (OR= 4.17, p=0.02) are the variables that achieved statistical significance at $p<0.05$ in the univariate analysis.

In the multivariate analysis, age, bleeding and abdominal pain were independently and significantly associated with colorectal cancer. Thus, a person's risk of colorectal carcinoma increases exponentially by 1.087 (CI95%= 1.14,1.03; p=0.0001) for every year of age, and is multiplied by 6.35 (CI95%=30.25,1.33; p=0.02) if they have rectal bleeding (as compared to patient's that do not have rectal bleeding) and 4.5 (CI95%=18.12,1.12; p=0.03) if they have abdominal pain (as compared to patient's that do not have abdominal pain). .

This results of this study suggest that physicians need to only inquire about age, rectal bleeding status and abdominal pain in order to determine a patient's risk of colorectal cancer, and that other factors will not help in determination of the risk. Physicians should inquire about weight loss as well when screening for colorectal cancer. Other symptoms are not associated with colorectal cancer.

II) Acknowledgments

I would like to thank Drs. Blanchard, Bernstein, and Hassard for their help in completing this project. Their advice and guidance were invaluable.

I would also like to thank the staff at the Health Science's colonoscopy suite for their patience for the first part of my first study. Also, of course, I would like to thank the staff of the Victoria Hospital, were most of my data was obtained, for your dedication to the project, and the St. Boniface colonoscopy staff, who worked on this even during the summer months! Thank you all for giving me the chance to do this.

I would like to thank "Mary" for helping financially, and Dr. Alvi for the picture of the colon cancer (page 104)

Finally, I owe a debt of gratitude to my family, especially Roxanne, for their patience.

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VII) Introduction, Rationale and Objectives

A) Health Importance of Colorectal Cancer

Colorectal cancer is an important medical problem in Canada. The lifetime probability of a diagnosis of colorectal cancer in a Canadian is 6.5%, or 1 in 16. The lifetime probability of a Canadian dying of colorectal cancer is 2.8%, or 1 in 36. Colorectal cancer is the third most common cancer and the third most common cause of death from cancer for both men and women. When both genders are taken together, colorectal cancer is the second most frequent cause of cancer deaths among Canadians (after lung cancer) (Health Canada, 2001). Table 1: Age-Standardized mortality rates of various diseases" shows the rates of various malignant and non-malignant diseases. There are an estimated 84,000 Potential Years of Life Lost (PYLL) in Canada due to colorectal Cancer. (See Table 2: Potential Years of Life lost Due to Cancer, Canada, 1997) While the age-standardized incidence and mortality rates for colorectal cancer have been decreasing since 1985, due to the aging population the actual number of colorectal cancers in Canada has been increasing over time. Thus, it is expected that colorectal cancer will continue to produce an increasing economic burden on the Canadian health care system, as well and an increasing morbidity for Canadians.

Table 1: Age-Standardized mortality rates of various diseases

	1980	1990	1994	1995	1996
	Both sexes				
	rate per 100,000 population				
All causes	**823**	**704**	**675**	**667**	**653**
Malignant neoplasms	187	192	188	185	185
Intestine, except rectum	25	22	20	20	19
Lung	42	50	50	49	49
Breast	0	0	0	0	0
All other malignant neoplasms	119	120	118	116	116
Diabetes	14	15	17	17	17
Diseases of the heart	292	202	184	180	175
Ischaemic heart diseases	242	161	143	138	133
All other heart diseases	50	41	41	42	42
Cerebrovascular diseases	76	52	49	48	47
Atheroclerosis	18	8	6	5	4
Respiratory diseases	55	60	59	59	58
Pneumonia and influenza	25	25	23	23	22
Bronchitis, emphysema and asthma	12	8	7	6	6
All other respiratory diseases	18	27	29	30	29
Chronic liver diseases and cirrhosis	12	8	7	7	7
Congenital anomalies	6	5	4	4	4
Perinatal mortality excluding stillbirths	6	4	4	4	4
Accidents and adverse effects	66	47	44	45	43
Motor vehicle accidents	22	14	11	11	10
Suicide	14	12	13	13	13
Homicide	2	2	2	2	2
Other accidents and adverse effects	28	19	19	19	19
Other causes	90	111	112	113	111

1. Rates are age-standardized using the 1991 population for Canada.

Source: Statistics Canada, Catalogue no. 82-221-XDE

Table 2: Potential Years of Life lost Due to Cancer, Canada, 1997

Potential Years of Life Lost Due to Cancer, Canada, 1997

	Potential Years of Life Lost (PYLL)					
	Total		Males		Females	
	Years	%	Years	%	Years	%
ALL CAUSES	3,052,000	–	1,655,000	–	1,398,000	–
All Cancers	894,000	100	434,000	100	459,000	100
Childhood Cancer (Ages 0-19)	17,200	1.9	9,400	2.2	7,700	1.7
Cancer Site						
Lung	233,000	26.0	132,000	30.4	100,000	21.9
Breast	95,000	10.6	–	–	95,000	20.7
Colorectal	84,000	9.5	43,000	9.9	42,000	9.0
Pancreas	40,000	4.5	19,000	4.3	21,000	4.6
Non-Hodgkin's Lymphoma	37,000	4.2	20,000	4.5	18,000	3.9
Leukemia	35,000	3.9	18,000	4.2	16,000	3.5
Brain	34,000	3.8	19,000	4.4	15,000	3.3
Prostate	33,000	3.7	33,000	7.5	–	–
Stomach	27,000	3.0	17,000	3.8	11,000	2.3
Ovary	25,000	2.8	–	–	25,000	5.4
Kidney	19,000	2.2	12,000	2.8	7,000	1.6
Oral	17,000	1.9	11,000	2.6	5,000	1.2
Multiple Myeloma	14,000	1.6	7,000	1.7	7,000	1.4
Bladder	15,000	1.7	10,000	2.3	5,000	1.0
Melanoma	13,000	1.5	8,000	1.8	5,000	1.1
Cervix	11,000	1.2	–	–	11,000	2.3
Body of Uterus	9,000	1.1	–	–	9,000	2.1
Larynx	7,000	0.8	6,000	1.3	1,000	0.3
Hodgkin's Disease	4,000	0.4	2,000	0.5	2,000	0.3
Testis	1,000	0.1	1,000	0.2	–	–

– *Not applicable*

Note: Figures are ranked in order of total PYLL for both genders combined and are calculated based on life expectancy. Count and percentage totals may not add due to rounding and to the exclusion of other sites. Childhood cancers are also included within the relevant sites.
Source: Cancer Bureau, CCDPC, Health Canada

B) Rationale for the Present Investigation

Patients have a better outcome if colorectal cancer is treated at an early stage. Finding it at this earlier stage is a clinical problem. The historical associations of many of the symptoms, signs and other risk factors of colorectal cancer are not proven. Previous studies on this topic have had somewhat inconsistent results and methodological difficulties. They have also tended to examine the relationship between the cancer and a single category of risk factor (e.g. diet or symptoms or family history). This makes independence of the association difficult to determine. For these reasons, and others outlined in this paper, physicians do not predict the colorectal carcinoma risk of their patients well based on clinical grounds alone.

This study combined several categories together into one questionnaire to determine the significant predictor variables, and how they might relate to one another. With this, physicians would have a better indication of which of the multiple symptoms and risk factors are truly predictive of colorectal carcinoma. They also might be able to estimate the likelihood of colorectal cancer in their patients. This might aide both the physician and patient in decision-making, and thus led to an earlier diagnosis and a decrease in the burden of the disease.

Finally, public education campaigns can target actual symptoms that are truly associated with the disease, as opposed to those that have historically only been thought to be associated.

C) Study Goal

To investigate the association between clinical history and colorectal cancer.

D) Study Objectives

1. To describe the patient population undergoing colonoscopies in participating colonoscopy suites in Winnipeg, MB

2. To determine the self reported risk factors associated with a diagnosis of colorectal carcinoma in a group of patients undergoing colonoscopies in Winnipeg MB.

3. To develop a statistical model that calculates the probability of Colorectal Carcinoma in a referred patient.

VIII) Background

A) Vital Statistics

1) Polyps

The estimated incidence of polyps ranges wildly, from 7 to 50%, depending on the study and the definition of "polyp" (e.g. the size of the polyp that is considered relevant by the study). Polyps, often multiple, occur most commonly in the rectum and sigmoid and decrease in frequency toward the cecum. About 25% of patients with cancer of the large bowel also have other polyps (Merck Manual, 1997). The prevalence of adenomas>1.0 cm on autopsy is around 7-10%, and that of cancer around 1-2% (Jensen, J; 1993). Typical yields in colonoscopies are 29-40% for both adenomas and cancers (Neugut, 1993).

2) Colorectal Cancer

Colorectal carcinoma causes significant morbidity and mortality in Canada and around the world.

(a) Canada

In Canada, lung, breast, prostate and colon cancer make up the majority of cancers. After lung and breast cancer, colon cancer is the third leading cause of cancer death in Canada. The lifetime probability of a Canadian being diagnosed with colon cancer is 6.3, or 1 in 16. The lifetime probability of a Canadian dying of colon cancer is 2.8%, or 1 in

36. (See Table 3: Probability of Developing Cancer by Age, and Lifetime Probability of Developing and Dying from Cancer, Canada", Figure 1: Probability of Developing Colorectal Cancer in the Next 10 Years by age, Canada)a" and Table 6: Actual Data for Deaths for Major Cancer Sites by Gender and Geographic Region, Canada, 1997 Canada"). The total number of colon cancers is probably underestimated due to non-aggressive investigation of the frail elderly, as well as misclassification of some deaths.

The probability of developing colorectal cancer increases with age (again see Table 3: Probability of Developing Cancer by Age, and Lifetime Probability of Developing and Dying from Cancer, Canada). Colorectal Cancer occurs most often in the proximal colon, then in the rectum, and least in the distal colon. (See Figure 4:Age-standardized Incidence rates for Colorectal Cancers by Subsite and Gender, Canada, 1979-1995..)

There were an estimated 16,600 new cases of colorectal cancer in 1999, and an estimated 6300 people will have died of colorectal cancer by the end of the year. There were an estimated 17, 200 new cases of colorectal cancer and 6400 deaths due to colorectal cancer in 2001. (Statistics Canada, 2001) (See Figure 2:Age-Specific Incidence and Mortality Rates, Colorectal Cancers, Canada, 1971-2001 and Table 4: Estimated New Cases and Deaths for Cancer by Sites and Gender, 2001). From international studies, the overall 5-year survival rate for colorectal carcinoma is about 50% (Kyle S; 1991) (Mansson J; 1990) (Bansal, 1996)

While the age-standardized incidence and mortality rates for colorectal cancer have been decreasing since 1985, due to the aging population the actual number of colorectal cancers in Canada has been increasing over time. (See Figure 5:New Cases and

Age- Standardized Incidence Rates (ASIR) for Colorectal Cancer, Canada, 1972-2001)

Canadian statistics are likely relatively accurate. Almost all Canadians are part of the Public Health Care system. The individual provincial registries monitor all hospital pathology laboratories and private offices for new patients with the diagnosis of colorectal cancer. It is unlikely that a diagnosis of colorectal cancer would not be included in the above statistical analysis.

Table 3: Probability of Developing Cancer by Age, and Lifetime Probability of Developing and Dying from Cancer, Canada

Probability of Developing Cancer by Age, and Lifetime Probability of Developing and Dying from Cancer, Canada

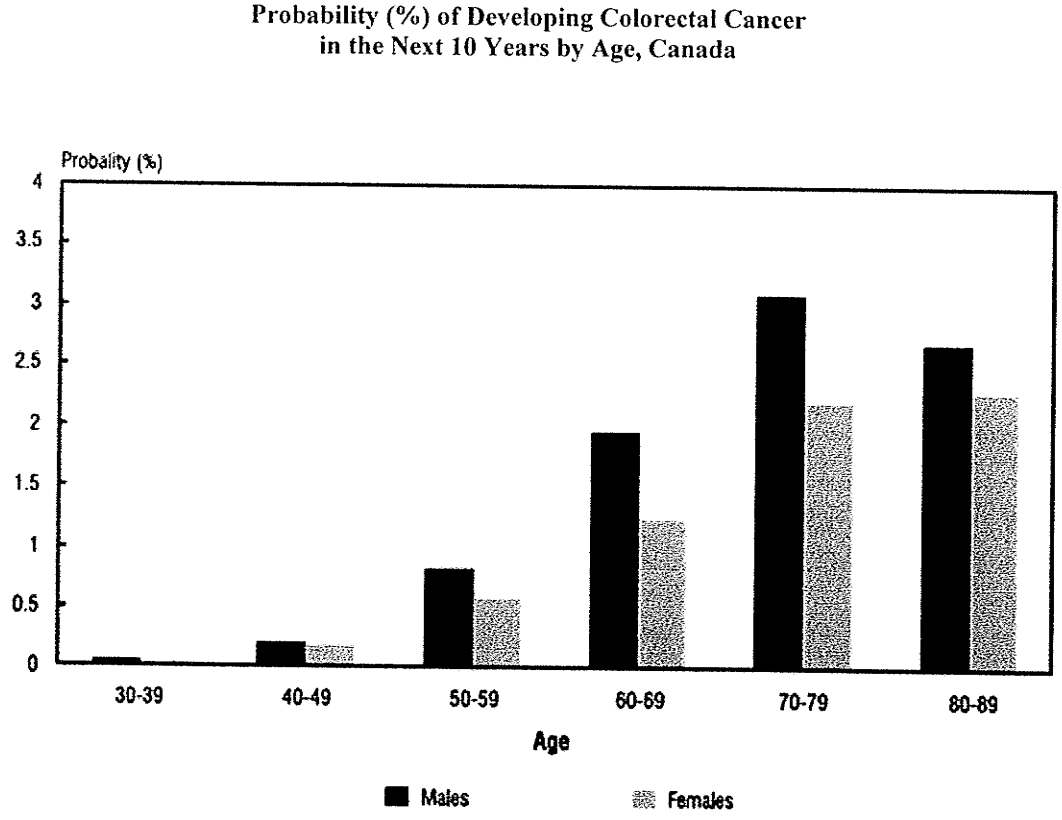
	Probability (%) of Developing Cancer in next 10 years by age group						Lifetime Probability (%) of: Developing		Dying	
	30-39	40-49	50-59	60-69	70-79	80-89	%	One in:	%	One in:
Male										
All Cancers	**0.7**	**1.6**	**5.6**	**14.2**	**20.9**	**17.6**	**40.0**	**2.5**	**26.7**	**3.7**
Prostate	–	0.1	1.0	4.1	6.3	4.9	11.2	8.9	3.6	27.5
Lung	–	0.2	1.1	3.1	4.4	3.3	8.8	11.4	8.1	12.4
Colorectal	0.1	0.2	0.8	2.0	3.1	2.7	6.3	15.9	2.8	36.2
Lymphoma	0.1	0.2	0.4	0.7	1.0	0.9	2.7	37.6	1.5	66.2
Bladder	–	0.1	0.3	0.7	1.3	1.3	2.6	38.8	0.9	108.8
Kidney	–	0.1	0.3	0.5	0.6	0.5	1.5	66.7	0.7	148.8
Oral	–	0.1	0.3	0.5	0.6	0.4	1.5	67.6	0.5	182.1
Stomach	–	0.1	0.2	0.4	0.7	0.7	1.5	69.0	1.0	96.2
Leukemia	–	0.1	0.1	0.3	0.6	0.6	1.4	73.0	0.9	110.9
Pancreas	–	–	0.1	0.4	0.5	0.5	1.1	87.7	1.2	87.0
Melanoma	0.1	0.1	0.2	0.3	0.3	0.3	1.0	97.1	0.3	335.6
Female										
All Cancers	**1.1**	**2.9**	**6.0**	**9.9**	**13.3**	**11.0**	**35.5**	**2.8**	**22.2**	**4.5**
Breast	0.4	1.3	2.3	3.0	3.2	2.2	10.6	9.4	3.9	25.8
Colorectal	–	0.2	0.6	1.2	2.2	2.3	5.5	18.2	2.5	39.4
Lung	–	0.2	0.8	1.7	2.1	1.2	5.3	19.0	4.5	22.4
Lymphoma	0.1	0.1	0.3	0.5	0.8	0.7	2.3	44.2	1.3	76.9
Body of Uterus	–	0.1	0.5	0.7	0.7	0.5	2.2	46.3	0.5	188.0
Ovary	0.1	0.1	0.3	0.4	0.5	0.3	1.5	69.0	1.1	94.3
Pancreas	–	–	0.1	0.3	0.5	0.5	1.2	84.7	1.3	79.4
Leukemia	–	0.1	0.1	0.2	0.3	0.4	1.0	98.0	0.7	137.0
Kidney	–	0.1	0.2	0.3	0.3	0.3	1.0	103.1	0.4	250.0
Melanoma	0.1	0.1	0.2	0.2	0.2	0.2	0.9	106.4	0.2	487.8
Bladder	–	–	0.1	0.2	0.3	0.4	0.9	116.3	0.4	258.4
Stomach	–	–	0.1	0.2	0.3	0.4	0.8	122.0	0.7	153.8
Cervix	0.1	0.2	0.1	0.2	0.2	0.1	0.8	123.5	0.3	350.9
Oral	–	–	0.1	0.2	0.2	0.2	0.6	163.9	0.3	374.5

– *Value less than 0.05*

Note: The probability of developing cancer is calculated based on age- and gender-specific cancer incidence and mortality rates for Canada in 1996 and on the abridged life tables based on 1995-1997 all cause mortality rates.The probability of dying from cancer represents the proportion of persons dying from cancer in a cohort subjected to the mortality conditions prevailing in the population at large in 1997. See *Appendix II: Methods* for details.

Source: Cancer Bureau, CCDPC, Health Canada

Figure 1: Probability of Developing Colorectal Cancer in the Next 10 Years by age, Canada)



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Source: Cancer Bureau, CCDPC, Health Canada

Figure 2:Age-Specific Incidence and Mortality Rates, Colorectal Cancers, Canada, 1971-2001

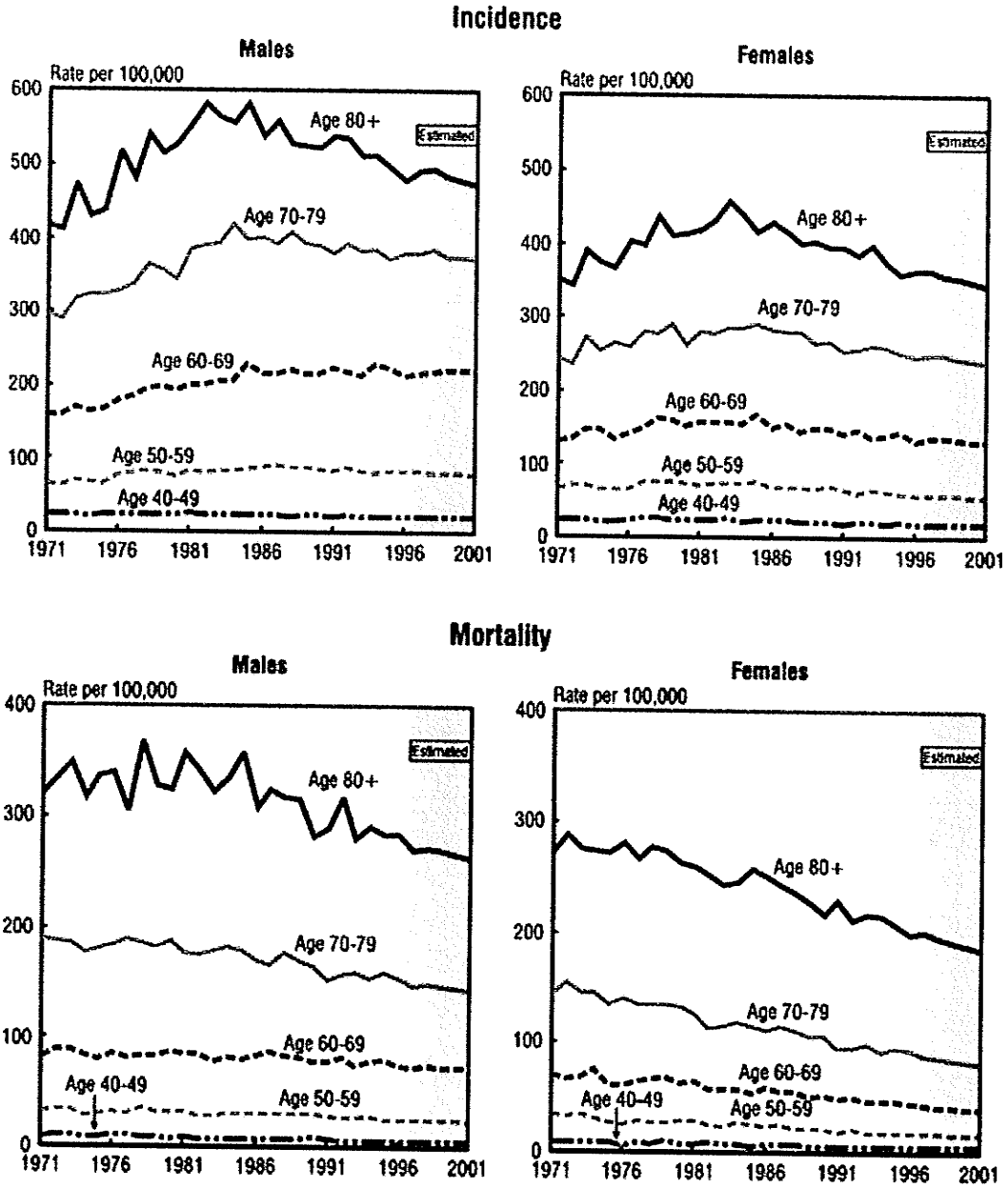


Table 4: Estimated New Cases and Deaths for Cancer by Sites and Gender, 2001

Estimated New Cases and Deaths for Cancer Sites by Gender, 2001

	New Cases 2001 Estimates			Deaths 2001 Estimates			Deaths/Cases Ratio 2001 Estimates		
	Total	M	F	Total	M	F	Total	M	F
All Cancers	**134,100**	**68,600**	**65,400**	**65,300**	**34,600**	**30,700**	**0.49**	**0.50**	**0.47**
Lung	21,200	12,100	9,200	18,000	10,700	7,400	0.85	0.89	0.80
Breast	19,500	–	19,500	5,500	–	5,500	0.28	–	0.28
Prostate[1]	17,800	17,800	–	4,300	4,300	–	0.24	0.24	–
Colorectal	17,200	9,300	7,900	6,400	3,400	3,000	0.37	0.37	0.38
Non-Hodgkin's Lymphoma	6,200	3,400	2,800	2,700	1,400	1,250	0.44	0.42	0.45
Bladder	4,700	3,500	1,250	1,500	1,050	460	0.32	0.30	0.37
Kidney	3,900	2,400	1,500	1,450	890	550	0.37	0.37	0.36
Melanoma	3,800	1,950	1,800	820	490	330	0.22	0.25	0.18
Leukemia	3,500	2,000	1,500	2,100	1,200	940	0.61	0.61	0.62
Body of Uterus	3,500	–	3,500	670	–	670	0.19	–	0.19
Pancreas	3,100	1,500	1,650	3,100	1,500	1,650	1.00	0.99	1.01[2]
Oral	3,100	2,100	980	1,050	730	320	0.34	0.34	0.33
Stomach	2,800	1,750	1,000	1,950	1,200	770	0.70	0.67	0.76
Ovary	2,500	–	2,500	1,500	–	1,500	0.60	–	0.60
Brain	2,400	1,300	1,050	1,550	880	670	0.66	0.67	0.64
Thyroid	1,900	510	1,400	160	50	110	0.09	0.10	0.08
Multiple Myeloma	1,700	960	760	1,250	670	590	0.73	0.70	0.77
Cervix	1,450	–	1,450	420	–	420	0.29	–	0.29
Esophagus	1,350	930	420	1,450	1,050	400	1.09[2]	1.15[2]	0.95
Larynx	1,250	1,000	240	520	430	90	0.42	0.42	0.38
Hodgkin's Disease	810	430	380	120	70	55	0.15	0.16	0.14
Testis	790	790	–	35	35	–	0.05	0.05	–
All Other Sites	9,500	4,900	4,600	8,700	4,600	4,100	0.91	0.93	0.89

– Not applicable

1 The number of new prostate cases was estimated on the basis of data years 1980-1989. Please refer to *Appendix II: Methods* for further details.

2 The high ratio (in excess of 1.0) for cancers of esophagus and pancreas may result from incomplete registration of this cancer before death. Please refer to *Appendix II: Methods* for further details.

Note: Incidence figures exclude an estimated 70,000 new cases of non-melanoma skin cancer (ICD-9 173). Total of rounded numbers may not equal rounded total number. Please refer to *Appendix II: Methods* for further details.
Source: Cancer Bureau, CCDPC, Health Canada

Figure 3:New Cases and Age- Standardized Incidence Rates (ASIR) for Colorectal Cancer, Canada, 1972-2001

New Cases and Age-Standardized Incidence Rates (ASIR)
for Colorectal Cancer, Canada, 1972-2001

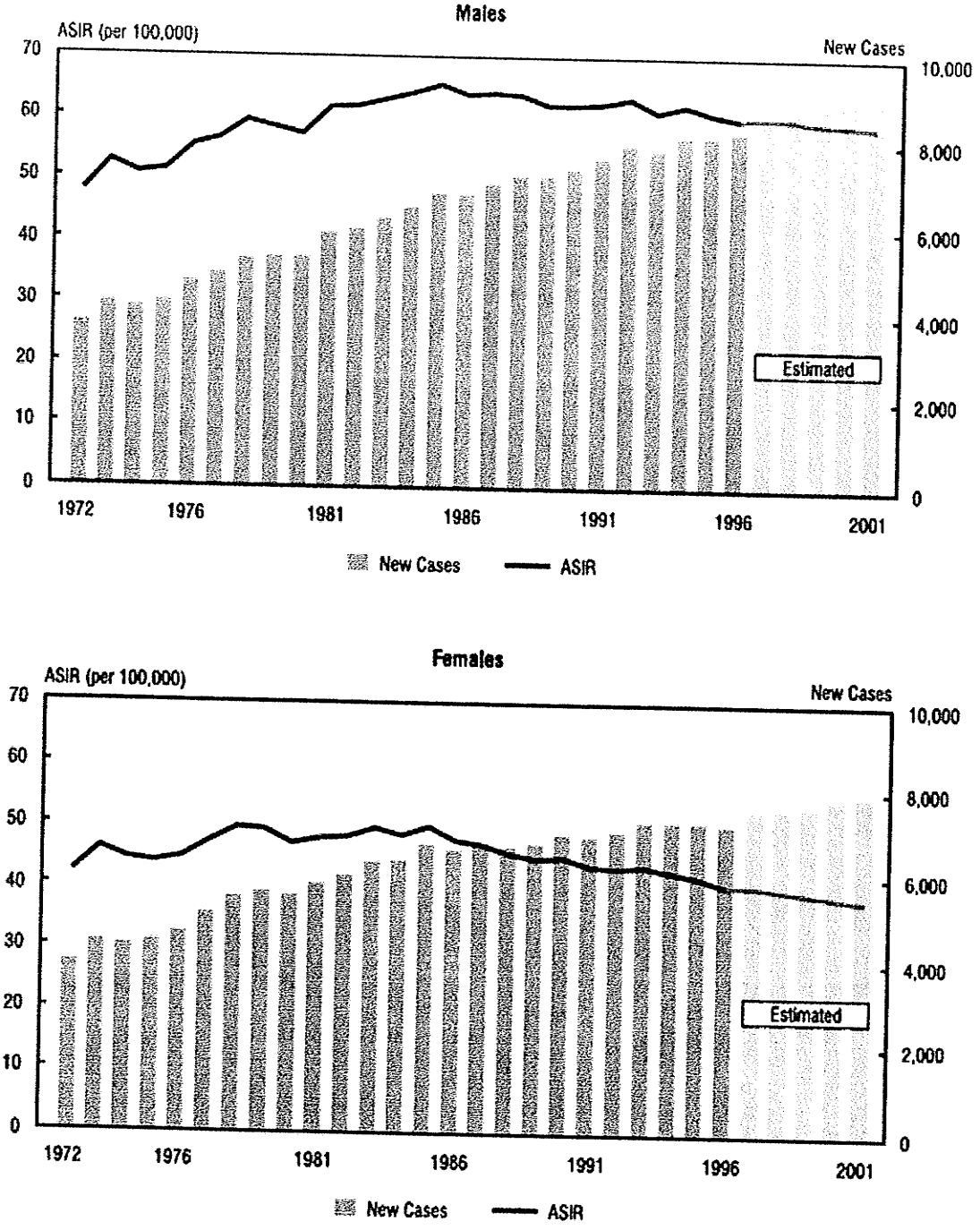
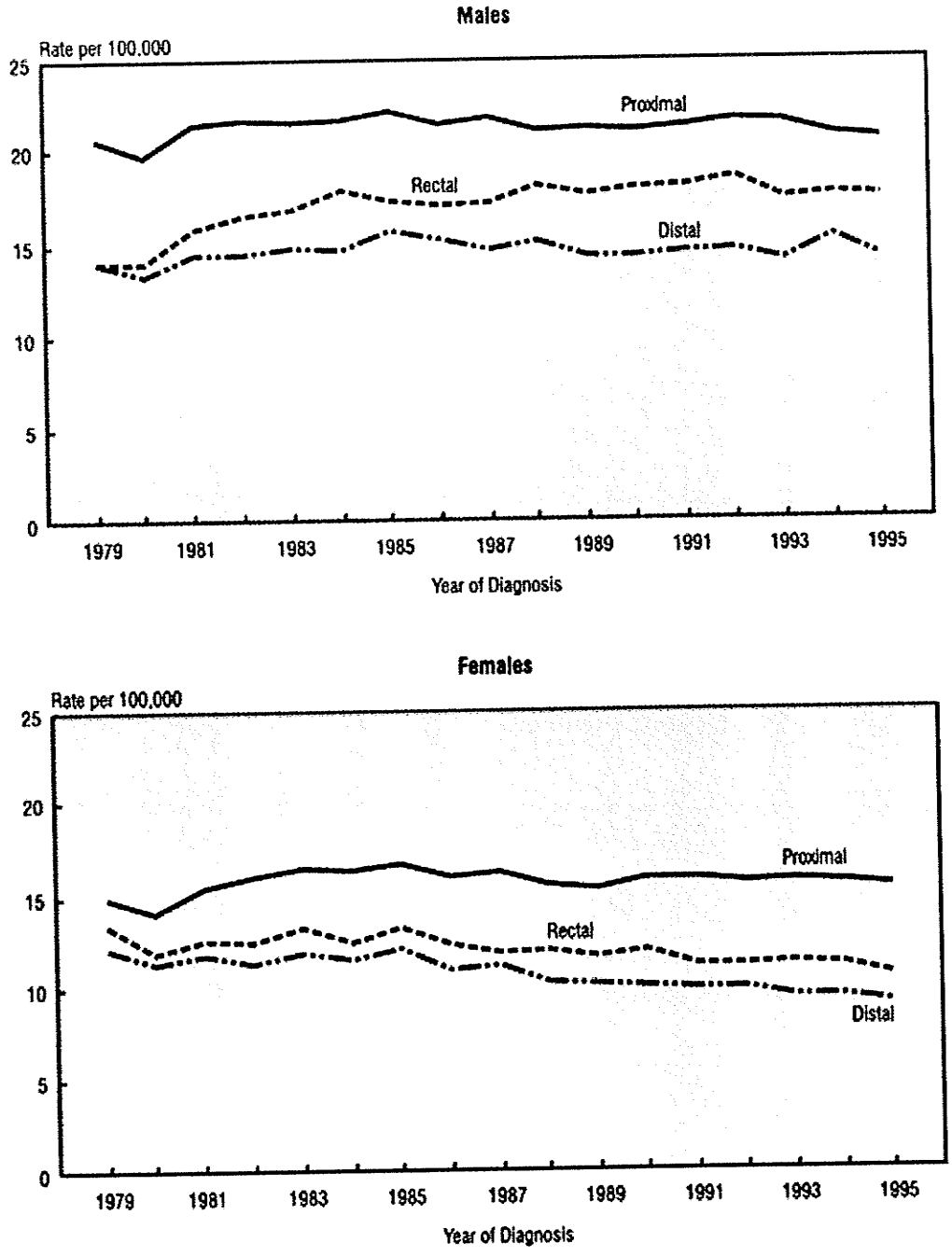


Figure 4:Age-standardized Incidence rates for Colorectal Cancers by Subsite and Gender, Canada, 1979-1995.

Age-Standardized Incidence Rates for Colorectal Cancers
by Subsite and Gender, Canada, 1979-1995



(i) Manitoba

In Manitoba, like Canada, lung, breast, prostate and colon cancer make up the majority of cancers. (See Table 5: Estimated Age-standardized Incidence Rates for Major Cancer Sites by Gender and Geographic Region, Canada, 2001). Colorectal Cancer was the third leading cause of cancer deaths in Manitoba in 1997. (See Figure 5: Estimates Age-Standardized Colorectal Cancer Rates per 100,000 by Province, Canada, 2001)

While Manitoba has a higher incidence of colorectal cancer than the Canadian average (especially in males), the mortality rate is less than the national average.

Health Canada estimated that there would be 400 new male cases and 330 female cases of colorectal cancer in Manitoba in the 2001 year. They also estimated that there would be 130 male deaths and 120 female deaths in Manitoba due to this cancer. In 1996, 450 male and 320 female colorectal cancers diagnosed, (see Table 6: Actual Data for Deaths for Major Cancer Sites by Gender and Geographic Region, Canada, 1997 Canada" and Table 7: Actual Data for New Cases for Major Cancer Sites by Gender and Geographic Region, Most Recent Year, Canada")

Table 5: Estimated Age-standardized Incidence Rates for Major Cancer Sites by Gender and Geographic Region, Canada, 2001

Estimated Age-Standardized Incidence Rates for Major Cancer Sites by Gender and Geographic Region, Canada, 2001

Rate per 100,000

	Canada[1]	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.
Males											
All Cancers	**444**	**370**	**460**	**493**	**499**	**491**	**423**	**476**	**374**	**400**	**446**
Prostate	118	95	113	142	154	111	108	140	78	114	163
Lung	77	53	92	86	95	105	68	75	60	64	58
Colorectal	59	72	66	66	61	63	59	66	55	56	52
Bladder	22	18	22	34	25	37	16	22	28	14	14
Non-Hodgkin's Lymphoma	21	13	18	20	21	22	21	24	18	18	20
Kidney	16	14	21	16	17	15	15	20	13	15	13
Oral	13	21	7	12	10	13	13	16	12	11	11
Leukemia	13	5	10	7	13	14	13	11	16	14	10
Melanoma	12	9	15	22	16	7	13	11	12	14	15
Stomach	11	18	9	10	14	13	10	10	9	10	10
Pancreas	9	2	13	7	12	11	9	9	8	10	9
Brain	8	7	4	8	7	10	8	7	7	7	8
Larynx	6	7	9	5	6	9	6	5	4	4	4
Multiple Myeloma	6	5	9	8	5	7	6	7	4	5	5
Females											
All Cancers	**344**	**302**	**407**	**362**	**353**	**351**	**344**	**364**	**322**	**341**	**321**
Breast	105	95	119	109	108	104	105	113	99	105	102
Lung	47	26	53	55	50	53	44	47	38	44	46
Colorectal	38	48	67	48	44	40	39	41	34	35	35
Body of Uterus	18	18	16	19	16	16	19	23	17	21	18
Non-Hodgkin's Lymphoma	15	12	14	13	19	15	15	16	13	14	13
Ovary	13	9	12	12	11	16	14	12	14	10	11
Melanoma	10	10	16	17	11	6	10	10	9	13	11
Thyroid	9	7	2	5	6	8	9	8	7	9	7
Pancreas	8	2	7	8	10	9	8	8	6	9	7
Cervix	8	9	15	9	8	7	9	9	9	8	8
Kidney	8	7	11	9	10	8	8	9	8	8	6
Leukemia	8	5	7	6	7	8	9	9	9	8	6
Bladder	6	4	3	10	7	9	4	5	8	4	4
Brain	6	3	4	4	5	7	6	5	5	5	5
Oral	5	4	1	5	4	4	6	6	4	5	5
Stomach	5	10	3	4	6	5	5	4	4	5	4
Multiple Myeloma	4	2	3	2	4	4	4	3	3	3	3

1 *Canada totals include provincial and territorial estimates*

Note: Rates for prostate cancer were estimated based on data years 1980-1989. Rates exclude non-melanoma skin cancer (ICD-9 173) and are adjusted to the age distribution of the 1991 Canadian population. Due to changes and improvements in source data and in methodology (as described in *Appendix II: Methods*), caution is needed if the 2001 estimates are compared to previously published estimates. These estimates may vary from actual figures.
Source: Cancer Bureau, CCDPC, Health Canada

Table 6: Actual Data for Deaths for Major Cancer Sites by Gender and Geographic Region, Canada, 1997 Canada

Actual Data for Deaths for Major Cancer Sites by Gender and Geographic Region, Canada, 1997[1] Canada

New Cases

	Canada	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	Y.T.	N.W.T.	Nu.
Males														
All Cancers	**31,600**	**630**	**160**	**1,150**	**910**	**8,700**	**11,300**	**1,250**	**1,200**	**2,300**	**3,900**	**20**	**20**	**15**
Lung	9,700	210	45	360	320	3,200	3,200	340	280	620	1,150	5	5	5
Prostate	3,600	75	20	140	100	770	1,300	170	230	320	470	–	–	–
Colorectal	3,200	50	10	90	70	990	1,200	120	130	210	340	–	–	–
Pancreas	1,400	20	10	50	35	370	490	50	40	120	190	–	–	–
Stomach	1,250	45	5	45	30	390	420	45	45	80	130	–	–	–
Non-Hodgkin's Lymphoma	1,200	10	5	50	40	280	430	80	45	95	180	–	–	–
Leukemia	1,100	15	5	30	25	270	430	45	50	95	130	–	–	–
Bladder	960	15	5	40	25	230	350	45	50	60	140	–	–	–
Brain	820	20	–	20	20	240	270	30	30	65	120	–	–	–
Kidney	820	15	5	30	30	210	290	45	25	65	110	–	–	–
Oral	710	15	5	30	20	190	260	30	15	45	90	–	–	–
Multiple Myeloma	580	5	5	20	20	150	210	25	20	35	70	–	–	–
Melanoma	400	5	–	20	10	75	180	15	15	35	50	–	–	–
Larynx	390	5	–	20	15	160	110	10	10	15	45	–	–	–
Females														
All Cancers	**27,100**	**460**	**110**	**1,100**	**720**	**7,300**	**9,800**	**1,200**	**960**	**2,000**	**3,500**	**15**	**15**	**10**
Lung	5,7600	60	30	250	140	1,600	1,950	250	180	420	820	5	5	5
Breast	4,900	80	15	180	120	1,350	1,850	220	160	390	600	–	–	–
Colorectal	2,900	65	15	95	70	920	1,000	120	110	160	340	–	5	–
Pancreas	1,450	20	5	55	50	380	530	55	50	140	180	–	–	–
Ovary	1,350	25	5	45	25	330	520	55	65	95	200	–	–	–
Non-Hodgkin's Lymphoma	1,050	10	5	40	35	240	430	50	40	65	130	–	–	–
Leukemia	800	20	5	30	25	200	340	40	35	70	110	–	–	–
Stomach	740	30	–	25	15	240	230	30	30	55	85	–	–	–
Body of Uterus	630	5	–	25	20	210	210	25	15	45	75	–	–	–
Brain	630	15	–	35	15	190	200	20	25	55	75	–	–	–
Multiple Myeloma	480	10	–	15	15	130	160	15	20	50	55	–	–	–
Kidney	470	5	–	25	20	140	150	20	20	35	60	–	–	–
Cervix	420	10	–	20	5	90	160	15	15	35	55	–	–	–
Bladder	410	10	–	20	15	100	130	25	20	30	60	–	–	–
Oral	320	–	–	15	5	75	120	15	10	20	50	–	–	–
Melanoma	270	5	5	10	15	40	120	15	5	20	45	–	–	–

– Fewer than 5 cases

[1] 1993-1997 average for Yukon, Northwest Territories, Nunavut

Note: Total of rounded numbers may not equal rounded total number, and an average is used for the territories.

Source: Cancer Bureau, CCDPC, Health Canada

National Cancer Institute of Canada: Canadian Cancer Statistics 2001

Table 7: Actual Data for New Cases for Major Cancer Sites by Gender and Geographic Region, Most Recent Year, Canada

Actual Data for New Cases for Major Cancer Sites by Gender and Geographic Region, Most Recent Year, [1] Canada

	New Cases													
	Canada	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	Y.T.	N.W.T.	Nu.
Males														
All Cancers	**61,500**	**980**	**330**	**2,200**	**1,800**	**15,400**	**23,100**	**2,700**	**2,400**	**4,900**	**8,100**	**30**	**35**	**20**
Prostate	14,800	250	85	580	550	2,700	5,800	730	620	1,400	2,400	5	5	–
Lung	11,300	150	70	370	350	3,500	3,900	450	380	750	1,250	5	5	10
Colorectal	8,200	180	55	290	240	2,100	3,200	420	310	680	1,050	5	10	5
Bladder	3,300	15	15	150	50	1,100	1,050	100	160	120	330	–	–	–
Non-Hodgkin's Lymphoma	2,700	45	10	80	75	690	1,000	140	110	220	370	–	5	–
Oral	2,100	70	10	55	45	500	840	90	75	150	230	–	–	5
Kidney	2,100	40	10	90	45	510	780	90	80	160	240	–	–	–
Stomach	1,850	55	5	45	60	530	630	70	60	120	220	–	–	–
Leukemia	1,850	15	10	35	45	470	760	70	100	170	210	–	–	–
Melanoma	1,600	15	5	65	50	210	690	65	50	150	280	–	–	–
Pancreas	1,450	5	5	40	55	390	490	50	45	120	180	–	–	–
Brain	1,200	15	5	35	40	330	430	40	40	95	140	–	–	–
Larynx	980	20	5	40	25	340	340	35	35	65	95	–	–	–
Multiple Myeloma	770	15	5	25	25	210	290	35	25	60	95	–	–	–
Females														
All Cancers	**57,100**	**880**	**330**	**2,000**	**1,600**	**14,500**	**21,600**	**2,400**	**2,000**	**4,800**	**7,600**	**30**	**35**	**15**
Breast	16,600	260	110	580	460	4,200	6,200	700	600	1,400	2,400	10	10	–
Colorectal	7,200	160	55	300	230	1,850	2,700	320	250	540	910	–	5	–
Lung	7,100	75	40	290	230	1,900	2,600	330	230	550	1,000	5	5	5
Body of Uterus	3,100	50	15	95	90	700	1,250	140	100	320	430	–	–	–
Non-Hodgkin's Lymphoma	2,300	30	5	55	70	590	840	100	85	180	340	–	–	–
Ovary	2,100	30	10	60	50	600	790	75	80	190	260	–	–	–
Melanoma	1,550	25	15	65	55	210	680	55	60	170	230	–	–	–
Pancreas	1,500	10	10	45	40	410	540	70	50	110	200	–	–	–
Cervix	1,450	35	10	40	45	320	590	60	60	150	190	–	–	–
Leukemia	1,400	15	5	35	25	350	590	70	50	120	150	–	–	–
Kidney	1,350	20	10	50	50	360	480	50	50	120	120	–	–	–
Thyroid	1,200	10	–	15	20	260	550	40	30	140	120	–	–	–
Bladder	1,150	5	–	60	20	360	380	35	60	45	120	–	–	–
Stomach	1,050	35	–	40	25	280	390	35	35	75	130	–	–	–
Brain	930	10	5	30	20	280	360	30	25	70	100	–	–	–
Oral	880	10	10	30	15	170	390	40	30	80	120	–	–	–
Multiple Myeloma	620	5	5	20	20	180	240	25	25	45	70	–	–	–

– Fewer than 5 cases

[1] 1996 for Canada, Quebec, Ontario; 1997 for Nova Scotia, Saskatchewan; 1998 for Newfoundland, Prince Edward Island, New Brunswick, Manitoba, Alberta, British Columbia; 1994-1998 average for Yukon, Northwest Territories, Nunavut

Note: Total of rounded numbers may not equal rounded total number, and an average is used for the territories. Counts exclude cases of non-melanoma skin cancer (ICD-9 173).

Source: Cancer Bureau, CCDPC, Health Canada

Figure 5: Estimates Age-Standardized Colorectal Cancer Rates per 100,000 by Province, Canada, 2001

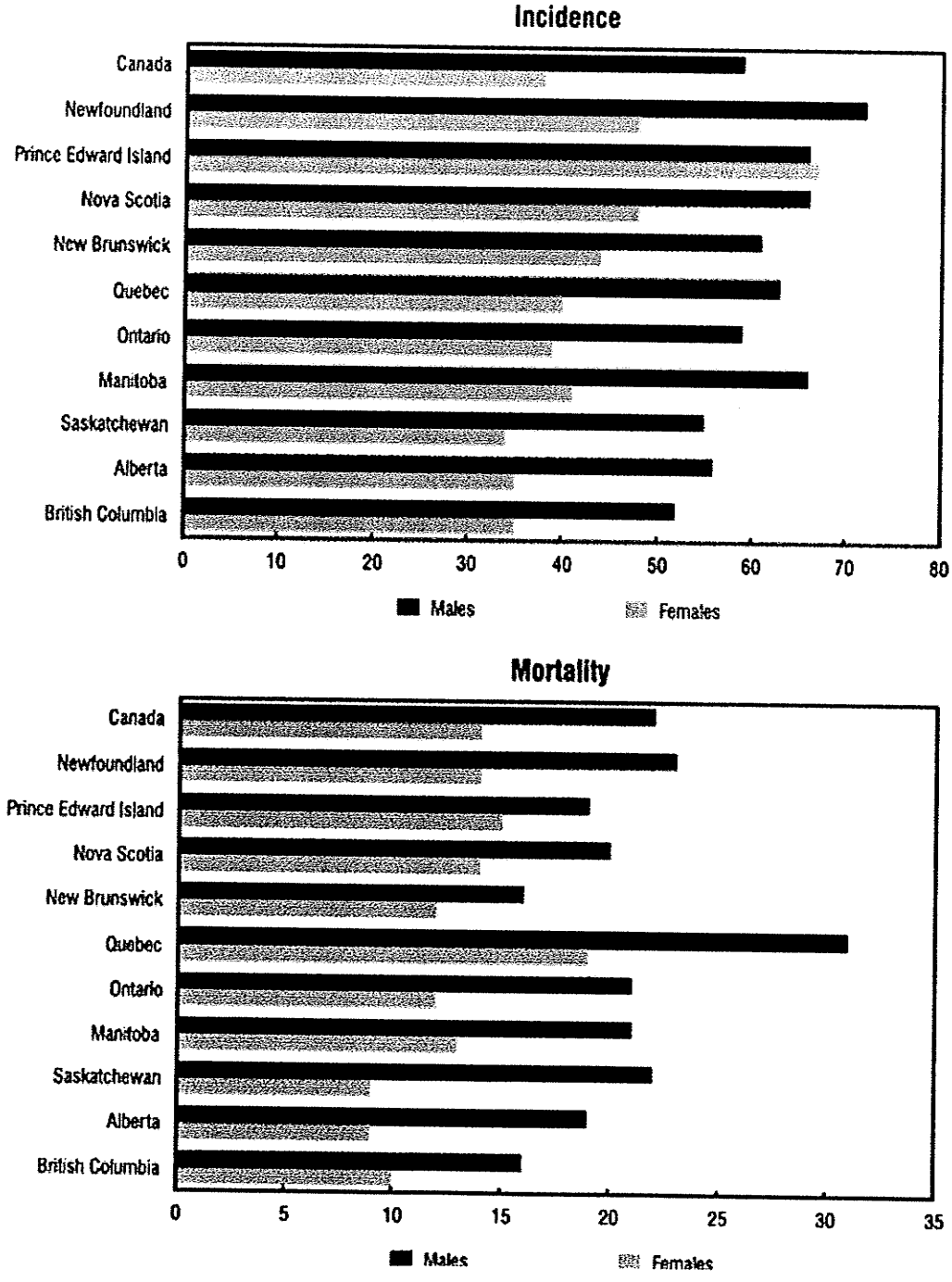


Table 8: shows the age-stratified incidence of colorectal cancer in 1999 in Manitoba. Rates are calculated per 100,000 population in the age group specified. (Manitoba Cancer Registry, 1999)

Table 8: Incidence of colorectal cancer in Manitoba in 1999

Age	Male	rate	Female	rate	total	rate
<30	0	0	0	0	0	0
30s	9	10.4	4	4.7	13	7.5
40s	20	23.2	18	20.9	38	22.1
50s	46	74	32	51.2	78	62.6
60s	110	263.9	76	172.5	186	217
70s	135	432.5	111	270.7	246	340.6
80+	63	427.9	111	396.8	174	407.6
total	383	67.8	352	60.5	735	64.1

Table 9 shows the age-stratified mortality due to colorectal cancer in Manitoba. This is based on ICD-9 coding as registered with Vital Statistics department, Province of Manitoba.

Table 9: Mortality of Colorectal cancer in Manitoba in 1999

Age	Male	rate	Female	rate	total	rate
<30	0	0	1	0.4	1	0.2
30s	1	1.2	0	0	1	0.6
40s	5	5.8	3	3.5	8	4.6
50s	12	19.3	15	24	27	21.6
60s	36	86.4	21	47.7	57	66.5
70s	55	176.1	38	92.7	93	128.7
80+	46	312.4	63	225.2	109	255.3

(b) Around the world

Colon cancer is a concern in many developed countries as can be seen by the numerous countries of origin of the other studies reviewed in the next section of this

paper. Many of these papers describe statistics similar to Canadian statistics noted above. Other countries, with similar standards of living as Canada describe much lower rates of colon cancer. Reasons for this are discussed in subsequent sections (e.g. in the section on Social/Environmental History). It may be expected that colorectal cancer will become even more of a global concern as the standard of living improves in other societies in the world, and life expectancies increase.

B) Difficulties with studying the risk factors

1) Polyps

In a referred population the prevalence of adenomas is around 10%, which is very similar to the prevalence found on autopsy (Jensen, J; 1993). In fact, the yield of adenomas is independent of indication for colonoscopy, suggesting that polyps are not symptomatic (Rex D; 1995). Polyps are thought to cause bleeding, though. This may be overt or occult, with the likelihood of bleeding being proportional to the size of the polyp. (McCrae, F, 1982) Thus, polyps are very difficult to detect based on clinical grounds alone. They require a colonoscopy or barium enema.

2) Carcinoma

(a) Introduction

Colorectal carcinoma may have more clinical features than polyps to indicate its presence. Even so, the diagnosis of colorectal cancer is difficult based on clinical

grounds alone[1]. The difficulty can come from many other sources also. Below, the difficulties have been divided (somewhat arbitrarily) into the following groupings: the patient, the cancer, the physician, the gold standard test, and finally previous studies. The last section includes a review of some of those studies.

(b) The patients and their symptoms

The patients with colorectal carcinoma can themselves cause delays in making a diagnosis.

For a physician to diagnose patients, they must present to the health care system. Some patients rarely see physicians due to anxiety, denial, fear, or financial concerns. In Crossland (1995), only 41% of respondents with self-reported rectal bleeding had consulted a physician for the problem. On the other hand, if a patient presents to physicians too often, then physicians may have difficulty determining which symptoms are important. The patient must also accept the proposed investigations (investigations for colon cancer are not pleasant). Finally, there are colorectal cancer patients who present at autopsy.

For one to use the patient's symptoms for predicting colorectal cancer, one must be able to assess their accuracy (both validity and reliability). Many patients do not recall their own histories well. In a mail questionnaire, of 149 respondents who claimed that they had previously been treated for a colonic neoplasm, only one half were correct when

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[1](Goulston, K; 1986) (Mant A; 1989) (Segal W; 1998), and see I)A)1)(d)The health care system

compared to hospital notes (Kewenter, J; 1989). Patients may have different definitions of a given symptom and attitudes towards it. For example, people define constipation differently (Curless, R; 1994) and women may have a different attitude towards symptoms than men (Steine S; 1992). Cultural differences may also obscure the definition of a given symptom. Patients may exaggerate or deny their symptoms (Curless, R, 1994b) and may change their story at different times and to different health care workers. How physicians ask question will make a difference on how the patient responds. A written question, as used in this study, may not lead to the same answers as an oral question in the office. All of the above inconsistencies may bring into question the accuracy of a patient's history.

Even if the patient's history is accurate, the patient may have symptoms from other diseases that may obscure the picture. There is a high prevalence (63%) of haemorrhoids concurrent with more significant colonic lesions (Goulston; 1986), both of which may cause rectal bleeding. Sixteen percent of those who have haemorrhoids also had a colonic cause for rectal bleeding (Mant A; 1986).

A large number of apparently healthy community adults have symptoms that have been associated with colorectal carcinoma. For example, 4 to 15% of adults in the community have reported rectal bleeding within the last 6 months (Helfand, 1997) (Dent, 1986) (Dent, O; 1985) (Kewenter, J; 1989) this is especially true in those over 70, i.e. those in one of the highest risk categories for colorectal cancer (Curless, R; 1994). Different community populations may have different rates of the same symptom.

Thus, a patient with colorectal carcinoma may help to delay the making of the diagnosis through their delay in presenting to the health care system, the accuracy of their histories and their concurrent diseases.

(c) The cancer

The cancer itself may be different from person to person and at different stages of its growth. The diagnosis of colorectal carcinoma is more difficult in the early stages as it may produce fewer symptoms then (Brazier, S; 1991) (Kyle S; 1991). Rex (1991) screened 210 asymptomatic patients and found that 25% of patients had adenomas and 1% had colorectal cancer.

On the other hand, cancers found because of acute symptoms are usually of a later stage. They are also more malignant as patients who present acutely have a higher fatality and complication rate than those presenting electively (Curless, R, 1994b). Kyle (1991) found that patients who presented emergently had symptoms of less than one-month duration while Mulch (1997) found that over 40% of patients who presented with bowel obstruction had previous symptoms which, if had been investigated, might have negated the need for emergency surgery.

Colorectal carcinoma in older patients might in fact be a different disease than that of younger patients (Curless, R, 1994b). The degree of cancer dysplasia seems to increase with patient age, as does the percentage of metastasises found at diagnosis (Kemppainen, M; 1993). This might explain why diagnosed older patients have worse outcomes. (Curless, R. 1994b)

In general, studies have found a poor correlation between length of symptoms and stage of disease. Several studies have found that symptom duration had no effect on colorectal carcinoma outcome when corrected for other factors (Raftery T; 1980) (Steine; 1992) (Steine S; 1994). In fact, symptom duration has been inversely related to outcome (Mulcahy H; 1997) (Segal W; 1998).

The aggressiveness of the cancer may also be important. According to some authors, accidentally found cancers, or those found upon screening, may be less aggressive than those found because of symptoms. (Mansson J; 1990)

Thus, the different stages and aggressiveness of the cancer will complicate the investigation of a patient with colorectal cancer.

(d) The health care system

Once a patient with colorectal cancer has presented and explained his/her symptoms, the physician must then consider its possibility in order to proceed to further investigations. To do this, most physicians use the "hypothetico-deductive" strategy to diagnose a problem (Sackett, 2nd ed). "It is the formulation, from the earliest clues about the patient, of a "short list" of potential diagnoses or actions, followed by the performance of those clinical (history and physical) and paraclinical (e.g. laboratory, x-ray) manoeuvres that will best reduce the length of the list." Physicians thus generally ask the patient questions to rule in or rule out a diagnosis that has been entertained because of the patient's presenting complaint. In summary, once the patient has presented to their physician with a symptom (e.g. rectal bleeding), the physician must

then think of the diagnosis of colorectal carcinoma and then must try to determine if the risk is high enough for further investigations, e.g. colonoscopy.

Studies have found a poor correlation between general practioners' assessment of risk for colorectal cancer and the diagnosis on colonoscopy (Mant; 1989) (Segal; 1998). An estimate of the positive predictive value of general practitioners' assessment of the likelihood of rectal bleeding coming from a colorectal cancer was 20.7% and that of a specialist was 34.2% (Goulston, K; 1986). One study found that referrals to a barium enema suite reflected the age and gender of the general practice population, suggesting that referrals were independent of symptoms (Steine, S; 1992). Physicians are better at excluding colorectal cancer. If a physician believes that a patient does not have cancer, based on history alone, then they will be right 95% to 98% of the time (Goulston, K; 1986).

Interestingly, though, Steine (1994) found that physicians "acted faster" ($p<0.01$) in their referrals of patients with colon cancer, compared to those who had normal barium enema studies, suggesting that there "could be differences in symptom severity perceived by the referring physicians but not by (their) questionnaire". This is in spite of the fact that the same author had previously conducted a study that suggested that "(age) does not seem to be sufficiently appreciated by physicians when they refer patients for radiologic examination of the colon" (Steine, 1994).

Different physicians might have different ideas of what is clinically relevant. For example, two studies investigating rectal bleeding found that flexible sigmoidoscopy would miss 2% of colon cancers. One is quoted "Flexible sigmoidoscopy

ultimately would have missed only a small number (2%) of proximal lesions..." and "flexible sigmoidoscopy will detect almost all substantial lesion" (Segal W; 1998)(also Church, 1991) while another study discussed the significant number of colonoscopies missed by this method (Goulston K; 1986)(Helfand, 1997) using similar numbers.

The experiences of the physicians are important. A general practioner who is responsible for 3000 patients will diagnose one colorectal cancer per year. (Mansson J; 1990) Thus, a general practioner will likely not learn first hand which case scenarios are most predictive of colorectal cancer. A physician may be more likely to think of colorectal carcinoma if he/she has recently diagnosed a patient with it, if he/she has recently been to an educational session on the subject or had been a teacher at some point that specialized in the subject. While important, the experience of a given physician therefore is not likely to be sufficient to create an unbiased understanding of which symptoms and risk factors are important. Because of this, physicians should base their decisions on studies.

(e) The colonoscopy

A "gold standard" is a test, or group of tests, which the medical community generally considers the ultimate test for a diagnosis. If it is positive, then the patient has the disease, and if it is negative, the patient does not to have the disease. The gold standard for colorectal cancer is colonoscopy, but there is debate about the relative merits of Air-Contrast Barium Enemas with Flexible Sigmoidoscopy versus Colonoscopy (Rex, D; 1995). The use of a given test seems to depend on the complaint. Physicians might be more likely to order a barium enema to investigate constipation and a colonoscopy

to investigate bleeding. (Rex D; 1995) Several studies have found the two to be equivalent diagnostically for the significant polyps greater than 1cm in size (Helfand, M; 1997). Note that abnormalities noted on Barium Enema generally are referred for colonoscopy (for biopsy)(Helfand, M; 1997).

The incidence of colorectal cancer in a referred population was about 3.3%, and the incidence of adenomas around 10%. The prevalence of adenomas>1.0 cm on autopsy is around 7-10%, and that of cancer around 1-2% (Jensen, J; 1993)

Because of concurrent diseases, the symptoms found on colonoscopy may not be associated to a diagnosis. For example, painful diverticuloisis is a recognized entity but about 40% of the asymptomatic western population has diverticuloisis. (Rex D; 1995)

Cancers may be missed if a patient is not investigated completely. For example, investigators who performed only a flexible sigmoidoscopy missed 3/13 cancers in a group of patients who presented with rectal bleeding (Helfand, M; 1997). Other studies have found a 2% false negative rate for flexible sigmoidoscopy alone (Segal W; 1998)(Church, 1991). This may be especially true in the elderly, as cancer appears to be located in the proximal colon in the elderly compared to younger patients. (Kemppainen M; 1993) The colonoscopy or barium enema needs to be complete to rule out cancer.

Finally, the expertise of the colonoscopists and the pathologists is obviously important in obtaining a diagnosis of colorectal cancer.

(f) Previous studies

(i) Introduction

Several studies have looked at tests, risk factors, and symptoms of colon cancer. Presented below is a review of some of these studies. The authors selected the articles based on a Medline search from 1990 - 1999. The search was with Silver Platter in the University of Manitoba Library. The general theme of the search strings was «(colonoscopy or barium enema) and ((colorectal carcinoma) or polyp) and (symptoms or (risk factors))>>. The authors reviewed the articles' references for further articles of interest. There were no selection criteria used to either include or exclude a given article.

This review has been grouped along the same lines as a traditional medical history, e.g. demographics (e.g. age/gender), history of present illness (e.g. symptoms), social history, examination etc. Studies are often difficult to interpret or combine, making generalizing difficult. Different studies used different groups of predictors and several different designs, thus making comparisons between the studies difficult. For example, one study might use "outlet type bleeding", while another might use "bright red rectal bleeding" for essentially (but not exactly) the same clinical entity. The prevalence of certain predictors will change depending on the study. As an extreme example, if the study included mostly men, then the known association between a personal history of breast cancer and colorectal cancer would not be apparent (Brazer, S; 1991).

(ii) Demographics

(1) Age

The risk of colorectal cancer increases with age. In fact, this is one of the most consistent predictors of colorectal cancer, as noted above in the section on Vital Statistics. The numbers presented in this section would suggest the age related relative risks (RR) in Table 10 (compared to a 30-39 yo).

Table 10: Relative Risks (RR) or Odds ratios (OR) based on age, of developing or being diagnosed with colorectal cancer

Age	30-39	40-49	50-59	60-69	70-79	Source
RR	1	2	8	18.5	26	(1)
OR	1	5.6	7.8	18.1	8.6	Steine (1993)
OR	-	-	1	10	-	Fitjen (1995)

(1) See Table 3: Probability of Developing Cancer by Age, and Lifetime Probability of Developing and Dying from Cancer, Canada

As noted in the section on Vital Statistics, very elderly patients may not be investigated as fully as younger patients. This would affect their apparent RR. The RR for an 85 yo is 19.5, which we might expect to be higher given the trend in the chart. All of the previous studies noted in this paper have shown an increase in colon cancer rates with age (as noted in Table 10: Relative Risks (RR) or Odds ratios (OR) based on age) Steine (1993), and Fitzen (1995).

(2) Gender

The estimated age-standardized incidence rate of colorectal carcinoma in Canadian males was 59/100,000 population, and for females was 38/100,000 population in 2001 (Health Canada, 2001; (see Table 5: Estimated Age-standardized Incidence Rates for Major Cancer Sites by Gender and Geographic Region, Canada, 2001). Thus, men are more likely to have colon cancer than women are, with a relative risk of about 1.5. Steine (1994) found that males had an (adjusted) oddsratio of 2.2 ($p=0.01$) for colorectal cancer. Colonoscopists are more likely to diagnose colon cancer in males. Women, though, are more likely to have a colonoscopy. Referral patterns might explain this. If a diagnosis of irritable bowel syndrome is more prevalent in women, then women may be more likely to have a colonoscopy for their symptoms. This may further decrease the perceived prevalence of colon cancer in that population, thus making it appear like women have even less colon cancer than they do (Brazer, S; 1991) (Steine, S; 1992). Some interactions may apply. For example, Neugut (1993) found that females with rectal bleeding have a higher rate of colon cancer, although the difference may not be clinically significant.

(3) Others

There are no known studies directly comparing ethnic origin and rates of colon cancer, although Bansal (1996) found no difference in colon cancer rates between whites and non-whites in their case-control study of Inflammatory Bowel disease patients and those without it. Sandler (1997) claims (without

references) that country of origin (North America, Northern Europe vs. Africa, Asia) is associated with a RR of >4.0. Sandler (1997) also claims that tall stature is associated with a relative risk of 1.1-2

(iii) History of Present Illness (or Symptoms)

Many signs and symptoms have been attributed to colorectal cancer. These include rectal bleeding, abdominal pain, a change in bowel habits, and the development of "pencil-thin" stools. When actually studied, though, many of these symptoms are not associated with the diagnosis of colorectal cancer. Blood in the stools is the only symptom that seems to have been consistently predictive of colon cancer in previous studies.

Previous studies dealing with the association between colorectal cancer and symptoms can be divided into two categories: primary care studies (mostly cohort studies) and tertiary care studies (mostly prevalence and case control studies). The former starts with a group of patients in a primary care setting and follows them forward over time, while the latter deals with patients already referred for either colonoscopy or barium enema. The studies that are included in this review are included because the information in the paper allowed for the completion of Table 31 in Appendix B: Summary of studies on symptoms.

(1) Primary Care Studies

As noted above, primary care studies start with a cohort of patients in a primary care practice. The exception is Niv (1989) that started with a screening

questionnaire to several kibbutzs in Israel.

There are several general difficulties with primary care studies.

- A large number of physicians and other health care personnel need to be dedicated to the study in order for it to be successful. Although this is true in any study, it is especially true in primary care studies due to the relative low prevalence of colorectal cancer in general practice.

- All of reviewed studies (but one) started with a cohort of patients with rectal bleeding, which means that this could not be studied as an independent factor.

- Patients are lost to follow-up due to their moving away from the study district, to death by other causes, and due to disinterest among many other reasons. One study found that 1/3 of patients who had rectal bleeding noted on a screening questionnaire dropped out of the study (Helfand; 1997). Another study that attempted to start with patients who presented to a family practice with rectal bleeding found that "fewer patients (were) included in the study than expected on the basis of the incidence rate of rectal bleeding in general practice of seven per 1000 people per year." (Fitjen, G; 1995) This study then accounted for the missing patients through patients presenting in different ways e.g. acutely.

- Primary studies are hard to blind. Investigators and patients know that the study is being performed and what the diagnosis of interest is.

- Not all patients in the primary care studies have a colonoscopy, thus the diagnosis of colorectal cancer might be missed in some of the patients (Goulston, K; 1986).

Because of these problems, primary care studies are hard to complete. Unfortunately, if the goal is to help general practitioners know who to refer onwards for investigation, then the primary care patients are the ones of most interest to us. The studies' results must be interpreted in light of their inadequacies, though.

Fitjen (1995) used a questionnaire of 290 patients who presented with overt rectal bleeding to 83 General Practioners in Limberg (Netherlands) to determine the predictive value of patient characteristics signs and symptoms for the presence of colorectal malignancy. Secondly, they tried to identify variables contributing to a multivariate prediction model. There was follow up at least one year later (mean time 20 months). The physician questionnaire had 70 variables, while the patient questionnaire had 150 variables. Two hundred and sixty nine patients finished protocol and 83 were referred on for further investigation.

Using univariate logistic regression, they found that age (see Table 10: Relative Risks (RR) or Odds ratios (OR) based on age, of developing or being diagnosed with colorectal cancer based on age, of developing or being diagnosed with colorectal cancer), a change in bowel habits (except constipation) (OR=18.4,

$p<0.01$)), nausea (OR=0.4, $p<0.01$), decreased appetite (OR=0.7, $p<0.05$), weight loss (OR=4.6, $p<0.05$), perianal eczema (OR=8.6, $p<0.05$), and a tumour felt or seen clinically was associated with colorectal carcinoma. Using multiple logistic regression, this study found that age (OR =8 (cut off at 50 yo)), change in bowel habits (OR=10) and blood mixed with the stool or on the stool (OR=8) to be significantly associated with colon cancer.

There were some difficulties with this study. Of the 290 patients, only 11% (32) were referred for either barium enema or colonoscopy, but there were nine cancers found (3.3%), and only six polyps (2%). This cancer rate seems high, especially as this is a primary care study, and there are far fewer polyps than expected given the number of cancers. This might explain the high OR for perianal eczema, only a few patients with this problem who happened to also have cancer would obscure this result. The "high" cancer rate might also be explained by the inclusion of 40 yo rectal bleeding patients, i.e. the patients most at risk for colorectal cancer. The referring GPs did not perform many of the laboratory tests. The authors had predicted that there should have been 1200 patients in the study, while there were only 290. There may be a referral bias to account for this discrepancy, as the final number of colorectal cancers was within the estimated range. Due to this referral bias, physicians may have been less likely to include patients with obvious minor problems. This study also had a large number of variables (at least 45) increasing the possibility of type 1 errors (false positive) in their analysis. Note that only 21 were lost to follow-up!

Mant (1989) tried to determine whether there are aspects of a patient's history or clinical features that would strongly suggest bleeding from a colorectal cancer or polyp. Fifty-eight Sydney (Australia) general practioners filled in a questionnaire when a patient presented to them with rectal bleeding of less than six months duration. The GPs were selected based on their referral patterns to the authors (who were the 7 colonoscopists in the study). Colonoscopy was the gold standard on most of the 148 included patients. There were initially 248 patients, with reasons for excluding patients including: referral not made, onset of bleeding > 6 months and the patient's age or co-morbidity excluding adequate investigation. Sixteen patients were diagnosed with cancer.

Using Chi squared analysis they found that blood mixed with the feces (OR =4.88, $p<0.05$) correlated significantly with the diagnosis of colorectal cancer. Haemorrhoids identified by the general practioner were associated with an OR of 0.28 ($P<0.05$). None of the other 15 factors studied were associated significantly with colorectal cancer. Their rate of cancer was 11%, while their polyp rate was 18%.

This study also had a few problems apart from those mentioned in the general Primary Care studies noted above. Statistical analysis involved only Chi squared that does not allow for investigation of independence of the variables. Forty percent of the patients with rectal bleeding were either excluded or refused to enter the study. They included one lymphoma in their analysis, which is a very different type of tumour, as well as one anal cancer. The authors of the study may have been

biased as they claim "Thorough investigation of patients aged 40 years and older with rectal bleeding of recent onset is mandatory" in the introduction of their paper.

Nørrelund (1996) attempted to determine the frequency of neoplastic conditions in patients with rectal bleeding presenting to general practices. They especially wanted to determine if a change in bleeding pattern was as predictive of a neoplasm as was new onset rectal bleeding. They also wanted to explain the associations between presenting symptoms and final diagnosis. They asked every fourth GP on the Danish medical association's list (n=750) to submit three to four patients with first episode of bleeding over 40 within previous six months. Excluded were patients with IBD, polyps, previous cancers, coagulation defect, melena stool. Once in the study, the General Practioners were then to try to organize a barium enema or colonoscopy. One hundred and eighty general practioners agreed, and 96 GP's entered 208 patients. The prevalence of colon cancer in their population was 15% (with 32 cases) and they found 16 polyps. All patients were followed to the end of the study (1991 to 1994) with no additional cases had being found.

They found that only age (OR=9.26, cut off age 70, $p<0.01$) and change in bowel habits (OR=0.44, $p=0.02$) were associated with colon cancer. Note that all of the patients had rectal bleeding and that the other five factors studied, including the bleeding pattern) was not significantly associated. In a second part of their study, using a different smaller cohort, change in bowel habits was not associated at all with colon cancer. Abdominal pain came close with an OR of .3. They used Mann-

Whitney's and Chi squared test, as well as logistic regression without specifying when they used which type.

One of the major drawbacks of this study was that there was a drop out rate of 50% of the physicians who initially said that they would participate in this study. Like in other primary care studies, there were only a few patients entered, but like Fitjen (1995), there seemed to be a high proportion of cancers. There was a long follow-up period, which makes missed cancers less likely.

Helfand (1997) determined whether a complaint of visible rectal bleeding that is elicited by a screening review of systems merits investigation and to assess the accuracy of a defined protocol to evaluate bleeding. In primary care clinics in a Portland vets centre, they administered an 8-item questionnaire, one of which was about rectal bleeding in the last three months. If the subject answered yes, the participant completed a longer questionnaire and FOB X6. The patient was then contacted 3 times in the first year re: their symptoms, and then the records (death cert., hospital records etc.) were pulled at the 8 to 10 year mark for final diagnosis. There were 297 patients identified with visible nonemergent rectal bleeding and 201 eventually were included.

They found 6.5% (13) of these had cancer and 24% had polyps. In this study, age (no OR specific for colorectal cancer were given) and duration of bleeding less than 2 months (OR=2 (calculated by myself from data in the paper)) were statistically significant specifically for colorectal cancer. The other 18 factors were not significant. They used Chi squared and logistic regression analysis

techniques. They used the combined end category of "serious illness", which included cancer, polyps, and IBD. This might obscure the picture as IBD might present very differently to colonic cancer.

There was an impressive 10 year follow up of 93% of the patients who did not have serious pathology in the first round of investigations. All of the 201 patients were fully investigated using Barium Enema and Flexible Sigmoidoscopy. In spite of this, one third of the potential patients did not complete the protocol. External validity from this study is questionable as only one patient was female and all were recruited from a Vets centre.

Niv (1989) sent out a questionnaire and FOB screening cards to 2590 patients over 40 years old in Northern Israel. The questionnaire was handed out in the first year and asked about 6 months of rectal bleeding, change in bowel habits, abdominal pain, or weight loss. First-degree relative cancers also were noted. One thousand seven hundred and ninety seven (1797) people responded. They were followed for the next 3 years. People who had a positive FOB had a colonoscopy. People who answered the questionnaire positively were assigned to various investigations at the discretion of the author.

They found that the predictive value of the FOB was 5 times that of the questionnaire, thus suggesting that symptoms (i.e. the questionnaire) did not contribute to the diagnosis. They used the Fisher's exact test, and did not look for independence amongst the variables. They did not breakdown the symptom categories, besides rectal bleeding versus non-bleeding symptoms.

This study is the only study reviewed in this paper that would not be subjected to a type of referral bias, namely that GPs who refer for further testing, either inside that study, or prior to the study, might in fact be different than those who do not. They had a higher degree of compliance than did other studies (69% responded to the initial invitation). They did not follow through on all patients with colonoscopies, and in fact, the author had a great deal of leeway in terms of which investigations patients underwent.

(2) Tertiary care studies

Tertiary care studies, like this study, solve many of the problems seen in primary care studies. There are fewer patients lost to follow-up, most to all patients have a complete bowel work-up, and they take less time.

The major difficulty with tertiary care studies is that of referral bias. Only patients who have been seen by a physician, and thought to have symptoms suggestive of a disease where a colonoscopy might beneficial will be included. That is, a patient needs to be referred in the first place to get a colonoscopy or barium enema. This referral bias could create problems when attempting to generalize to a general practitioner's office (Brazer, S; 1991), which, as noted above, is our population of interest.

Curless (1994) is the only case-controlled study reviewed in this paper. In Britain, Curless compared 273 patients with a histological diagnosis of colorectal cancer to community controls. Using Chi^2, and controlling for age, they found that

the ORs were statistically significant for all of the symptoms in their questionnaire, which is different from any other study reviewed in this paper (see Table 31 Previous Studies on Symptoms)! This might suggest that it is easier to differentiate between a patient who has cancer and a healthy person than between a patient with cancer and another patient with a more benign colorectal problem.

This type of study is especially subjected to recall bias, which may explain their high ORs. The patient's knowledge that they do or do not have cancer may influence their ability to "remember" symptoms in their past. This study suggests that symptoms in younger people would be more significant than in people over the age on 70. In their study, they also found that elderly people would more likely report symptoms relating to the GI tract, than younger people.

Jensen (1993) studied the prevalence of colorectal neoplasms among 149 consecutive symptomatic patients, aged 52-74, referred for double-contrast barium enema. The referral was made because of clinical symptoms that seem to have been determined by the General Practioners' referral letters. Their goal was to ascertain whether there was a correlation between symptoms (including occult blood in stools) and the diagnosises of neoplasia or diverticula. A Sigmoidoscopy to 60cm was also done.

Using Fisher's two-tailed exact test, they found no correlation between the five symptoms in their questionnaire and colonic cancer. They had a 3.4% cancer rate (5 cases), and 10 adenomas.

This was a small study, and included only a few symptoms and tests.

Segal (1998) administered a questionnaire to patients before their endoscopy. It was administered by physicians to 103 outpatients greater than 45 years of age with bright red blood per rectum (not a positive FOB). Excluded were those needing transfusion or hospital admission. This was done in the San Francisco General Hospital and Veterans Hospital in 1995. Their goal was to determine if specific clinical symptoms associated with rectal bleeding could predict colon cancer.

Using Chi squared and Student's t test, they found that blood mixed with the stools, several episodes of hematochezia pre month, and a shorter duration of bleeding prior to investigation were significantly associated with "substantial lesions" with p values less than 0.05. Unfortunately, Odds ratios were not quoted. The other 24 questions were not predictive of the 36 (35%) "substantial lesions" found, four of which were cancers.

Like the previous study, this small study may not have had the power to detect differences.

Neugut (1993) assessed the clinical yield of colonoscopy in patients who presented with rectal bleeding versus persistent abdominal pain or change in bowel habits in the absence of bleeding. They questioned (methods not clear) 1172 consecutive colonoscopy patients age 35–84, 861 with rectal bleeding, 113 with pain, 154 with change in bowel habits, 44 with both pain and change. There was a

relatively high colorectal cancer rate (7.8%), and a normal polyp rate of 23.5%.

Only univariate analysis was used in this study, and the exact method of analysis was not specified. They found that non-bleeding symptoms predicted colorectal cancer *as well* as did rectal bleeding in males, but rectal bleeding was a significantly better predictor of colon cancer in women than were non-rectal bleeding symptoms. Their statistical analysis did not attempt to analyze the numerical association between diagnosis and symptoms e.g. compute odds ratios. They found 91 cancers, with a prevalence rate of 9.1% in overt rectal bleeders, 7.2% in occult rectal bleeders, 4.4%, 5.8%, and 6.8% in patients with abdominal pain, change in bowel habits and both (pain and change) respectively.

In 1989, it may have been more common for patients to have a barium enema initially (as implied in the discussion). The cancer rate may have been artificially high in this study as it included those patients who had had a positive barium enema. This study also is limited by access, i.e. in the US private health care system; many people do not have access to colonoscopies.

Steine (1994) looked at 2416 consecutive primary health care referred patients in a radiologic outpatient clinic in Oslo, Norway who were to have an Air Contrast Barium Enema. One thousand eight hundred and fifty two (1852) patients gave consent immediately before the BE and filled out their questionnaire. They wanted to determine the predictors of polyps or cancer.

They found 55 cancers (2.9%), with a 10% polyp rate. Using Chi squared

they found that age, rectal bleeding, loss of weight and male sex were positive predictors of cancer, while abdominal pain, fatigue and nausea were negative predictors of colon cancer (No odds ratios quoted). With multiple logistic regression, this study found age 40-79 (OR = 8.6 – 27.8, see Table 10: Relative Risks (RR) or Odds ratios (OR) based on age, of developing or being diagnosed with colorectal cancer), male gender (OR=2.2, p=0.01), rectal bleeding (OR=2.7, p<0.01) and loss of weight (OR=2.6, p=0.01) being associated with colorectal cancer. They also found that the length of patients' symptoms was *not associated* with cancer.

This study was by far the closest in design to the current study. They used barium enemas as their "gold standard", which has been shown to miss some cancers and smaller lesions, as noted by the authors and in Neugut (1989). In the 190 patients who subsequently had a colonoscopy, no cancers were found.

(iv) Past Medical/Surgical History

In a small (112 cancer patients and 108 controls) hospital based Italian case-control study, Femandez (1997) found that diabetes (OR=4.6, CI 1.2-17) and cholelithiasis (OR =5.2, CI 1.1-24.2) were associated with colonic cancer. Note though, that this study had 75-part questionnaire. This they claimed was in keeping with previous studies without referencing them. Sandler (1997) claims that a history of a previous cholycystecomy is associated with a RR of 1.1-2. In addition, a personal history of breast, uterine and ovarian cancer have been linked to colon cancer (Brazer, S; 1991), especially if the pelvis has been irradiated (RR 2.1-4)

(Sandler, 1997). A proven personal history of colorectal neoplasm is thought to increase the risk of a subsequent neoplasm by four (This was likely an odds ratio) (Kewenter, J, 1989).

Ulcerative colitis is associated with an absolute risk of 30% after 35 years, and a RR>4.0 (Sandler, 1997). The risk of colon cancer starts 8-10 years after the diagnosis of Ulcerative colitis, and increases 1%/year in the 3rd and 4th decades (Bansal, 1996). Crohn's disease also carries an increased risk of colorectal cancer, (Bernstein, 2001). Persons with previous colonic polyps have a threefold increase in cancer risk (Sandler, 1997). Sclerosing cholangitis has also been associated with colorectal carcinoma in patients with Inflammatory Bowel Disease (Bansal, 1996). Certain rare familial conditions also are associated with colon cancer, especially early colon cancer. These include Peutz-Jeghers syndrome and familial polyposis.

(v) Medications

Studies have found a protective effect for use of ASA, with a R.R. or O.R. of about .75 (Dubois, 1996, which was a review article). Certain medications, such as Warfarin, may increase the likelihood of rectal bleeding, which may then increase the likelihood of investigation. (ASA may work in the same way)

(vi) Family History

The relative risk for a first-degree family member with colorectal cancer ranges from 1.7 to 2.1. (Burt, 1996;Fuchs, 1994;Winawer, 1996; Ahsan, 1998; Pariente, A. Fernandez 1997). The relative risk is increased with family members

who were diagnosed at and before age 50 (RR = 3.5 +, depending on age of relative), and with two or more affected relatives (RR = 2.8), (Fuchs, C; 1994) or with multiple generations of family members diagnosed with colorectal cancer or polyps (OR 2.16) (Gaglia, P; 1995). There is a tendency for early age of onset and right-sided carcinomas in patients with a positive family history (Gaglia, P; 1995). At least one study found no increased risk over base line with one first-degree family member, except when that family member was diagnosed at less then 60 (Rex D; 1995). Note also that some studies have found that the excess risk of colorectal cancer due to family history does not change substantially when other factors are taken into account (Fernandez, E; 1997, which references three other studies).

Some authors feel that colon cancer and polyps are inherited by a partially penetrant susceptibility inheritance (Fuchs, C; 1994). This would determine susceptible persons, while other factors (e.g. diet) would cause expression of the cancer genes (Fernandez, E; 1997). There is also evidence that first-degree relatives of patients with newly diagnosed colonic adenomas (polyps) are at an increased risk of colon cancer (Ahsan, 1998). This would support the adenoma/cancer connection.

(vii) Social/Environmental History

La Vecchia (1996) found that intake of diets rich in animal fats (OR=1.1, CI=1-1.3) or red meat (OR=1.6, CI 1.4-1.9), and diets low in Beta- Carotene (OR = 2.2, CI 1.8-2.7) or ascorbic acid (OR=1.3, CI 1.8-2.7) were associated with colorectal cancer. This study was a large (1326 cases, 2024 controls) Italian

hospital based case-control study with a 75-question survey administrated by a study employee. They used unconditional multiple logistic regression to produce the above adjusted ORs. The difficulty with this type of study, beside the recall bias noted above for case-control studies, is that current diet of a patient with colon cancer may not be as relevant as the patient's diet 10 years ago when the cancer may have first started. This makes any association between diet and cancer difficult to substantiate. This makes the investigation of nutrient intake and colon cancer difficult to study. Finally, even if an association can be proven between intake and cancer, it must still be proven that changing the diet will prevent future cancers.

Two case-control studies have associated smoking more than 40 pack years in men to colorectal cancer: (Lee, 1993) (OR = 2.2 (1.2-3.8) with a significant linear trend) and (Olsen, 1993) OR = 2.7.

(viii) Examination

A mass felt on rectal examination or on examination of the abdomen is highly suggestive of cancer in general, but studies investigating the actual likelihood are sparse. This is likely because the vast majority of non-emergent cancers are found in patients with a normal exam. (Fijten, G; 1995) In their study, reviewed above, Fitjen found that the abdominal exam did not contribute to the probability of finding cancer. A clear mass found on abdominal or rectal exam is not a diagnostic dilemma, of course.

(ix) Initial Laboratory

A positive fecal occult blood (FOB) smear has been associated with colon cancer (Kewenter, J; 1989) (with a RR as much 19), as has iron deficiency anaemia (Guthrie J; 1994) (Lee J; 1998). Fitjen (1995) (see review above) found that a "low haemoglobin" (gender specific) produced an OR of 8.8 ($p<0.01$), an ESR>30 had an OR of 14, and that a WBC>10^9 /l was associated with an OR of 26.3 ($p<0.01$). In fact, except for one small study of selected patients, the FOB has always proved superior to a symptom related questionnaire in predictive value for colonic tumours (Niv Y, 1992). FOB is said to find 1 –2 cancers per 1000 tested (Silman, 1983). A specific review of FOB screening was not done at this time, mostly because it has been done previously.

The negative predictive value of fecal occult blood may be more important than the positive predictive value in asymptomatic patients, and in symptomatic patients with normal haemoglobin and no hematochezia. In one study, the prevalence of adenomas and cancer in a symptomatic population was equal to that of an asymptomatic screened population when anaemia and hematochezia were taken into account (Rex D; 1995). Repeated annual screening with FOBT of the same population has been reported to yield a lower rate of positive test results with higher predictive values (Niv Y; 1992).

3) Conclusion

Making the diagnosis of colorectal cancer is difficult based on clinical grounds alone. This is due to patient factors, the cancer itself, inefficiencies in the health care system and difficulties with the gold standard tests involved. As

far as risk factors are concerned, previous studies have found that increasing age, male gender, living in an affluent country, some symptoms (especially rectal bleeding), certain medical conditions, diet and examination have been associated with colorectal cancer. Many of the studies did not control for other risk factor categories. This study will attempt to combine questions from patients' demographics, past history, medications, family history, and of course, symptoms into one analysis to determine independence of the variables, and try to include a substantial number of patients for increased statistical power.

IX) Objectives and Methodology

A) Study Goal

To investigate the association between clinical history and colorectal cancer.

B) Study Objectives

1. To describe the patient population undergoing colonoscopies in participating colonoscopy suites in Winnipeg, MB
2. To determine the self reported risk factors associated with a diagnosis of colorectal carcinoma in a group of patients undergoing colonoscopies in Winnipeg MB.
3. To develop a statistical model that calculates the probability of Colorectal Carcinoma in a referred patient.

C) Methodology

1) Design Rationale and Overview

(a) General Overview of the operations of the study.

The study took place in three colonoscopy suites in Winnipeg MB. The nursing staff asked patients who were about to undergo a colonoscopy if they

wished to participate in the study. Once verbal (and then written) consent was obtained, the patients completed the written questionnaire themselves. The questionnaire results were then compared to the final diagnosis of the colonoscopy.

(b) Subject Selection and Case Definition

(i) Participant Selection

Three Winnipeg colonoscopy suites agreed to participate in the study. They were in the Health Sciences Centre, St. Boniface General Hospital, and Victoria General Hospital. The subjects consisted of consecutive non-emergent patients undergoing colonoscopies in the participating hospital based colonoscopy suites in Winnipeg, Manitoba. Patients either would have been referred to the colonoscopist by a primary care physician, typically their family physician, or be having a follow-up colonoscopy.

Excluded: Patients were excluded if (1) they could not complete the survey independently, e.g. those who could not read or write English or those who were too ill; (2) they did not sign the consent form; (3) the patient did not have enough time to start the survey.

(ii) Predictor Variables (Risk Factor) Determination

The survey questions comprised the predictor variables. The survey was mostly a series of closed- ended questions. There were also a few open-ended questions in the patient's survey. (See Appendix E: Consent Form, Appendix G: The rational

behind the survey questions. and Appendix F: The Questionnaire itself)

The survey took approximately fifteen minutes for the patient to complete. The survey questions were based on a Medline search from 1990 - 1999. The search was with Silver Platter in the University of Manitoba Library. The general theme of the search strings was «(colonoscopy or barium enema) and ((colorectal carcinoma) or polyp) and (symptoms or (risk factors))>>. The references from the articles selected above were reviewed for further articles of interest. There were no specific selection criteria used to either include or exclude a given article. The questions in the survey were based on those symptoms or risk factors that have been statistically correlated to colon cancer or colonic polyps in these studies. The questions' validity and reliability were tested only in the piloting stage. There was not a formal protocol to test the questions otherwise.

Several grade eight students reviewed the survey and the consent form to ensure that the wording was at a grade eight level. The survey was piloted in The Health Sciences Centre with 31 surveys.

(iii) Outcome Variable (Diagnosis) Determination and Case Definition

A case of colorectal cancer was defined by the patient's ICD-9 code as determined by the hospital's health records department. The ICD-9 code is based on the information contained in the patient's chart, including the final pathological diagnosis. The request for these codes occurred at least three months after the last

colonoscopy survey was done in the given facility. This allowed time for all pathology and other reports to be completed and returned to the chart. ICD-9 codes were only retrieved from those patients who signed the consent form. The ICD-9 codes used were 153, 154 and 230.3. These codes are for Colon neoplasm, Rectal Neoplasm and Carcinoma-in-situ respectively. The inclusion of the carcinoma-in-situ coding is in keeping with previous studies, notably Neugut (1993). The Health Record Departments were also asked for the total number of colonoscopies done during the study period, and the average age and gender breakdown. With this, comparison was made between those who completed the study and those who potentially could have. In the case of more than one diagnosis, the most severe was used in the analysis.

2) Data Collection and Management

(a) Distribution of the survey

The author distributed the consent form, explanatory letter, and survey to the different colonoscopy suites at the start of the project. The survey was distributed in the hospital, along with other documentation such as consent forms for the procedure and pre-op questionnaires. The suite's staff distributed the survey. It was completed while the patient was waiting for the colonoscopy. In some cases, the survey was completed partially after the colonoscopy, but before the patient left the hospital. The colonoscopy suite nursing staff dealt with the patients' questions about the survey and they witnessed the co-signature on the consent.

The Study was conducted over the following dates:

The Health Science Centre: Nov. 22, 2000 – March 30, 2001

The Victoria Hospital: March 27, 2001 – June 30, 2001

The St. Boniface Hospital: May 5, 2001 – July 26, 2001

(b) Ethics and Confidentiality

The Research Ethics Board at the University of Manitoba and all the institutions' internal projects review committees had accepted the protocol.

All potential colonoscopists gave verbal agreement to their and their patient's participation, by telephone or e-mail before the study. The nursing staffs were given an in-service of the study, as well as guidelines to potential questions and an introductory statement regarding the survey

A paid receptionist primarily entered the data. The primary author removed the consent letter so that no identifying data were available to her. The data were stored on the primary author's laptop, in the program NCSS, which required a password to access, and was generally not accessible via the Internet.

3) Data processing and analysis

(a) Descriptive analysis of patients undergoing colonoscopy

The number of colon cancers and the average age and gender of the

participants was tabulated. In addition, a comparison was made between those who did and did not participate, as well as other groupings as noted.

(b) Analysis of Survey Questions

The questions of the survey were grouped for the univariate logistic regression analysis. The groupings were according to the content of the question. For example, non-specific symptoms (weight loss, nausea, loss of appetite) were grouped together. The grouping of the questions is outlined in Appendix H: Analysis of the self-reported risk factors. The analysis determined the odds ratios, and their confidence intervals, associated with each question grouping. Continuous variables (age, BMI, year of birth) were maintained as such. The rest were converted to dichotomous variables. A negative answer to the question was considered the baseline.

Thus, the data were grouped into 21 variables for the initial analysis. Questions 4 and 5, the two branching questions, were further split into six and eight individual variables respectively (underlined above). The variable "GenSx" was divided into its components after the univariate analysis was performed. Thus, there were 39 variables involved in the initial analysis. These variables are defined in Table 11, as they are used in the rest of this paper.

Table 11: Definition of variables

Variable	Description
GenSx	General non-specific symptoms (weight loss, nausea, distension, appetite)

Variable	Description
lowhgSx	Anaemia symptoms (tired, short of breath, "low on iron"
bleeding	Evidence of blood in stools (either grossly or occult)
Pain	Abdominal pain
Change	Constipation or diarrhoea (comparison of now to six months ago)
difference	Difference in bowel movements (straining more, thinner stools, soiled etc.)
Fhx	Family history of colon cancer
Fhxother	Family history of other cancer
Meds	ASA or Warfarin use
Chole	Previous gallbladder removal
IBD	History of Inflammatory Bowel Disease
Polyps	History of colonic polyps
colonoscopy	History of previous colonoscopies
Visits	Visited a doctor more than 4 times in the last year
Health	Self-described below average health
Bmi	A measure of height to weight

Variable	Description
exercise	Regular physical activity
smoking	Amount smoked, in pack-years
Ethnic	European origin vs. non-European
Age	In years
Gender	Gender
Question 4	Breakdown of "Pain" above
pain6mths	Pain starting in the last six months
Freq	Pain felt weekly or more
Night	Pain at night
withBM	Pain with bowel movements
Worse	Pain getting worse in last 6 months
Eating	Pain with eating
Question 5	Breakdown of "bleeding" above
Mixed	Blood mixed with stools

Variable	Description
Cover	Blood covering stools
separate	Blood separate from stools
Dark	Blood dark in colour
Red	Blood red in colour
increased	Amount of blood increasing in last 6 months
12mths	Bleeding in last year
seenweekly	Blood seen at least weekly
GenSx	Breakdown of "Gen Sx" above
lost weight	Lost more than 10 lbs in last 6 months
Appetite	Lost appetite in the last 6 months
Nausea	Increased nausea in the last 6 months
Distended	Increased bloating in the last 6 months

(c) Missing Data

Missing data from continuous variables were not included in the analysis by

the NCSS program. For most of the categorical independent variables, a "No response" answer was treated as a negative response. The exception was gender, where questionnaires without this information were not included in the analysis. This was true for both the univariate and multivariate questions.

(d) Analysis over 40

Most studies dealing with colon cancer exclude subjects under the age of 40. This is reasonable given that only people over the age of 40 are truly at risk for colorectal cancer (as is seen in the Vital Statistics section above). The multivariate analysis below takes into account age, and therefore sub-dividing the study population is not needed. Unfortunately, the univariate analysis does not take into account age. Analysis was also performed including only patients who are over the age of 40.

(e) The final Statistical Model

A forward selection multivariate logistic regression analysis was then performed using the variables delineated above (in the univariate analysis) using NCSS. The first run of this model is included the appendixes. Each variable was analyzed on an individual basis, and the strength of the association noted. The strongest association was included in the model, as determined by the lowest p-value. The remaining variables were then re-enter, along with the first variable, in a univariate analysis. Again, the variable with the strongest association was kept in the model. This process was repeated until there were no further variables that

could be added to the model which would have made the model statistically better.

The dependent variable was the presence or absence of colorectal cancer as determined by the ICD-9 codes. Again, for these variables, continuous variables (age, BMI, year of birth) were maintained as such. The rest were converted to dichotomous variables. A negative answer to the question was considered the baseline for the most part.

Interactions were investigated for the variables that were found to be significant in the multiple regression analysis.

All data were entered into an Excel program, and then transferred into NCSS Version 6.0.22 for processing.

X) Results

A) Survey and Colonoscopy Patient Characteristics (Descriptive Analysis)

1) Demographics of participants undergoing colonoscopies

Table 12 shows the descriptive statistics of those who completed the study, broken down by hospital.

Table 12 : Patients included in the study

	Health Sciences	Victoria	St. Boniface	Total
Ave. age (years)	53	58	57	56
% Males	46.3%	41.2%	48.1%	43.45%
# Cancers	3	6	3	12
Total #patients	162	401	79	642

Table 13 shows the number of patients per hospital, divided according to if they are over or under the age of 40.

Table 13: The number of patients over forty per hospital

	Health Sciences	Victoria	St. Boniface	Total
Missing age	15	16	1	32

Under 40	23	38	13	74
Over 40	124	348	64	536
Total	162	402	78	642

2) Comparison between those who did and did not do the survey

Table 14 shows the total number of patients who had colonoscopies during the study period, and were thus possible candidates for inclusion in the study. This table also shows the percentage of patients' surveys that were included in the study compared to the total number of patients who had colonoscopies.

Table 14: Total number of patients who had colonoscopies during the study period and Percentage completion

	Health Sciences	Victoria	St. Boniface	Total
%Male (of total)	46.75%	40.20%	44.35%	42.4%
Ave Age (of total)	55	57	57	56
#Patients (total)	569	605	330	1504
#Finished*	162	402	78	642
%Finished	28.47%	66.28%	23.94%	42.7%

(* #Finished = number of questionnaires that there were ICD-9 codes for.)

As can be seen, comparing Table 12 and Table 14, there does not appear to be a large difference between the gender and the age of those who completed the

survey, and those who did not. More specifically, the calculated Chi square value for the gender comparison between those who finished the survey and those who did not was 0.51 [Chi squared (@ p=0.05, df =1)) = 3.84). Similar calculations could not be done for age, as more information would be needed (e.g. the standard deviation of the ages of the excluded group for a t-test)

Table 15 shows where the potential patients were "dropped out" of the study.

Table 15: Excluded patients

	HSC	Victoria	St. Boniface	Total
Total number of potential patients	569	605	330	1504
Refused/ not able to complete	398	196	251	862
No ICD-9 Coding	9	7	1	17
Included	162	402	78	642

3) Number of Colon Cancers

There were 12 patients who were coded with an ICD-9 code of 153, 154 or 230.3 which are the ICD-9 codes for colorectal cancer and carcinoma-in-situ. There was also one patient with the coding for a secondary malignancy, which was a lymphoma. The carcinoma-in-situ was included in the analysis, while the lymphoma was not. Therefore, there were 12 cancers. This is a gross rate of 1.9%. 5.92% of the patients surveyed said that they had had a diagnosis of colon cancer previously.

4) Stated reason for the colonoscopy

Question 1 was a general introductory question. It was "What was the main problem that initially took you to your doctor, and that lead to the test that you will be having today". (See XVII)Appendix F: The Questionnaire itself for the actual questions)

Table 16: Question 1 shows the number of positive answers to question 1. Many patients gave more than one answer, so the numbers do not add up.

Table 16: Question 1 : Stated reason for the colonoscopy

	HSC	VIC	STB	Total
Q1i "I had problems that needed investigation"	97	217	36	350
Q1ii "I had a previous history of bowel cancer"	43	81	25	149
Q1iii "Someone in my family had bowel cancer"	25	110	18	153
Q1 iv "I am uncertain why I am having the test"	10	5	2	17
Total number of patients	162	402	78	642

5) Completion of the Survey and missing data

Question 27 dealt with the number of patients who completed the survey before the colonoscopy, partially before and partially after or totally after the colonoscopy. Missing answers were taken to mean that the patient started the survey, but did not have time to finish it. (Visual inspection of the data would suggest that this is accurate.) Table 17: Question 27 delineates the result of this question:

Table 17: Question 27 : Completion of the Survey

Q27	HSC	STB	VIC	Total
Totally before	97	74	339	510
Before & after	21	1	17	39
Totally after	26	2	28	56
Uncertain	4	0	6	10
No-response or missing	14	1	12	27
Total	162	78	402	642

Therefore, of the 642 questionnaires that have an ICD-9 code associated with it, 95.8% (615/642) of patients who started the survey completed it.

The rest of the data that were missing can be seen in Appendix J.

6) Other Diagnosises

Table 18 shows the other diagnosis of the colonoscopies in the study. (Groupings of ICD-9 codes made by the primary author).

Table 18: Frequency Distribution of groupings of diagnosises

Groups	HSC	STB	VIC	Total
Cancer	4	2	7	13
Diverticula	14	3	21	38
Haemorrhoids	9	3	32	44

Inflammatory	26	12	32	70
Normal	52	27	234	313
Other	21	2	2	25
Polyps	36	29	74	139
Total	162	78	402	642

Note that there were 13 cancers in the above table. One of these was a lymphoma, and was not included in the regression analysis as a "colorectal cancer", and one was a carcinoma-in-situ, which was included in the analysis.

B) Self-reported Characteristics (Univariate Analysis)

1) Description of continuous variables

The bmi, smoking, and age variables are continuous variables, and Table 19 shows their characteristics. Age is measured in years, bmi = kg/m^2; Smoking = pack*years, and the data includes the never-smokers.

Table 19: Characteristics of continuous variables

	Age	Bmi	Smoking
Mean	56.5	27.06	12.6
Std. Deviation	14.11	5.13	17.09

2) Odds ratios associated with the variables

Using the groupings noted in the section labelled "Data processing and analysis",

univariate logistic regression analysis was performed. (See Appendix H: Analysis of the self-reported risk factors for the calculation of the groupings, and Table 34: Groupings of questions) for a more complete description of the groupings.) This, and the number of patients who answered a given dichotomous variable positively for all three suites, is shown in Table 20). Note that the branched parts of questions 4 and 5 were only analyzed among those patients who had answered question 4 or 5 positively in the first place.

Table 20: Odds ratios and confidence intervals of the univariate analysis

Variable	OR	95%CI (high)	95%CI (low)	p	Description	%+
Gen Sx	`4.44	20.73	0.95	0.06	General non-specific symptoms	
lowhgSx	1.86	6.42	0.54	0.33	Anaemia symptoms	48.7
bleeding	**5.77**	**26.90**	**1.24**	**0.03**	**Evidence of blood in stools**	**44.5**
Pain	**3.54**	**13.28**	**0.949**	**0.06**	**Abdominal pain**	**46.9**
change	2.06	9.76	0.44	0.36	Constipation or diarrhoea	09.9
difference	1.74	8.15	0.37	0.48	Difference in bowel movements	72.2
Fhx	0.54	2.54	0.12	0.44	Family history of colon cancer	28.8
fhxother	1.02	3.51	0.29	0.98	Family history of other cancer	36.0
Meds	1.00	4.68	0.21	1.00	ASA or Warfarin use	18.2
Chole	2.96	10.27	0.85	0.09	Previous gallbladder removal	16.5
IBD	0.00	hi	0.00	0.98	History of IBD	08.0

polyps	1.16	4.44	0.30	0.83	History of colonic polyps	24.4
colonoscopy	0.66	3.07	0.14	0.59	History of previous colonoscopies	25.2
Visits	1.09	3.60	0.33	0.89	Visited a doctor > 4 + in last year	52.5
Health	1.43	6.74	0.30	0.65	Self-described below average health	13.5
Bmi	0.94	1.07	0.83	0.37	A measure of height to weight	n/a
exercise	0.49	1.87	0.13	0.30	Regular activity	42.9
smoking	0.99	1.04	0.94	0.58	Amount smoked, in pack*years	n/a
Ethnic	.816	1.51	0.66	0.74	European origin vs. non-European	70
Age	**1.08**	**1.14**	**1.02**	**<0.01**	**In years**	**n/a**
gender	0.42	1.36	0.13	0.15	Males	42.6
Question 4					About abdominal pain/discomfort (N=309)	
pain12mth	5.984	47.828	0.0916	0.0916	Pain starting in the last six months	73.1
freq	0.804	2.905	0.7390	0.7390	Pain felt >= weekly	46.0
night	0.000	++	0.9699	0.9699	Pain at night	29.8
withBM	0.965	4.655	0.9644	0.9644	Pain with bowel movements	19.1
worse	0.720	2.841	0.6395	0.6395	Pain getting worse in last 6 months	37.2
eating	0.523	2.062	0.3547	0.3547	Pain with eating	45.0
Question 5					About blood in stool (N=293)	
mixed	1.034	4.729	0.226	0.9654	Blood mixed with stools	33.1

cover	0	+++	0	0.9727	Blood covering stools	25.6
seperate	0.486	2.559	0.092	0.3948	Blood separate from stools	35.2
dark	0.689	5.87	0.081	0.7337	Blood dark in colour	15.7
red	0.843	4.47	0.159	0.8411	Blood red in colour	59.7
increased	2.043	10.93	0.382	0.4037	Amount of blood increasing in last 6 months	13.7
12mths	++	++	106.9	0.9711	Bleeding in last year	50.5
seenweekly	0.310	2.622	0.037	0.2824	Blood seen at least weekly	27.0
Gen Sx						
lost weight	**4.17**	**14.11**	**1.23**	**0.02**	**Lost more than 10 lbs in last 6 months**	**11.1**
Appetite	1.82	8.43	0.39	0.45	Lost appetite in the last 6 months	10.0
Nausea	0.73	3.35	0.16	0.69	Increased nausea in the last 6 months	21
Distended	0.84	2.79	0.25	0.77	Increased bloating in the last 6 months	37.3

CI= 95% Confidence Intervals, * = significant Odds ratios at p = 0.05, %+ = % of questionnaires with positive answer (N=642 patients). For questions 4 and 5, the numbers quoted are a percentage of the patients who answered the original question positively.

3) Age

The variable age needs further discussion. As noted above, the odds ratio for this variable is 1.08/year. This was derived from the original univariate equation as

noted in Equation 1: Univariate age equation from logistic regression analysis:

Equation 1: Univariate age equation from logistic regression analysis:

$$OR\ (\text{delta age}) = \exp\left[(7.71 \times 10^{-2}) * (\text{delta age})\right]$$

This translates into the following Table 21: Odds Ratios by Age:

Table 21: Odds Ratios by Age

Age	35	45	55	65	75
OR	1	2.2	4.7	10.2	22.2

4) Analysis over the age of 40

Excluding those under the age of 40, the variables bolded above in Table 19: Characteristics of continuous variables change to those in Table 22: Variables stratified to those only over 40 years.

Table 22: Variables stratified to those only over 40 years.

Variable	OR	95% CI (hi)	95% CI (lo)	p
pain	3.57	13.52	0.94	0.06
age	1.08	1.14	1.02	0.01
bleeding	6.31	29.25	1.36	0.02
lost weight	3.3	12.69	0.85	0.08

No other factors were close to being statistically significant. These numbers, while not identical, are similar to those presented above for the entire data set.

A sub-analysis of the data was done on bleeders over the age of 40. This was done to mimic the previous studies' inclusion criteria. Again, the only significant variable was age. Notably, pain and weight loss were not found to be significant under these conditions.

5) Summary

As can be seen, age (OR = 1.08/year, p=0.004), bleeding (OR 5.77, p=0.0257), and weight loss (OR= 4.17, p=0.02) are the variables that achieved statistical significance at $p<0.05$ in the univariate analysis.

C) Development of the final statistical model (Multivariate Analysis)

1) Significant variables

A forward selection logistic regression analysis was then performed, as described above. The initial univariate analysis is outlined in the appendixes. The final logistic regression equation variables are shown in Table 23: Final Logistic Regression Variables.

Table 23: Final Logistic Regression Variables

Variable	Reg. Coeff.	Std. Error	Chi squared
bleeding	1.848814	0.7961857	5.39
pain	1.50357	0.7079942	4.51

age	8.36E-02	0.0253536	10.86
model		df=3	22.68

Table 24: Final Logistic Regression OR, CI and p values" rearranges the above data into ORs, CI's, and related p values.

Table 24: Final Logistic Regression OR, CI and p values

Variable	Odds Ratio	95%CI (hi)	95%CI (lo)	p
bleeding	6.352281	30.24521445	1.334144	0.020228
pain	4.497717	18.0156105	1.122885	0.033695
age	1.087143	1.142530782	1.034439	0.000982
model				0.000047

Thus, a person's risk of colorectal carcinoma increases exponentially by 1.087 (CI95%= 1.14,1.03; p=0.0001) for every year of age, and is multiplied by 6.35 (CI95%=30.25,1.33; p=0.02) if they have rectal bleeding (as compared to patient's that do not have rectal bleeding) and 4.5 (CI95%=18.12,1.12; p=0.03) if they have abdominal pain (as compared to patient's that do not have abdominal pain). These numbers are both statistically significant and clinically significant.

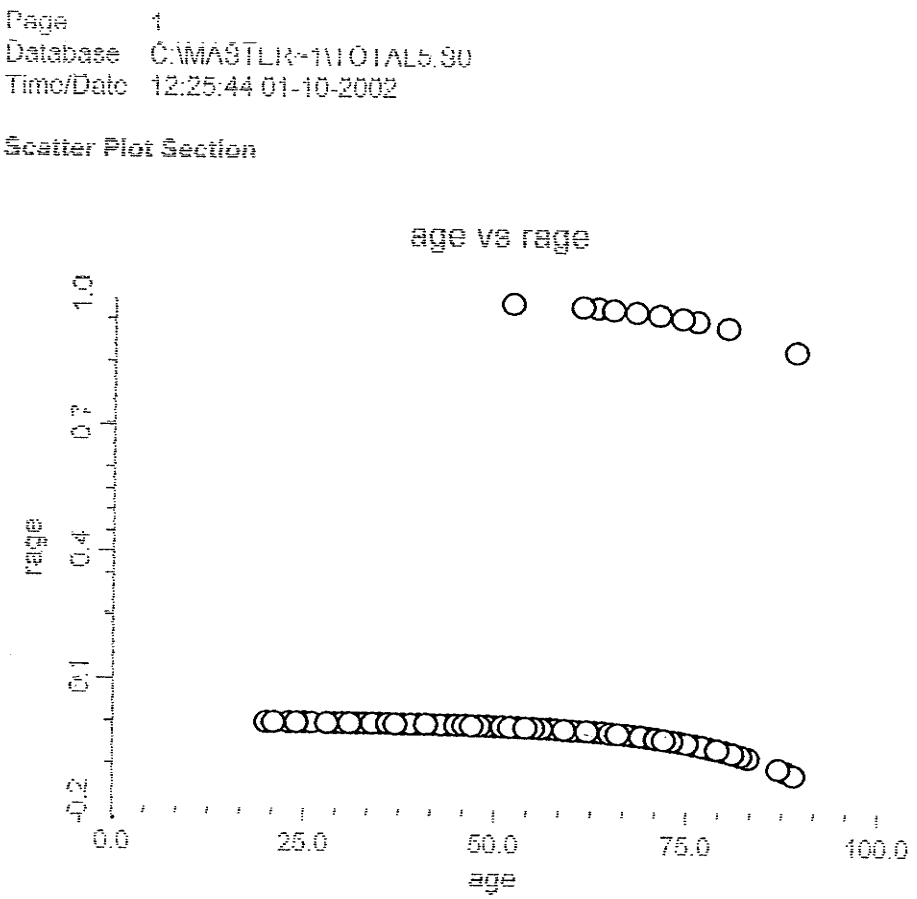
Note that removing all known cases of previous cancer from the model (5.9% of the patients surveyed) did not make a significant difference to the final logistic regression equation results.

2) Analysis of Residuals and Interactions

Residuals were plotted for age (the only continuous variable which showed significance). There appeared to be a possible change in the residuals as the patient aged, but when this was investigated with an age*age term, it was not found to be significant.

Interactions were also explored with wt. loss, age, bleeding, and pain. Adding the respective interactions of these variables to each other to the simpler models did not improve the models significantly.

Figure 6:Residual analysis of age



XI) Discussion

A) Survey and Colonoscopy Patient Characteristics

1) Age

Using the multiple logistic regression equation, we could complete Table with our data, as is shown in Table 26: Comparison of age odds ratio between different studies.

Table 26: Comparison of age odds ratio between different studies.

Age	30-39	40-49	50-59	60-69	70-79	Source
RR	1	2.9	8.3	28.9	45	Health Canada (1999)
OR	1	5.6	7.8	18.1	8.6	Steine (1993)
OR	-	-	1	10	-	Fitjen (1995)
OR	1	2.2	4.7	10.2	22.2	This paper

Thus, this study's odds ratios for age are similar to other sources in that the incidence/prevalence of colon cancer increases with age. Also, note that comparing

the RR to the OR is like comparing "apples" to "pears"[2]. They both express similar concepts, except the RR describes the increased risk of getting colon cancer in those age groups, while the OR describes the increased risk of having colon cancer in a prevalence study.

2) Gender

The Health Canada Statistics, as well as other studies mentioned in the previous studies section, suggest that there is an association between gender and colon cancer rate even though this study did not find an association. The power of this study may not have been great enough to see this association.

3) Cancer rate and missing data

The cancer rate of 1.9% was marginally lower than other tertiary care studies, which had rates of 2-3%. The other studies, though, excluded patients under the age of 40. When this is done to this study's data, the cancer rate was 2.2% (12/532). Although thought to be unlikely, cancers may have also been missed if the ICD-9 coding was incorrect. There were no missing ICD-9 codes (that is all included surveys had an ICD-9 code). Finally, some of the other studies exclude follow-up studies, which this study did not. All of these factors may have decreased our gross cancer rate.

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[2] # Note that "pears" is used, rather than the usual "oranges". "Pears" expresses the concept that the two concepts of OR and RR have many similarities, but that they are not exactly the same.

Forty tree percent of eligible patients completed the survey. This was felt to be a good capture rate, considering that the staff that helped with the gathering of the data were not paid extra for their work. In addition, some of the data (especially in St. Boniface hospital) were gathered during the summer months (holidays).

Ninety five percent of the patients answered question 27. As seen in Appendix J: Patient answers., several patients answered question 27 without answering some of the previous questions. Based on a review of the actual survey responses, it was felt that for the majority of cases, these respondents read the other questions but either did not feel that the questions were applicable to them or did not understand the questions. For this reason, it was decided to include all of the "No response" answers to most of the categorical questions with the negative answers. The alternative, which would be to ignore these "no response" answers, would have greatly biased the results, as many patients did not respond to some of the multiple "tick-off" answers. Missing values for gender and all of the continuous variables were not included in the analysis, as discussed in the section above on analysis.

B) Self-reported Characteristics: comparison to other studies

1) Symptoms

Rectal bleeding has been generally accepted as a risk factor for colon cancer. So much so, that many studies start with a cohort of patients with rectal bleeding. Four studies that were found looked at the association of rectal bleeding and cancer, though (Niv, 1989; Curless, 1994; Neugut, 1993; Steine, 1994). Niv, 1989 was a

mail-out questionnaire to the general public, Curless, 1994 was a case-control study with community controls while the latter two's methods were closest to this study's design. The average OR that were calculated from these studies was only 2.2. Note that an OR of 2.2 is in fact within the CI of this study.

Abdominal pain presents an interesting situation. Steine(1992), likely the best article reviewed in this paper, had shown a protective effect for pain and colorectal cancer. This paper found a correlation between CRC and abdominal pain. This discrepancy may be explained by referral patterns. Many patients who undergo colonoscopies have a different diagnosis. In this study's case, the 2X2 table is shown in Table 27: 2X2 table for cancer and pain

Table 27: 2X2 table for cancer and pain

		Cancer		
		Yes	No	
Pain	Yes	9	289	298
	No	3	341	344
		12	630	642

To repeat, the Odds Ratio associated with this is 3.54 and it is significant statistically. The 2X2 table for Steine (1992) is presented below.

Table 28: 2X2 Table for pain in Steine(1992)

		Cancer		

		Yes	No	
Pain	Yes	27	1269	1296
	No	28	508	536
		55	1777	1852

This produces an odds ratio of 0.6, which is statistically significant. There were more patients in this study with abdominal pain and CRC, and this would account for some of the differences between the two studies. Even so, the most striking thing comparing these two 2X2 tables is not how abdominal pain is related to CRC (the sensitivity), but more the difference in the patients who do not have CRC,(the specificity). In our study, there were more people who did not have pain than had pain. In Steine(1992), the reverse is true, changing the comparison data. That study may have had more people with Inflammatory Bowel Disease, for example, than this study did. Thus the comparison group is important in the analysis.

Another example of this can be seen in the findings of Curless (1994) where on OR of 13.4 was found for Pain and Colorectal Cancer. This study was a case-control study, using community members as controls. They were thus comparing recently diagnosed colon cancers (relatively sick people) with generally healthy people. The ORs in this type of study tend to be higher than those comparing "potentially sick people" to recently diagnosed patients, as in this study. The difference in methodologies is also the reason why it is difficult to combine many of the studies listed in Appendix G. A true meta-analysis may over come some of

these differences, and produce a higher external validity in the process.

Finally, the fact that abdominal pain was not significant in the univariate analysis but became significant in the multivariate analysis suggests that the association is not straight forward.

Beyond these two topics, though, we can compare this study's data with the previous studies reviewed in the Background above, and in Table 29:Comparison between this study and previous studies.

Table 29:Comparison between this study and previous studies for significant variables

Variable	OR (present study)	p	OR (other studies) *[3]	Description
Bleeding	5.77	0.03	2.20	Evidence of blood in stools within the last six months
Pain	3.54	0.06	0.70	Abdominal pain
lost weight	4.17	0.02	2.47	Lost more than 10 lbs in last 6 months

The univariate association between weight loss and colorectal cancer is supported by the other studies (Nørrelund, 1996, Curless, 1994, Steine, 1994, Fitjen, 1995, Mant, 1989 and see Appendix B). While this association can be understood, weight loss may be associated with a later, and less curable, disease state.

[3] Taken directly from Table 31 Previous Studies on Symptoms

One final comment on this study's 2X2 table (Table 8). As there were only 12 cancers, one of the cells of the table has an expected value of less than 5 patients, making the analysis potentially unstable. This was true of bleeding as well, where one cell had only 2 patients in it. Chi squared analysis should probably be replaced with Fisher's exact test.

2) Past Medical History, Medications and Social/Environmental

This study did not find a statistically significant association between colorectal cancer and these subjects in either the univariate or the multivariate analysis. This may reflect the lack of power of the study or a real lack of association between the variables.

The fact that this study did not find an association between a history of polyps and colorectal cancer is interesting. The reason for this may lie in the fact that any found polyps are removed, thus eliminating their potential to be come cancerous. Patients who have been found to have polyps are re-colonscoped regularly, thus reducing their cancer risk. Only patients who have not been investigated previously go on to have cancer. These latter patients will not have a "history" of polyps. Unfortunately, this lack of association may also be because patients do not know their own history, as has been suggested previously in this paper.

3) Family History

This study did not find an association between family history and colorectal cancer. This may be because the previous studies were, for the most part, case-

control studies. As mentioned above, these types of studies tend to find higher oddsratios for their variables than do prevalence studies like this as case-control studies compare potentially sick patients to healthy community persons. Although not delineated in the results section, there was no association in this study between patients who had a family history of colorectal cancer in a member of the family who was less than 65 at diagnosis (OR=2.8, p=0.22).

4) Examination and Laboratory

These characteristics were not investigated in this study, except for if a patient claimed that a laboratory test showed bleeding. These patients were combined with other rectal bleeders.

C) The final model: how well does it predict colorectal cancer risk?

The main advantage of the univariate variable analysis above is in its ability to produce a differential diagnosis. That is, given the data from this study, if a patient presents with weight loss, then colorectal cancer should be entertained in the differential. A patient who presents with other bowel symptoms, such as a change in bowel habits, does not have an increased risk of colon cancer (compared to a patient who did not have a change in bowel habits). In other words, a change in bowel habits is not associated with colon cancer. (So even if a colon cancer was discovered after a patient was referred to colonoscopy because of the symptom of "a change in bowel habits", their rate of diagnosis would have been the same even if

they had not had a change in bowel habits. The symptom was irrelevant, and a screening colonoscopy would pick up the same number of colorectal cancers in the "symptomatic" and the "non-symptomatic" groups.)

The multiple regression analysis helps clinicians to estimate the actual risk a patient may have of colorectal cancer. It weeds out the overlap between variables, so that an estimate of the independent ORs can be made. Our final multivariate model is noted in

Equation 2: Final statistical Model.

Equation 2: Final statistical Model

$$\text{Log odds} = -11.3167 + 0.0836*(\text{age}) + 1.85*(\text{bleeding status}) + 1.5*(\text{pain})$$

This produces ORs of 1.08 (per year, compounded) for age, 6.35 for bleeding status and 4.5 for abdominal pain.

The first two variables agree with most to all of the other studies reviewed in this paper in that the two most important factors when addressing colon cancer are age and bleeding status. A discussion of the factors affecting each of these variables in noted above. How well this will predict the risk of colon cancer for a given patient depends on how well the (referred) study population reflects the physicians' population, as well as the other issues of the study design discussed below.

D) Issues of study design

1) Advantages of the study

This study has several advantages over previous studies. As discussed in depth above, previous studies on risk factors for colorectal carcinoma have tended to investigate the relationship between the cancer and a single category of risk factor. When trying to get an over-all picture of colorectal cancer risk factors, it is impossible for clinicians to estimate the risk of colorectal cancer in their patients without assuming independence of the factors. This study combined several categories together in one questionnaire. Thus, the question of independence of the different factors can be evaluated. One large advantages of using multiple logistic regression analysis is its ability to control for confounding bias.

Distribution of the survey was done before the colonoscopy, with the intent to control recall bias. The patient could not know the results of his/her upcoming colonoscopy. Patients (and pathologists) were blinded to the study topic, but colonoscopists were not.

Colonoscopy suites were chosen as they provide a relatively high concentration of patients who potentially could have colon cancer. It is understood, though, that colonoscopies are done for many reasons. A survey in the general population (e.g. at the GP's office) would never have a high enough concentration of patient's with the target disorder to make it feasible. Mailing out the questionnaire would have been far more expensive, and likely would have had a

much poorer response rate. It would have been difficult also to ensure that patients who finished the survey actually had a colonoscopy in the end.

The study was relatively easy and inexpensive to implement. The colonoscopy staff generally did not spend a great deal of time on the study, as the patients themselves completed the questionnaire. This study depended heavily on the cooperation of the colonoscopy staffs and the patients (of which, I am very grateful!!!)

The completion rate of 42% was an indication of how well the survey was completed. Note that under ideal circumstances, the completion rate would be even higher. The study unfortunately went over the summer months in St. Boniface Hospital, and there were inefficiencies on the primary author's part in the Health Sciences as this was the first institution that was used.

The completion of the variables was very good in this study. All patients involved in the study had the "gold standard test" performed, thus their final diagnosis is known. Patients generally had enough time to complete the survey, as indicated by the 96% of patients who answered the last question, Question 27

2) Difficulties with the study

Many of the difficulties listed in "Difficulties with studying the risk factors" are applicable to this study. For example, there may have been problems with patients understanding the questions. This should have been limited as the questionnaire was reviewed by five Grade 8 students, who claimed to understand

the contents and wording. In addition, the accuracy of the answers, as discussed in Section I)A)1)(b):The patients and their symptoms, could not be assessed. This is especially true as this was a written survey, while most physicians ask questions orally.

There were a low number of actual cancers found in this study. This would have decreased the power of this study to determine more subtle associations (and, therefore, increase the number of false-negative outcomes, or beta (type II) errors). Perhaps "abdominal pain" would have become statistically significant if there were more patients, for example. One way to increase the number of cancers would be to distribute the survey to patients who have recently been diagnosed with colon cancer, and accept the recall bias associated with it.

This study does suffer from referral bias (a type of selection bias). All of these patients were referred to a colonoscopy suite. Nevertheless, most non-emergent cancers are diagnosed this way and therefore need to have a colonoscopy for the diagnosis. This is also the place where there is a high concentration of colorectal cancer patients who do not know that they have it. This is how we controlled for recall bias.

The other effect of this referral bias is to decrease the specificity of the analysis, as the number of similar diagnosises increases with referral bias, thus increasing the number of false positive compared to community controls.

Emergent patients were generally excluded from the study, as they would be

too sick to complete the questionnaire and they may not have been diagnosed in the colonoscopy suite (e.g. they may have been diagnosed in the OR). This was not thought to be important as the primary objective of this study was geared to general practioners' offices, and because patients presenting urgently tend not to be a diagnostic problem (i.e. they need further investigation). In addition, this study was not dealing with emergent cases, length-bias sampling was not as much of an issue. Unfortunately, out of necessity, people who could not read English at a grade 8 level were excluded also, thus creating a bias towards educated English-speaking patients. Note that the ages and genders was not significantly different between those who completed the questionnaire and those who did not.

In the analysis, multiple questions were included in the model. This increases the chance of false positive outcome (alpha (type I) errors). However, multiple questions are also asked in the physicians' offices, and they need to be addressed. In addition, in this study, the significance values are quite large, and therefore less likely to be by chance alone.

Misclassification bias could occur if the ICD-9 coding was incorrect, either due to a fault in the colonoscopy or due to a fault in the Health Records Departments. This was not examined. Also unknown are the number colonoscopies that were incomplete. Only one ICD-9 code was examined per questionnaire. There was no follow-up to this study, though, so future diagnosises would not be known. This did not allow for an estimation of concurrent diseases, e.g. the prevalence of haemorrhoids and colon cancer.

This study was not able to look at diet as a risk factor, as it was felt that the written questionnaire would not produce accurate answers on this subject.

Thus, like most studies, there are several problems with this study and the results need to be interpreted in light of that. The other studies that were reviewed also had their advantages and disadvantages.

E) Conclusion

1) Implications of current study

This results of this study suggest that physicians need to only inquire about age (OR = 1.08/yr, (95% CI = 1.03,1.13), rectal bleeding status (OR = 6.35, (95% CI = 1.33,30.25.0) and abdominal pain (OR = 4.35, (95% CI = 18.02,1.22) in order to determine a patient's risk of colorectal cancer, and that other factors will not help in determination of the risk. Physicians should inquire about weight loss (OR= 4.17, p=0.02) as well , when screening for colorectal cancer. Other symptoms were not associated with colorectal cancer.

2) Future research

Another similar study would be helpful to establish external validity. A larger study may include more cancers within the analysis, thus improve the sensitivity for detecting associations among the other variables. Similarly, a meta-analysis of the current known studies may produce similar results. It is unlikely that any further studies would disagree with the possibility of an association between colorectal cancer and age

or rectal bleeding, but the absolute value of the odds ratios may change depending on the sampling techniques.

The ideal study would start with unscreened primary care patients, and proceed to colonoscopy, but this study would be technically very difficult.

XII) Appendix A: Anatomic, Pathologic and Clinical Aspects of Colorectal Cancer

(a) Anatomy and Physiology of the Colon

The human digestive tract (the Gastrointestinal Tract) is a tubular structure that is approximately 30 to 40 cm long at birth and reaches 1.5 m in length in the adult. After the food has been digested in the mouth, stomach and small intestine, the colon's function is to solidify the stool before it is passed. The rectum's function is to store the stool until it is passed. The colon is also known as the large intestine. The walls of the tube are composed of several layers, see Figure 6:The Digestive Tract and Figure 7:Cross section of the bowel wall)

Figure 7:The Digestive Tract

(Source: Wheater (1987))

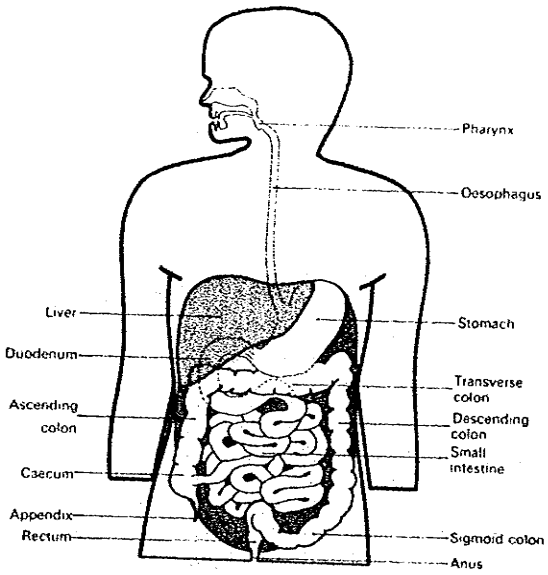
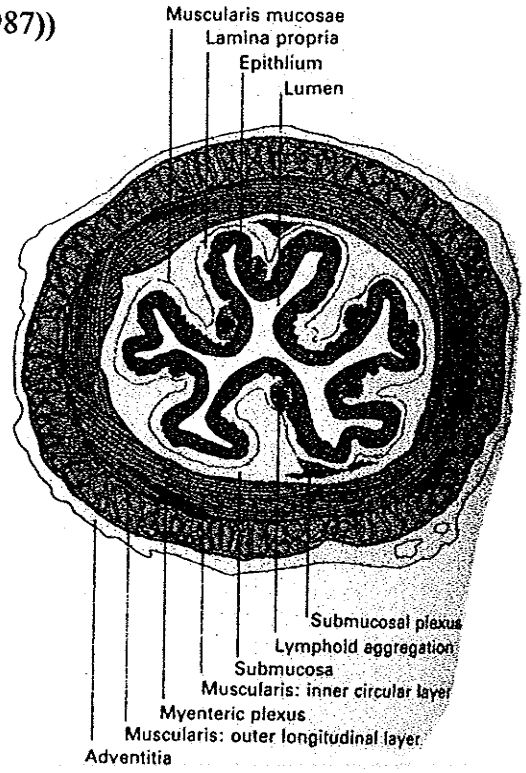


Figure 8:Cross section of the bowel wall

(Source: Wheater (1987))



(b) Polyps and the Natural History of Colorectal Cancer

A "polyp" is any piece of tissue that grows from the colon wall and protrudes into the digestive tract. A polyp can be dome shaped (sessile), or have a stem and look like a mushroom (pedunculated). Such lesions are classified histologically as either neoplastic (the adenomas and carcinomas) or non-neoplastic. The adenomatous polyps can further be divided histologically (on the basis of its predominant glandular pattern) into tubular adenomas (the most common), villous adenomas, or a combination of the two, labelled tubulovillous. The dysplasia of the adenoma can be divided into mild, moderate, and severe. They are also classified according to their site of origin, i.e. from the right or left side of the bowel and their size (Feldman, 1998).

Polyps are felt to be precursors to colorectal cancer (Johnson D; 1990) (Feldman, 1998). The risk of malignant transformation is positively correlated to an increasing size, increasing villous histology and higher degrees of dysplasia. These factors are all interrelated and tend to increase together within the polyp. Based on mathematical models, it has been proposed that it takes about 2-3 years for a polyp to grow to 1cm, and then 7-8 years for a polyp to further grow into a cancer (Johnson D; 1990).

(c) Investigations for Colorectal Cancer and Polyps

Polyps and cancers are found by one of two tests, barium enema, or colonoscopy. In Canada, both of these studies require a physician referral, usually by their family physician. Both of these studies also require a "cleaning out" phase before the study, which tends to be unpleasant for the patient.

A barium enema involves multiple X-Rays being taken while an opaque dye being introduced into the rectum. By tilting the patient on a bed made specifically for this purpose, the dye flows with gravity into the rest of the colon. Sometimes air is then introduced into the colon, thus producing an "air contrast Barium Enema", which allows for better visualization of the colon. Barium enemas are older, less expensive, and generally easier for family physicians to order than colonoscopies, but biopsies cannot be obtained with a Barium Enema.

Colonoscopy involves introducing a 120 cm tube with a video camera into the rectum and colon, for direct visualization of the colonic interior. Other shorter "scopes" also exist, which are easier to perform but which cannot go as far in the colon. They are called flexible sigmoidoscopy, rigid sigmoidoscopy, and proctoscopy. Biopsies can be taken with all of the "scopes". Colonoscopy is felt to be the Gold Standard test, i.e. the test that all other tests measure up to for investigating the colon. Colonoscopy is costly and has a small but important risk for morbidity (Gaglia P; 1995)

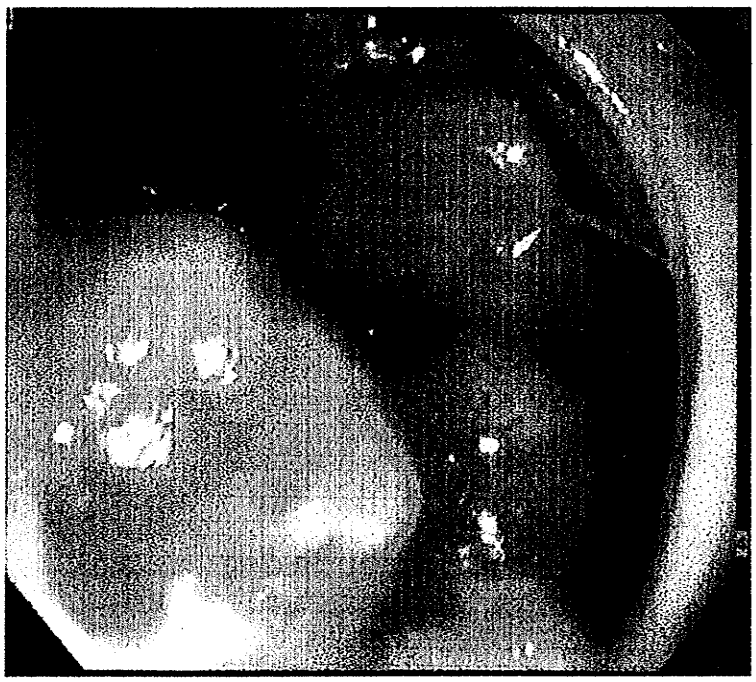
(d) Classification of Colorectal Cancer

Until recently, the Dukes pathological classification was used widely for the classification of the colorectal cancer. It was based on the depth of the primary invasion, and lymphatic spread. (Feldman, 1998)

Recently, though, the TNM system has been used, not only for colorectal carcinoma, but also for any tumour. The American Joint Committee has adopted this system for Cancer Staging and End Results. The "T" describes the primary tumour (e.g.

amount of invasion); the "N" describes lymph node involvement, while the "M" denotes distant metastasis. (Abeloff, 2000)

Figure 8: Picture of Colon Cancer



XIII) Appendix B: Summary of studies on symptoms

The studies (that were reviewed in the Section: History of Present Illness (or Symptoms)) were chosen because the articles included enough data to create the synopsis that follows.

The purpose of the Table 30: General 2X2 Table below was to get an estimate of the odds ratios that might encounter in this study. This was not an official meta-analysis, as there was no inclusion/exclusion criteria set up for selection of the studies included. The studies that were included were those that were found in the Medline search noted in the "Study Design" section and with enough published information that the following 2X2 table could be completed.

Table 30: General 2X2 Table

		Cancers		
		present("cases")	absent("non-cases")	
symptom	present	a	b	(a+b)
	absent	c	d	(c+d)
		(a+c)	(b+d)	total (a+b+c+d)

Table 31 Previous Studies on Symptoms

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+
lost appetite	Helfand,1997	18	30	42	111	1.59		1.37	
lost appetite	Curless, 1994	118	155	19	254	10.18		6.21	
lost appetite	Fitjen, 1995	1	14	41	213	0.31	3.89	0.35	2.71
Tired	Curless, 1994	117	156	65	208	2.40		1.80	
Tired	Steine, 1994	114	127	1143	468	0.37	0.46	0.67	0.70
Nausea	Steine, 1994	69	172	495	1116	0.90		0.93	
Nausea	Fitjen, 1995	1	14	67	187	0.28	0.88	0.35	0.91
Distension	Curless, 1994	106	167	45	228	3.22		2.36	
Distension	Steine, 1994	170	71	1219	392	0.77	0.57	0.93	0.80
BLD in stool	Niv,1989	11	28	96	94	0.38		0.56	
BLD in stool	Curless, 1994	142	131	34	239	7.62		4.18	
BLD in stool	Neugut, 1993	204	162	421	387	1.16		1.07	
BLD in stool	Steine, 1994	57	184	232	1379	1.84	2.20	1.64	1.66
dark bld	Kewenter, 1993	1	14	4	130	2.32		2.23	
dark bld	Mant, 1989	6	21	18	100	1.48	1.97	1.38	1.82

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+
Firstnoticebld< 2mths	Helfand, 1997	7	6	61	127	2.43			
New or recently changed bleeding [4]	Nørrelund, 1996	22	2	134	43	3.53	3.37	.29	.70
bld mixed	Helfand, 1997	38	10	99	54	2.07		1.22	
bld mixed	Segal, 1998	18	18	19	48	2.53		1.76	
bld mixed	Fitjen, 1995	6	9	62	192	1.91		1.56	
bld mixed	Mant, 1989	18	9	34	84	5.19	3.07	2.35	1.76
bld on paper	Helfand, 1	45	3	142	11	1.16		1.01	
bld on paper	Segal, 1998	30	6	56	11	0.98		1.00	
bld on paper	Kewenter, 1993	3	12	26	108	1.04	2.16	1.03	1.25
red bld	Kewenter, 1993	6	9	22	112	3.39	3.39	2.44	2.44
bld separate stool	Segal, 1998	17	19	42	25	0.53		0.75	
bld separate stool	Fitjen, 1995	5	10	176	78	0.22		0.48	
bld separate stool	Mant, 1989	11	16	82	36	0.31	0.34	0.60	0.62

[4] Timing of "new" not specified.

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+
SLIDE	Helfand, 1997	16	32	32	121	1.89		1.59	
SLIDE	Neugut, 1993	85	281	151	657	1.32	1.37	1.24	1.28
Dyschezia	Helfand, 1997	11	37	69	84	0.36		0.51	
Dyschezia	Curless, 1994	98	175	21	252	6.72		4.67	
PAIN	Nørrelund, 1996	21	33	69	241	2.22		1.75	
PAIN	Curless, 1994	140	133	20	253	13.32		7.00	
PAIN	Neugut, 1993	25	341	90	718	0.58		0.61	
PAIN	Kewenter, 1993	7	8	73	61	0.73		0.86	
PAIN	Steine, 1994	154	87	1143	468	0.72		0.90	
PAIN	Fitjen, 1995	3	12	132	122	0.20		0.35	
PAIN	Mant, 1989	6	21	37	81	0.63	0.70	0.71	0.80
Chge Bwl habits	Helfand,1997	2	46	2	152	3.48		3.40	
Chge Bwl habits	Helfand,1997	14	34	40	113	1.16		1.12	
Chge Bwl habits	Nørrelund, 1996	29	25	79	231	3.39		2.11	

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+
Chge Bwl habits	Curless,1994	194	79	4	269	165.15		48.50	
Chge Bwl habits	Neugut,1993	42	324	112	696	0.81		0.83	
Chge Bwl habits	Kewenter, 1993	9	6	71	63	1.33		1.13	
Chge Bwl habits	Steine,1994	95	146	730	881	0.79		0.87	
Chge Bwl habits	Fitjen,1995	7	8	71	183	2.27		1.67	
Chge Bwl habits	Mant,1989	13	14	44	74	1.59	1.37	1.31	1.23
increased BM	Helfand, 1997	10	38	49	104	0.56		0.65	
increased BM	Nørrelund, 1996	9	45	39	271	1.39	0.98	1.32	0.98
Looser	Helfand, 1997	25	23	78	75	1.05	1.05	1.02	1.02
lost weight	Nørrelund, 1996	10	44	34	276	1.84		1.69	
lost weight	Curless, 1994	129	144	22	251	10.22		5.86	
lost weight	Steine, 1994	55	186	298	1313	1.30		1.23	
lost weight	Fitjen, 1995	4	11	38	216	2.22		1.88	
lost weight	Mant, 1989	4	23	11	107	1.72		1.62	

Question	Study	a	c	b	d	OR	aOR	LR +	aLR+
lost weight	Helfand,1997	4	44	22	131	0.54	2.47	0.58	2.01
Soiled	Segal, 1998	7	29	17	50	0.71		0.77	
Soiled	Curless, 1994	50	223	8	265	7.43	2.85	6.25	2.51
mucous	Helfand,1997	8	40	30	123	0.82		0.85	
mucous	Curless, 1994	80	193	16	257	6.66	3.12	5.00	2.54

Where aOR = weighted (to study size) odds Ratios for the variable; aLR+ = weighted (to study size) Likelihood ratios for the variable and where the variables are

lost appetite	the patients had lost their appetites recently
BLD in stool	the patients had seen blood in their stools
dark bld	the patients had dark blood in their stools
dyschezia	the patients had painful bowel movements
firstnoticebld>6mths	the patients had noticed blood in their stools over 6 months ago
firstnoticebldnew	the patients had noticed blood in their stools within the last 6 months
Chge Bwl habits	the patients had noticed a change in their bowel habits
increased BM	the patients had noticed an increase in the frequency of their bowel movements

looser	the patients had noticed looser stools recently
lost weight	the patients had lost weight
bld mixed	the patients had noticed blood mixed in with the stools
mucous	the patients had noticed mucous in the stools
nausea	the patients had felt nausea recently
PAIN	the patients had noticed abdominal pain
bld on paper	the patients had noticed blood on the toilet paper
red bld	the patients had noticed bright red blood in their stools
bld separate stool	the patients had noticed blood separate from their stools
SLIDE	the patients had a Fecal Occult Blood test done
soiled	the patients had soiled their pants
tired	the patients had felt tired recently
lost appetite	the patients had lost their appetite

Looking at Table 31, several observations can be made.

General symptoms, such as lost appetite and feeling tired, tend not to show consistency between the studies. The odds ratios tend to "bounce around", with the extreme example of "lost appetite", with a range of 10.18 to 0.31. This would suggest that general symptoms are not co-related with colon cancer, or that it has not been studied enough.

The relationship between blood in stools and colorectal cancer has been studied to a

greater degree. Most of the odds ratios presented are greater than one, with a few exceptions. Blood noted separate from the stools is negatively related to the diagnosis of cancer. This may be because it is more likely to be from fissures or haemorrhoids.

Pain, in general, is negatively associated to colon cancer. This may seem counter intuitive, but the explanation may lie in the realization that these studies, for the most part, were done on elective patients. Perhaps, for colon cancer, if it is to produce pain, patients may be more likely to present to the Emergency department as the primary reason would be for a bowel obstruction. Patients with never previously diagnosed colon cancer do present with pain caused by their cancer to the emergency departments. (How to incorporate these patients into a study is the question.)

The presented ORs for a change in bowel habits suggest that, like the general symptoms above, there is no relationship to colon cancer, or that it is weak.

Weight loss appears to be associated with cancer, but marginally so, but incontinence and mucous in the stools are inconsistently so. Weight loss, as a symptom, is difficult to define, and substantial weight loss is likely associated (if at all) with end-stage disease.

XIV) Appendix C: Likelihood ratios and Odds Ratios

A) Definition of a likelihood ratio

One way to calculate the probability of a patient having colon cancer is using the following general equation derived from Bayes' Theorum:

Equation 3: Bayes' Theorem

Posterior odds = Prior odds * (Likelihood ratios#1)*(Likelihood ratio#2)...;

Or, if only one likelihood ratio is involved:

Equation 4: Definition of likelihood ratio

Likelihood ratio = [Posterior Odds] / [Prior odds] where:

1. Posterior odds = the odds of disease after a test result is known.

2. Prior odds = the odds of disease before knowing the test result.

In this study, the "test" would be the presence or absence of a symptom or risk factor. A positive likelihood ratio (LR+) is calculated for patients that have the symptom or risk factor in question, and a negative likelihood ratio (LR-) for the patients who do not have the symptom or risk factor in question.

B) Changing odds ratios to likelihood ratios.

Unfortunately, the logistic regression equation used in this study gives us the

independent odds ratio for the symptom or risk factor, not the likelihood ratio. We have to convert the odds ratio to the likelihood ratios. One method for accomplishing this is presented below. (Note that information on how to convert odds ratios to likelihood ratios is not prevalent in the literature.) Given the following Table 31: 2X2 Table:

Table 31: 2X2 Table

		Gold Standard		
		+	-	
Test	+	A	B	A+B
	-	C	D	C+D
		A+C	B+D	TOTAL

A few definitions are:

1. "Gold standard" = the "test" which proves or disproves decisively whether the patient has the disease or not. In our example, it was the colonoscopy.

2. "Test" can be anything that you want to compare to the gold standard. In our case, the easiest example would have been bleeding status.

3. "Odds Ratio" = (a/c)/(b/d) = (ad)/(cb)

4. "Specificity" = d / (b+d)

5. "Sensitivity" = a / (a+c)

6. "Likelihood ratio (Pos. test)" = (a/(a+c)) / (b / (b+d)) = Sensitivity / (1-Specificity)

7. "Likelihood ratio (Neg. test)" = (c/(a+c)) / (d / (b+d)) = (1-Sensitivity) / Specificity

8. "Prior Odds" (for the study population) = (a+c)/(b+d)

9. "Posterior Odds" (for the study population) (given Positive test) = a / c

10. "Posterior Odds" (for the study population) (given Negative test) = b / d

Note that the odds ratio compares the odds of a disease given a positive test to the odds of disease given a negative test. The (LR+) compares a positive test to baseline (or prior odds), and (LR-) compares a negative test to base line. Likelihood ratios are independent of prevalence and a function of the test alone, like sensitivity and specificity are.

The general logistic regression equation is:

Equation 5: General Logistic Equation

$$\text{Ln (Odds of disease)} = K + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \text{etc.}$$

Since the prior odds are the odds of the disease prior to any test being performed, the prior odds of the disease would be set at the average prevalence of the symptom in the whole study population, or

$$\text{Ln (prior odds of disease)} = K + \beta_1 (\text{mean } x_1) + \beta_2 (\text{mean } x_2) + \text{etc.}$$

The odds of the disease after the test result is known, for example if x_1 was positive and therefore set at 1, would be calculated as:

Ln (posterior odds of disease)= $K + \beta_1 (1) + \beta_2(\text{mean } x_2)$+ etc.

Since the likelihood ratio is defined as the ratio of the posterior odds to the prior odds (see Equation 4: Definition of likelihood ratio), then the likelihood ratio for a positive x_1 is: Ln (posterior odds of disease / prior odds of disease) =

Ln (posterior odds of disease) - Ln (prior odds of disease) =

$[K + \beta_1 * (1) + \beta_2*(\text{mean } x_2)+ \text{etc.}]- [K + \beta_1 *(\text{mean } x_1) + \beta_2 *(\text{mean } x_2)+ \text{etc.}] =$

$\beta_1 * (1) - \beta_1 * (\text{mean } x_1) = \beta_1 * (1 - \text{mean } x_1)$

Anti-logging this, one gets: $\exp [\beta_1 * (1 - \text{mean } x_1)] = [\exp (\beta_1)] \wedge (1 - \text{mean } x_1)$

and since the odds ratio associated with $x_1 = \exp (\beta_1)$,

Then, the final equation is:

Equation 6: Applied definition of likelihood ratios

Likelihood Ratio for a positive test = (odds ratio) ^ (1 - mean x_1)

Likewise, the Likelihood Ratio for a negative test = (odds ratio) ^ (0 - mean x_1). A continuous variable needs to be partitioned before likelihood ratios can be calculated. Using a similar argument as above, with the value of interest of the continuous variable replacing the value of one, Equation 6: Applied definition of likelihood ratios is changed to:

Likelihood Ratio for a continuous variable = (odds ratio) ^ (X - mean x_1)

Where X = the value of interest of the continuous variable.

C) Calculating likelihood ratios for this study's data.

One can calculate the likelihood ratios for pain and bleeding using the above formulas and the data from our study in Table 24: Final Logistic Regression OR, CI and p values on page 83.

Forty four percent of the study population had abdominal pain, while 50% had rectal bleeding. Using these prevalences and Equation 6: Applied definition of likelihood ratios, the following likelihood ratios can be calculated:

	Bleeding	Pain
Odds Ratio	6.352281	4.497717
Prevalence	0.5	0.44
Positive likelihood ratio	2.5204	2.321
Negative likelihood ratio	0.3968	0.51604

Age, being a continuous variable, needs to be partitioned before likelihood ratios can be calculated. It is convenient to use decades for the partitions. Using the average age of 56, the LR for age 45 would be = 1.087143 ^ (45 – 56) = 0.40

Likewise, for the other ages:

Table 32: Likelihood ratios for age categories

Age	45	55	65	75	85
LR	0.40	0.92	2.12	4.89	11.28

Thus for the 72 yo patient with rectal bleeding, but no pain, the odds of him having colon cancer (i.e. posterior odds) =

Prior odds[▽] * LR (age72) * LR(+ bleeding) * LR (- pain) =

(0.019) * (4.89) * (2.52) * (0.52) = 0.1217,

or a prevalence of 10.9% after the odds are converted to a prevalence. I will send my patient for colonoscopy!

[▽] 0.019 is the prevalence of colorectal caner in the study population, thus the prior odds of disease(approx.)

XV) Appendix D: Preliminary Logistic Regression

The following shows the first step of the forward logistic regression analysis.

Variable	Regression Coefficient	Standard Error	Chi-Square	Prob Level
			Beta=0	
lowhgsx	0.7757338	0.6175436	1.58	0.209058
bleeding	1.884169	0.7787617	5.85	0.015544
pain	1.264068	0.6714441	3.54	0.059753
change	0.6235653	0.7862255	0.63	0.427712
difference	0.6853564	0.7796178	0.77	0.379351
fhx	-0.7317194	0.7795208	0.88	0.347896
fhxother	-0.1329052	0.617948	0.05	0.829709
meds	-0.099527	0.7814782	0.02	0.898657
chole	0.9393244	0.6217767	2.28	0.130862
IBD	-12.3265	461.9861	0.00	0.978714
polyps	0.4181993	0.6192894	0.46	0.499492
colonoscop	-0.5402395	0.7799637	0.48	0.488531
visits	-0.0953086	0.5828348	0.03	0.870104
health	0.2623621	0.7834131	0.11	0.737703
bmi	-0.0595952	0.0667200	0.80	0.371743

exercise	-0.8174087	0.6715057	1.48	0.223499
smoking	-0.0140465	0.02594943	0.29	0.588297
age	0.07647624	0.02668168	8.22	0.004154
gender	0.8126123	0.6321283	1.65	0.198611
wtloss	1.463967	0.6262299	5.47	0.019400
distended	-0.1746551	0.6179133	0.08	0.777443
nausea	-0.3256487	0.7806341	0.17	0.676562
appetite	0.6002502	0.7860653	0.58	0.445097
Filter	"Q4=yes"	Pain		
pain12mth	1.789053	1.060493	2.85	0.091603
freq	-0.2184265	0.6554703	0.11	0.738956
night	-13.10732	347.7706	0.00	0.969935
withBM	-0.0357891	0.8029157	0.00	0.964447
worse	-0.3278884	0.6999567	0.22	0.639469
eating	-0.6472763	0.6994148	0.86	0.354730
Filter	"Q5=yes"	Bleeding		
mixed	0.0336383	0.77556	0.00	0.965404
cover	-13.12492	383.5291	0.00	0.972701

separate	-0.7209808	0.8472708	0.72	0.394800
dark	-0.3719422	1.093109	0.12	0.733660
red	-0.1705567	0.8505651	0.04	0.841073
increased	0.7145383	0.8557558	0.70	0.403729
12mths	13.17899	4.3403	0.00	.971145
seenweekly	-1.170775	1.089095	1.16	0.282376

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XVI) Appendix E: Consent Form

Introduction

We are investigating the connection between peoples' histories and their diseases.

On the following pages is a survey that has been distributed to Manitobans, like yourself, who are about to have a procedure, called a colonoscopy. Completion of the survey is voluntary. Today's procedure will continue even if you do not complete the survey. Your participation in this study, though, will help doctors to diagnosis patients in the future. The survey typically takes from 5 to 15 minutes to fill out, and can be filled out while you are waiting to have the colonoscopy.

If you wish to participate in the study, please sign the consent form below and then fill out the survey on the following pages. After finishing the survey, hand the completed survey and the consent form back to the nursing staff. The colonoscopy will then proceed as usual. In addition to the survey we may also ask your specialist questions about your case. We will review the results of any biopsies (or samples) that may be taken during your procedure. The results of this study may be published or presented in public forums. However, your name will not be used or revealed. As much as is possible, your answers and other information will be kept confidential. You will receive no payment or reimbursement for participation in this survey. If, at a later date, you wish to withdraw your survey from the study, you can do so by contacting Dr. Morham at the telephone number or e-mail addresses below, or by contacting the colonoscopy suite. You may keep this top page for your future reference. If you do not wish to participate in the study then please hand the questionnaire, the consent form and this page back to the nurse. Your decision not to participate will not affect your medical care.

If you have any questions, please ask the nursing staff, or contact Dr. A. Morham at the address below. For questions about your rights as a research participant, you may contact The University of Manitoba Faculty of Medicine Research Ethics Board at (204) 789-3389.

Bowels: also known as "Large intestines"or "Gut"/Colonoscopy: the test that you will be having today
Stools: also known as "poop", "crap", or "feces"/ Bowel movement: going to the washroom and producing stools

Anthony Morham, MD
office (204) 233 9415
343 Tache, St Boniface

ummorham@cc.umanitoba.ca

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Consent

I have read, and understood, what is written above. I have had the opportunity to discuss this research study with the study staff. I have had my questions answered by them in language I understand. I understand that my participation in the study is voluntary. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of my medical records by Dr. Anthony Morham and The University of Manitoba Faculty of Medicine Research Ethics Board.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Patient's signature _____date_____Patient's printed name_____
Translator's signature _____date_____Name/Relationship to patient_____

Witness signature_____date_____Witness' printed name_____

.....

OR:

I do not wish to participate in your study.

Patient's Signature_____date_____ Patient's printed name_____

Nursing Notes:_____

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Anthony Morham, MD
office (204) 233 9415
343 Tache, St Boniface
page X/10
ummorham@cc.umanitoba.ca

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XVII) Appendix F: The Questionnaire Itself

Thank you for taking the time to answer the following questions.

1: What was the initial problem that lead to the test (colonoscopy) that you will be having today?
(Check the most appropriate answer below)

- I had symptoms (or complaints) that need to be investigated ..... O
- I had a previous history of cancer, polyps, or other growths in my bowel and this is a re-check.(For other names for "bowels", see below) O
- Someone in my family had bowel cancer..... O
- I am uncertain why I am having the test done today..... O
- Other (please explain)..... O

The following questions deal with symptoms (or complaints) that you may or may not have had.

2: With respect to your weight, within the last 6 months, have you:
(Check the most appropriate answer below)

- Gained weight?..... O
- Neither lost nor gained weight? ..... O
- Lost less than 10 lb. (4.5 kg)?..... O
- Lost 10 lb. (4.5 kg) or more? ..... O
- I am uncertain if I have lost or gained weight? ..... O

3: Within the last 6 months, have you:

(Check the most appropriate answer to each)	Yes	No	Uncertain
1) Felt that your stomach is more distended (or bloated) than usual?	O	O	O
2) Felt more nausea (or feeling sick) than usual?.....	O	O	O
4) Felt more tired than usual?.....	O	O	O
5) Felt more short of breath than usual?.....	O	O	O
6) Felt more chest pain than usual?.....	O	O	O
7) Been told by your doctor that you are low on iron?.....	O	O	O
8) Persistently lost your appetite?	O	O	O

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Anthony Morham, MD
office (204) 233 9415
343 Tache, St Boniface

ummorham@cc.umanitoba.ca

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4: Within the last 6 months, have you noticed any abdominal (or stomach) pain or discomfort?
(Check the most appropriate answer)

Yes	No	Uncertain
O	O	O
⇓	⇓	⇓
⇓	⇓	⇓

If you answered Yes to 4, Please answer the following questions (below):

If you answered No or uncertain to 4, please go to 5 (on the next page).

⇓

4a: When did you first notice the pain or discomfort?
(Check the most appropriate answer below)

- **Within the last month** ..... O
- **Up to 3 months ago** ..... O
- **Up to 6 months ago** ..... O
- **Up to12 months ago** ..... O
- **Over12 months ago** ..... O
- **I am uncertain** ..... O

4b: Within the time above, how often have you noticed the pain or discomfort?
(Check the most appropriate answer below)

- **Daily** ..... O
- **Weekly** ..... O
- **Monthly** ..... O
- **Only once or twice** ..... O
- **I am uncertain** ..... O

4c: The pain or discomfort: (Check the most appropriate answer to each)

	Yes	No	Uncertain
1) Occurs at <u>night</u>	O	O	O
2) Occurs only <u>with bowel movements</u>	O	O	O
3) Has been <u>getting worse</u> in the last 6 months	O	O	O
4) Occurs with or after <u>eating</u>	O	O	O

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343 Tache, St Boniface
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5: Within the last 6 months, have you seen blood in your stools? (Check the most appropriate answer)	Yes	No	Uncertain
	O	O	O
	⇓	⇓	⇓

If you answered Yes to 5, Please answer the following questions (below):

If you answered No or uncertain to 5, please go to 6 (below).

5a: The blood:(Check the most appropriate answer to each)	Yes	No	Uncertain
1) Was mixed in with the stools	O	O	O
2) Was covering the stools	O	O	O
3) Was separate from the stools	O	O	O
4) Was dark in colour	O	O	O
5) Was bright red in colour	O	O	O
6) Has increased in amount in the last 6 months?	O	O	O

5b: When did you first notice blood in your stools? (Check the most appropriate answer below)	
- Within the last 3 months	O
- Up to 6 months ago	O
- Up to12 months ago	O
- Up to 24 months ago	O
- Over 24 months ago	O
- Uncertain	O

5c: Within this time, how often did you notice the blood? (Check the most appropriate answer below)	
- With each bowel movement.	O
- With every 2nd to 7th bowel movements.	O
- With every 8th or more bowel movements.	O
- Uncertain	O

6: Do you look in the toilet at your stools with every bowel movement or every other bowel movement? (Check the most appropriate answer)	Yes	No	Uncertain
	O	O	O

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343 Tache, St Boniface
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11: In the last 6 months, have you noticed any other new symptoms (or complaints) that were not discussed above and which you think might be related to why you are having the test (called a colonoscopy) today?

_____

_____

_____

The following questions deal with your family's medical history.

12: To the best of your knowledge, how many, if any, of your children, parents, or sisters or brothers were first found to have bowel cancer when they were younger than 60 years old?
(Check the most appropriate answer below)

- None ..... O
- 1 ..... O
- 2 or more ..... O
- Uncertain ..... O

13: To the best of your knowledge, how many, if any, of your children, parents, or sisters or brothers were first found to have bowel cancer when they were 60 years old or older?
(Check the most appropriate answer below)

- None ..... O
- 1 ..... O
- 2 or more ..... O
- Uncertain ..... O

14: To the best of your knowledge, have your children, parents, sisters or brothers ever had any of the following diseases?

(Check the most appropriate answer to each)	Yes	No	Uncertain
1) Uterine (or womb) cancer	O	O	O
2) Breast cancer	O	O	O
3) Ovarian cancer	O	O	O
4) Prostate cancer	O	O	O

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Anthony Morham, MD
office (204) 233 9415
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The following deals with your medical history.

15: Please answer the following questions about YOUR medical history.

(Check the most appropriate answer to each)	Yes	No	Uncertain
1) Have you taken aspirin (also known as ASA, or Entrophen) regularly, that is at least twice a week for at least ten years?	O	O	O
2) Do you take a medication known as Coumadin (Warfarin)?	O	O	O
3) Have you had your gallbladder removed?	O	O	O
4) Do you have Ulcerative Colitis or Crohn's disease?	O	O	O
5) Have you had any cancers?	O	O	O

If you have had cancer, what kind of cancer(s) did you have? ***(Please fill in the blank below)***

_____

16: I have had: (Check the most appropriate answer)

- **No colonoscopies prior to this one** ..... **O**
- **One colonoscopy prior to this one** ..... **O**
- **Two or more colonoscopies prior to this one** ..... **O**
- **Uncertain** ..... **O**

17: In the last year, approximately how many times did you visit a doctor?
(Check the most appropriate answer)

- **One to three times** ..... **O**
- **Four to Eight times** ..... **O**
- **More than eight times** ..... **O**
- **Uncertain** ..... **O**

18: In general, how would you describe your health? ***(Check the most appropriate answer)***

- **I have above average health for my age** ..... **O**
- **I have average health for my age** ..... **O**
- **I have below average health for my age** ..... **O**
- **Uncertain.** ..... **O**

The following deal with general questions about you.

19: About how much do you weigh? ***(Please fill in the blank and circle the units)*** _____ **pounds/kg.**

20: About how tall are you? ***(Please fill in the blank and circle the units)*** ..... _____**(feet inches/cm)**

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office (204) 233 9415
343 Tache, St Boniface
page X/10
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21: How would you describe your family of origin? ***(Check the most appropriate answer)***

European	O
North American Aboriginal origin	O
African	O
Asian	O
Another not listed here	O

22: Do you currently participate in any regular activity or program (either on your own or in a formal class) designed to improve or maintain your physical fitness?

	Yes	No	Uncertain
(Check the most appropriate answer)..	O	O	O

23: If you have ever smoked cigarettes, how many years in your life have you smoked?
(Please fill in the blank) ..... _____

24: If you have ever smoked cigarettes, during the time that you smoked, on average how many cigarettes did you smoke each day?
(Please fill in the blank) ..... _____

25: In what year were you born? ***(Please fill in the blank)***..... _____

26: Are you a male or a female? (Check the most appropriate answer)

- Male	O
- Female	O

26: I completed this survey: (Check the most appropriate answer)

- Totally before the colonoscopy	O
- Partially before and partially after.	O
- Totally after the colonoscopy	O
- Uncertain	O

Thank you for taking the time to fill out this questionnaire. If you have any questions, please feel free to call the lead investigator below.

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office (204) 233 9415
343 Tache, St Boniface
page X/10
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343 Tache, St Boniface
page X/10
ummorham@cc.umanitoba.ca

XVIII) Appendix G: The rational behind the survey questions.

General Questions: Question 1 indicates why the patient is having the test. It was also an opening question of a general nature.

Symptoms: Questions 2-6, and 7- 11 concerns the subject's symptoms. Questions 2 and 3 deal with general symptoms. Question 4 deals with abdominal pain. Questions 5 - 6 deals with blood in the stool and Questions 8 - 10 deal with changes in bowel habits. Question 11 is an open-ended question in an attempt to retrieve any other relevant symptoms.

Laboratory and other Investigations: Question 7 is to determine if the patient has had a positive fecal occult blood test.

Family History: Questions 12-14 determine the subject's family history of colon cancer and other associated cancers.

Medications: Part of Question 15 determines ASA and Warfarin use.

Personal Medical/Surgical History: Question 15 concerns the personal medical history of the patient.

Social/Environmental Factors: Question 16 and 17 will be used to calculate the patient's BMI. Question 19 is a question to determine if a person exercises regularly. Question 20 will be used to determine how many pack years a person has smoked. It was

felt that it would be too difficult to inquire about nutrition in this study format. To investigate this well, a nutritionist would need to interview patients directly, which was not possible in this format. Questions in the survey would be difficult to validate. Finally, the subjects would not have time to complete the survey in the given protocol if it contained the necessary multiple nutrition questions.

Age/Gender and other Demographics: Question 21 and 22 will determine age and gender of the patient respectively. Question 18 will determine the patient's ethnic background.

Health: Question 23 - 25 will determine health care usage, and how healthy the patient perceives him or herself to be. Both how healthy a patient really is, and their anxiety level will likely determine the answer to these questions.

Completion: Question 26 will determine if the questionnaire was completed before the results of the colonoscopy are known. The questionnaire ideally would be completed before the colonoscopy, but time constrictions may not have allowed this, and hence this question must be asked.

Examination: There are no questions dealing with the examination in the patient's questionnaire.

XIX) Appendix H: Analysis of the self-reported risk factors

A univariate logistic regression analysis was used to determine the odds ratios, and their confidence intervals, associated with each variable noted below. For these variables, continuous variables (age, BMI, year of birth) were maintained as such. The rest were converted to dichotomous variables. A negative answer to the question was considered the baseline.

The questions were grouped for the univariate logistic regression analysis. The groupings were according to the content of the question. For example, non-specific symptoms (weight loss, nausea, loss of appetite) were grouped together. The actual groupings for the analysis are outlined below.

Note: (1) "Combined" means that any positive answers would be acceptable (essentially an "OR" Boolean operation); (2) Independent means that separate log regression analysis were made for each answer; (3) The labels are references for the rest of the paper.

Table 34: Groupings of questions

Question/Combination	Description	Label
Q1, 6, 7 11, 27	Not analysed at this point	
Q2 (1 =iv, 0= else) and Q3 i, ii, viii (1="yes"; 0=else)	General non-specific symptoms	**"gensx"**
Q3 iii, iv, v (1="yes"; 0=else)	Symptoms of low haemoglobin (anaemia)	**"lowhgsx"**

Question/Combination	Description	Label
Q3 vi, Q5, Q7 (1="yes"; 0=else)	Evidence of blood in stools	**"bleeding"**
Initial part of Q4 (1="yes"; 0=else)	General question on pain	**"pain"**
Subsequent parts to Q4		
-Q4a (1 = answers 1,2,3,4; 0 = else)	When the pain first occurred (divided at the 12 month level)	"12mths"
-Q4b (1 = answers 1,2; 0 = else)	The frequency of the pain	"freq"
- Q4c (i-iv) independent, (1="yes"; 0=else)	Various aspects of the pain	"night", "wBM", "worse" and "eating" respectively
Subsequent parts to Q5		
- Q5a (i-vi) independent, (1="yes"; 0=else)	Various aspects of the bleeding	"mixed", "cover", "seperate", "dark", "red" and "increased" respectively
-Q5b (1 = answers 1,2,3; 0 = else)	When the patient first noticed the blood, cut off was placed at 12 months	"12mths"
-Q5c (1 = answer 1; 0 = else)	How often the patient saw the blood, cut off point at seen weekly	"seen weekly"
Q 8, 9	*	**"change"**

Question/Combination	Description	Label
The answers in Q10 were combined (i-vii) (1="yes"; 0=else)	Indicate a change in bowel habits	**"Difference"**
Q12 & 13 were combined (1= answers 2 or 3 of Q12 or Q13; else =0)	Family history of colon cancer	**"fhx"**
The answers to Q14 (i-v) were combined (1="yes"; 0=else)	Family history of other cancers	**"fhxother"**
Q15 parts 1&2 were combined (1="yes"; 0=else)	Medications	**"meds"**
Q15 parts 3-6 were dealt with independently, (1="yes"; 0=else)	Previous history of gallbladder removal, Inflammatory bowel disease and colonic polyps	**"chole", "IBD", and "polyps" respectively**
Q16 (1= answer 3; 0 = else)	Number of previous colonoscopies	**"colonoscopy"**
Q17 (1= answer 2, 3; 0 = else)	Number of previous doctor visits	**"visits"**
Q18 (1= answer 3; 0 = else)	Self-perception of health	**"health"**
Q19, 20 (continuous)	Used to calculate the BMI	**"Bmi"**
Q21 (1="1"; else=0)	European vs. non-European	**"ethnic"**
Q22 (1="yes"; 0=else)	Regular exercise	**"exercise"**
Q23, Q24	Used to calculate the number of pack-years	**"smoking"**
Q25 (continuous)	Recalculated as 2001 – answer	**"age"**

Question/Combination	Description	Label
Q26 (1 = male, 0 = female)		**"gender"**

* For Q8, 9, a positive answer occurred if a difference of two points between the questions was found. This was felt to indicate a change in bowel habits (constipation or diarrhoea).

Thus, the data were grouped into 22 variables for the initial analysis (bolded above). Question 4 and Question 5, the two branching questions, were further split into six and eight individual variables respectively (underlined above). Thus, there were 36 variables involved in the initial analysis.

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Colonoscopy Study
Anthony Morham, MD CCFP

XX) Appendix I: Guidelines for Nursing Staff

Study Goal: To help physicians diagnose colorectal ca.
Study Objectives:

1. To describe the patient population undergoing colonoscopies in participating colonoscopy suites in Winnipeg, MB.
2. To describe current reasons for elective referral to colonoscopy suites in Winnipeg MB
3. To determine the self reported risk factors associated with a diagnosis of colorectal carcinoma in a group of patients undergoing colonoscopies in Winnipeg, MB.
4. To develop a statistical model that calculates the probability of colorectal carcinoma in a referred patient.
5. To compare the physician's stated reason for the colonoscopy to that of the patient's understanding of the reason.

To investigate the above, we will be distributing a questionnaire to colonoscopy suites in Winnipeg, starting with the Health Science Centre. The questionnaire typically takes from 5 to 15 minutes to fill out. The patient will fill it out while they are in the recovery room waiting to have the colonoscopy. Completion of the survey is voluntary. The questionnaire will be attached to the back of the packet already in place that is initiated when the patient arrives.

The admitting recovery room nurse's role is to ask the patient if he/she wishes to participate in the study. This would be done after the patient finishes with the admission (to the suite). If consent is given, the nurse would hand the survey to the patient. The nurse might introduce the study with something like: "There is a physician who is studying the symptoms of patients in Winnipeg who are having colonoscopies. Would you like to complete one of his questionnaires?" It would be great if the nurse could also witness the consent form at some point. Completed questionnaires are placed in the "Consent signed" box. Questionnaires without a signed consent are placed in the "No consent signed" box. Partially completed questionnaires are dealt with as discussed below.

The contents of the boxes will be picked up at least monthly (usually more often). The questionnaire is meant to be self-explanatory. If questions do arise, it is hoped that the nurses involved would be able to answer them, given the guidelines below. My number and cell phone number will also be available, if required. You will not get paid for doing this.

If you wish, you can introduce the study with this:

"**Finally, this is a survey that we are conducting here.** (*Show the actual survey).* **Dr. Morham is the lead investigator. You doctor has said that it is okay for you to participate in this study. It involves several questions about your history, and you would fill out the questionnaire yourself. This sheet has more information about the study. Do you want to read it? If, after reading the sheet, you want to do**

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the questionnaire, then fill it out and I will collect it later." (*Remember to co-sign the consent form.)*

Possible problems:

1. **Patient says: "I don't understand the question"**: Please don't answer it for them. Ask them to take their best guess, and write down any qualifiers/suggestions on the side of the page that they think are needed.
2. **Patient cannot write questionnaire for any reason,** e.g. cannot read/write English well, is too sick etc.: If the person cannot complete the questionnaire by him/herself, then their questionnaire should be placed in the "no consent signed" box. If present, and there is time, one may ask if the translator would be interested in helping. As far as you are concerned, this is the only patient who you should not give the questionnaire to.
3. **Patient doesn't sign consent**: Place in the box.
4. **Patient doesn't complete the questionnaire prior to the procedure**: Try to have the patient complete the questionnaire after the procedure, preferable when the effects of the medications have subsided. The questionnaire should then follow the chart until the patient leaves the suite.
5. **Patient doesn't start the questionnaire prior to the procedure**: same as above.
6. **Patient doesn't complete the questionnaire before leaving the department**: If the consent form is signed, even partially completed questionnaires should be placed in the box.
7. **The suite becomes very busy, and you don't feel that there is time for the patient to do the questionnaire**. Patient and staff care obviously comes first.
8. **I wish to comment on a patient's questionnaire:** On the consent form, there is a space which you can use, only if you wish to, to write a comment to myself e.g. patient had MI therefore could not complete survey (I don't know exactly what you would write, but I thought that it would be a good idea to give you a way of communicating things to me about a patient.)
9. **You run out of supplies (pencils, questionnaires) :** Different ways of contacting me will be on the questionnaire and on the boxes.
10. **What about in-patients:** If an in-patient can write the questionnaire, then they should.
11. **How long will this study be going on?** I am hoping to keep it going until there are 250 completed questionnaires, or 6 months, which ever comes first.

XXI) Appendix J: Patient answers.

Frequency Distribution of Q1i

Q1i	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
0	289	292	45.02	45.48	|||||||||||||||||
1	350	642	54.52	100.00	|||||||||||||||||||

Frequency Distribution of Q1ii

Q1ii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
0	490	493	76.32	76.79	|||||||||||||||||||||||||||||||
1	149	642	23.21	100.00	|||||||||

Frequency Distribution of Q1iii

Q1iii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
0	486	489	75.70	76.17	|||||||||||||||||||||||||||||||
1	153	642	23.83	100.00	|||||||||

Frequency Distribution of Q1iv

Q1iv	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|

0	622	625	96.88	97.35	
1	17	642	2.65	100.00	

Frequency Distribution of Q2

Q2	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
1	126	129	19.63	20.09	
2	303	432	47.20	67.29	
3	76	508	11.84	79.13	
4	69	577	10.75	89.88	
5	51	628	7.94	97.82	
No response	14	642	2.18	100.00	

Frequency Distribution of Q3i

Q3i	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
No	277	280	43.15	43.61	
No Response	80	360	12.46	56.07	
Uncertain	44	404	6.85	62.93	
Yes	238	642	37.07	100.00	

Frequency Distribution of Q3ii

Q3ii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
No	357	360	55.61	56.07	
No Response	130	490	20.25	76.32	

Uncertain	14	504	2.18	78.50	|
Yes	138	642	21.50	100.00	||||||||

Frequency Distribution of Q3iii

Q3iii	Count	Cumulative Count	Cumulative Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	243	246	37.85	38.32	|||||||||||||||
No Response	86	332	13.40	51.71	|||||
Uncertain	25	357	3.89	55.61	|
Yes	285	642	44.39	100.00	|||||||||||||||||

Frequency Distribution of Q3iv

Q3iv	Count	Cumulative Count	Cumulative Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	369	372	57.48	57.94	||||||||||||||||||||
No Response	139	511	21.65	79.60	||||||||
Uncertain	20	531	3.12	82.71	|
Yes	111	642	17.29	100.00	||||||

Frequency Distribution of Q3v

Q3v	Count	Cumulative Count	Cumulative Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	411	414	64.02	64.49	|||||||||||||||||||||||
No Response	154	568	23.99	88.47	||||||||
Uncertain	21	589	3.27	91.74	|
Yes	53	642	8.26	100.00	|||

Frequency Distribution of Q3vi

Q3vi	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	400	403	62.31	62.77	||||||||||||||||||||||||
No Response	139	542	21.65	84.42	||||||||
Uncertain	19	561	2.96	87.38	|
Yes	81	642	12.62	100.00	|||||

Frequency Distribution of Q3vii

Q3vii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	399	402	62.15	62.62	||||||||||||||||||||||||
No Response	144	546	22.43	85.05	||||||||
Uncertain	32	578	4.98	90.03	|
Yes	64	642	9.97	100.00	|||

Frequency Distribution of Q4

Q4	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	283	286	44.08	44.55	|||||||||||||||
No Response	14	300	2.18	46.73	|
Uncertain	28	328	4.36	51.09	|
Yes	314	642	48.91	100.00	||||||||||||||||

Frequency Distribution of Q5

<table>
<tr><th></th><th></th><th>Cumulative</th><th></th><th>Cumulative</th><th>Graph of</th></tr>
<tr><th>Q5</th><th>Count</th><th>Count</th><th>Percent</th><th>Percent</th><th>Percent</th></tr>
<tr><td>Missing</td><td>3</td><td>3</td><td>0.47</td><td>0.47</td><td>|</td></tr>
<tr><td>NO</td><td>2</td><td>5</td><td>0.31</td><td>0.78</td><td>|</td></tr>
<tr><td>No</td><td>362</td><td>367</td><td>56.39</td><td>57.17</td><td>||||||||||||||||||||||</td></tr>
<tr><td>No Response</td><td>18</td><td>385</td><td>2.80</td><td>59.97</td><td>|</td></tr>
<tr><td>Uncertain</td><td>27</td><td>412</td><td>4.21</td><td>64.17</td><td>|</td></tr>
<tr><td>Yes</td><td>230</td><td>642</td><td>35.83</td><td>100.00</td><td>||||||||||||||</td></tr>
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Frequency Distribution of Q6

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<tr><th>Q6</th><th>Count</th><th>Count</th><th>Percent</th><th>Percent</th><th>Percent</th></tr>
<tr><td>Missing</td><td>3</td><td>3</td><td>0.47</td><td>0.47</td><td>|</td></tr>
<tr><td>No</td><td>102</td><td>105</td><td>15.89</td><td>16.36</td><td>||||||</td></tr>
<tr><td>No Response</td><td>25</td><td>130</td><td>3.89</td><td>20.25</td><td>|</td></tr>
<tr><td>Uncertain</td><td>14</td><td>144</td><td>2.18</td><td>22.43</td><td>|</td></tr>
<tr><td>Yes</td><td>498</td><td>642</td><td>77.57</td><td>100.00</td><td>|||||||||||||||||||||||||||||||</td></tr>
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Frequency Distribution of Q7

<table>
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<tr><th>Q7</th><th>Count</th><th>Count</th><th>Percent</th><th>Percent</th><th>Percent</th></tr>
<tr><td>Missing</td><td>3</td><td>3</td><td>0.47</td><td>0.47</td><td>|</td></tr>
<tr><td>No</td><td>510</td><td>513</td><td>79.44</td><td>79.91</td><td>|||||||||||||||||||||||||||||||</td></tr>
<tr><td>No Response</td><td>29</td><td>542</td><td>4.52</td><td>84.42</td><td>|</td></tr>
<tr><td>Uncertain</td><td>35</td><td>577</td><td>5.45</td><td>89.88</td><td>||</td></tr>
<tr><td>Yes</td><td>65</td><td>642</td><td>10.12</td><td>100.00</td><td>||||</td></tr>
</table>

Frequency Distribution of Q8

	Cumulative	Cumulative	Graph of

Q8	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
1	76	79	11.84	12.31	||||
2	203	282	31.62	43.93	|||||||||||
3	218	500	33.96	77.88	||||||||||||
4	98	598	15.26	93.15	||||||
5	20	618	3.12	96.26	|
6	11	629	1.71	97.98	|
No response	13	642	2.02	100.00	|

Frequency Distribution of Q9

Q9	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
1	47	50	7.32	7.79	||
2	206	256	32.09	39.88	||||||||||
3	245	501	38.16	78.04	||||||||||||
4	89	590	13.86	91.90	|||||
5	14	604	2.18	94.08	|
6	23	627	3.58	97.66	|
No response	15	642	2.34	100.00	|

Frequency Distribution of Q10i

Q10i	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	292	295	45.48	45.95	|||||||||||||||
No Response	153	448	23.83	69.78	||||||||
Uncertain	17	465	2.65	72.43	|

Yes	177	642	27.57	100.00	

Frequency Distribution of Q10ii

Q10ii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
No	246	249	38.32	38.79	
No Response	160	409	24.92	63.71	
Uncertain	24	433	3.74	67.45	
Yes	209	642	32.55	100.00	

Frequency Distribution of Q10iii

Q10iii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
No	224	227	34.89	35.36	
No Response	141	368	21.96	57.32	
Uncertain	27	395	4.21	61.53	
Yes	247	642	38.47	100.00	

Frequency Distribution of Q10iv

Q10iv	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	
No	237	240	36.92	37.38	
No Response	160	400	24.92	62.31	
Uncertain	38	438	5.92	68.22	
Yes	203	641	31.62	99.84	
a	1	642	0.16	100.00	

Frequency Distribution of Q10v

Q10v	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	359	362	55.92	56.39	||||||||||||||||||||
No Response	192	554	29.91	86.29	||||||||||
Uncertain	5	559	0.78	87.07	|
Yes	83	642	12.93	100.00	|||||

Frequency Distribution of Q10vi

Q10vi	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	266	269	41.43	41.90	|||||||||||||||
No Response	174	443	27.10	69.00	|||||||||
Uncertain	37	480	5.76	74.77	||
Yes	162	642	25.23	100.00	|||||||||

Frequency Distribution of Q10Vii

Q10Vii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	3	3	0.47	0.47	|
No	272	275	42.37	42.83	|||||||||||||||
No Response	192	467	29.91	72.74	||||||||||
Uncertain	73	540	11.37	84.11	||||
Yes	102	642	15.89	100.00	|||||

Frequency Distribution of Q12

		Cumulative		Cumulative	Graph of
Q12	Count	Count	Percent	Percent	Percent
Missing	4	4	0.62	0.62	|
1	493	497	76.79	77.41	||||||||||||||||||||||||||||||
2	69	566	10.75	88.16	||||
3	12	578	1.87	90.03	|
4	33	611	5.14	95.17	||
No response	31	642	4.83	100.00	|

Frequency Distribution of Q13

		Cumulative		Cumulative	Graph of
Q13	**Count**	**Count**	**Percent**	**Percent**	**Percent**
Missing	4	4	0.62	0.62	|
1	431	435	67.13	67.76	|||||||||||||||||||||||||||
2	113	548	17.60	85.36	|||||||
3	25	573	3.89	89.25	|
4	38	611	5.92	95.17	||
No response	31	642	4.83	100.00	|

Frequency Distribution of Q14i

		Cumulative		Cumulative	Graph of
Q14i	**Count**	**Count**	**Percent**	**Percent**	**Percent**
Missing	4	4	0.62	0.62	|
No	416	420	64.80	65.42	||||||||||||||||||||||||||
No Response	135	555	21.03	86.45	||||||||
Uncertain	39	594	6.07	92.52	||
Yes	48	642	7.48	100.00	||

Frequency Distribution of Q14ii

Q14ii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
No	408	412	63.55	64.17	||||||||||||||||||||||||
No Response	131	543	20.40	84.58	||||||||
Uncertain	23	566	3.58	88.16	|
Yes	76	642	11.84	100.00	||||

Frequency Distribution of Q14iii

Q14iii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
No	413	417	64.33	64.95	||||||||||||||||||||||||
No Response	167	584	26.01	90.97	|||||||||
Uncertain	30	614	4.67	95.64	|
Yes	28	642	4.36	100.00	|

Frequency Distribution of Q14iv

Q14iv	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
No	392	396	61.06	61.68	|||||||||||||||||||||
No Response	145	541	22.59	84.27	||||||||
Uncertain	34	575	5.30	89.56	||
Yes	67	642	10.44	100.00	||||

Frequency Distribution of Q14v

Q14v	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent

Missing	4	4	0.62	0.62	|
No	262	266	40.81	41.43	||||||||||||||
No Response	159	425	24.77	66.20	||||||||
Uncertain	111	536	17.29	83.49	|||||
Yes	106	642	16.51	100.00	|||||

Frequency Distribution of Q15i

Q15i	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
No	488	492	76.01	76.64	||||||||||||||||||||||||||
No Response	40	532	6.23	82.87	||
Uncertain	12	544	1.87	84.74	|
Yes	98	642	15.26	100.00	|||||

Frequency Distribution of Q15ii

Q15ii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
2	1	5	0.16	0.78	|
No	553	558	86.14	86.92	||||||||||||||||||||||||||||||
No Response	52	610	8.10	95.02	|||
Uncertain	11	621	1.71	96.73	|
Yes	21	642	3.27	100.00	|

Frequency Distribution of Q15iii

Q15iii	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|

No	491	495	76.48	77.10	
No Response	38	533	5.92	83.02	
Uncertain	2	535	0.31	83.33	
Yes	107	642	16.67	100.00	

Frequency Distribution of Q15iv

Q15iv	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	
No	492	496	76.64	77.26	
No Response	44	540	6.85	84.11	
Uncertain	51	591	7.94	92.06	
Yes	51	642	7.94	100.00	

Frequency Distribution of Q15v

Q15v	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	
No	301	305	46.88	47.51	
No Response	93	398	14.49	61.99	
Uncertain	84	482	13.08	75.08	
Yes	160	642	24.92	100.00	

Frequency Distribution of Q15vi

Q15vi	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	
No	462	466	71.96	72.59	
No Response	38	504	5.92	78.50	

Uncertain	16	520	2.49	81.00	|
Yes	122	642	19.00	100.00	|||||||

Frequency Distribution of Q16

Q16	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
1	297	301	46.26	46.88	||||||||||||||||||
2	147	448	22.90	69.78	|||||||||
3	163	611	25.39	95.17	||||||||||
4	4	615	0.62	95.79	|
No response	27	642	4.21	100.00	|

Frequency Distribution of Q17

Q17	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
1	265	269	41.28	41.90	||||||||||||||||
2	208	477	32.40	74.30	||||||||||||
3	128	605	19.94	94.24	|||||||
4	18	623	2.80	97.04	|
No response	19	642	2.96	100.00	|

Frequency Distribution of Q18

Q18	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62	|
1	144	148	22.43	23.05	||||||||
2	348	496	54.21	77.26	||||||||||||||||||||

3	86	582	13.40	90.65	|||||
4	39	621	6.07	96.73	||
No response	21	642	3.27	100.00		

Frequency Distribution of Q19

Q19	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	39	39	6.07	6.07	||

Frequency Distribution of Q20

Q20	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	41	41	6.39	6.39	||

Frequency Distribution of Q21

Q21	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	5	5	0.78	0.78		
1	450	455	70.09	70.87	||||||||||||||||||||||||||
2	28	483	4.36	75.23		
3	1	484	0.16	75.39		
4	10	494	1.56	76.95		
5	99	593	15.42	92.37	||||||
No response	49	642	7.63	100.00	|||

Frequency Distribution of Q22

Q22	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62		

No	329	333	51.25	51.87	||||||||||||||||||
No Response	30	363	4.67	56.54		
Uncertain	5	368	0.78	57.32		
Yes	274	642	42.68	100.00	||||||||||||||||

Frequency Distribution of Q23

Q23	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	53	53	8.26	8.26	|||

Frequency Distribution of Q24

Q24	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	62	62	9.66	9.66	|||

Frequency Distribution of Q25

Q25	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	32	32	4.98	4.98		

Frequency Distribution of Q26

Q26	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
Missing	4	4	0.62	0.62		
1	271	275	42.21	42.83	||||||||||||||
2	344	619	53.58	96.42	||||||||||||||||||||
No response	23	642	3.58	100.00		

Frequency Distribution of Q27

<table>
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<tr><th>Q27</th><th>Count</th><th>Count</th><th>Percent</th><th>Percent</th><th>Percent</th></tr>
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<tr><td>1</td><td>510</td><td>514</td><td>79.44</td><td>80.06</td><td>||||||||||||||||||||||||||||||||</td></tr>
<tr><td>2</td><td>39</td><td>553</td><td>6.07</td><td>86.14</td><td>||</td></tr>
<tr><td>3</td><td>56</td><td>609</td><td>8.72</td><td>94.86</td><td>|||</td></tr>
<tr><td>4</td><td>10</td><td>619</td><td>1.56</td><td>96.42</td><td>|</td></tr>
<tr><td>No response</td><td>23</td><td>642</td><td>3.58</td><td>100.00</td><td>|</td></tr>
</table>

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XXIII) CV

190 LYNDALE DRIVE • WINNIPEG MB CANADA• R2H 1K3
PHONE (204) 233 - 9415 • E-MAIL UMMORHAM@CC.UMANITOBA.CA

ANTHONY MORHAM

EDUCATION

1985 – 1987 University of Western Ontario London, ON
2 years of Science (Chemistry)

1987 - 1991 University of Ottawa Ottawa, ON
Doctor of Medicine

1991 - 1993 Dalhousie University Halifax, NS
Family Medicine Residency

1995 - 2002 University of Manitoba Winnipeg, MB
Master's Program, Community Health

PROFESSIONAL EXPERIENCE

1993 – 1995 Winkler Medical Clinic Winkler, MB
Family Physician
- Including clinic, ER, obstetrics, in-patient and OR assist work

1996 – 2000 Stonewall Medical Group Stonewall, MB
Family Physician
- Including clinic, ER and in-patient work
- 1998 – 2000 Chief of Staff, Stonewall and District Hospital

2000 – 2001 St. Boniface Clinic Winnipeg, MB
Family Physician
- Including clinic and in-patient work
- Occasional shifts in various ER/Urgent Care departments

2001 - present Concordia Hospital Stonewall, MB
Emergency Department Physician

Professional memberships: CFPC, CPSM, MMA, CMA, CMPA
Courses: ATLS (2000), ACLS (2001)