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Risk and risk reduction factors for colon and rectal cancer

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Abstract

Colorectal cancer (colon and rectal cancer combined) is the third most frequent cancer in the U.S., with at least 120,00 new cases diagnosed per year. Dietary factors appear to play the most important role in the risk of colorectal cancer. Animal products and obesity are important risk factors, while vegetable products, other than sweeteners, and low body mass index (BMI) are important risk reduction factors. In addition, vitamin D, generally from solar ultraviolet-B (UVB) radiation, is a very important risk reduction factor, and explains why colorectal cancer mortality in the U.S. is two times higher in the northeast than in the southwest. The latest results from the literature regarding risk and risk reduction factors for colorectal cancer are reviewed in this essay.

Introduction

Colorectal cancer (colon and rectal cancer combined) is the third most frequent cancer in the U.S. In 2004, there are expected to be 106,000 colon cancer cases and 41,000 rectal cancer cases, with 57,000 deaths due to both cancers. Only breast cancer (217,000 cases) and lung cancer (174,000 cases) are more frequent, and only lung cancer takes more lives (160,000) [Jemal et al., 2004].

Diet and colorectal cancer

The first study linking diet to colon cancer was by Dennis Burkitt, who found that Africans had much lower colon cancer rates than did Europeans [Burkitt, 1971a, b]. The African diet contained much more fiber, leading to much larger stools [Burkitt, 1971a, b]. However, epidemiologic evidence supporting the fiber hypothesis has been rather spotty. A recent study of colon cancer rates in South Africa concluded that the low prevalence of colon cancer in black Africans cannot be explained by dietary "protective" factors, such as fiber, calcium, vitamins A, C and folic acid, but may be influenced by the absence of "aggressive" factors, such as excess animal protein and fat, and by differences in colonic bacterial fermentation [O'Keefe et al., 1999]. On the other hand, a recent paper reported that the risk of colorectal adenoma (the precursor of colorectal cancer) decreased by 41% for every additional 5% unit of fiber intake/day [Mathew et al., 2004]. Red meat fat increased the risk by 20%, and white meat fat decreased the risk by 67% for every additional 5% unit of respective intake/day.

The primary risk factor for colon cancer is animal products, which are high in

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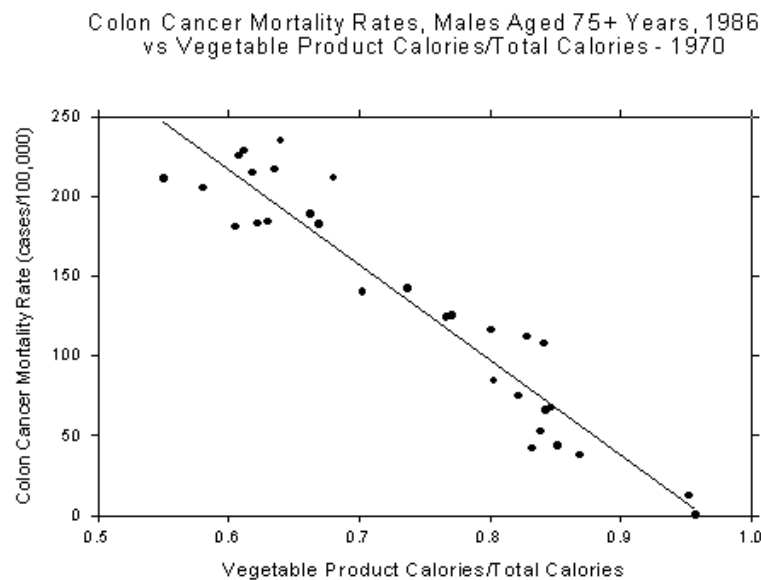
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Position of health organizations and agencies in Australia, Canada, New Zealand, the United Kingdom, and the United States, and the World Health Organization, on UV radiation and vitamin D

saturated fat and protein. Animal fat has been identified as a major risk factor for colon cancer in ecologic studies [Armstrong and Doll, 1975; Hursting et al., 1990]. As shown in Figure 1, when colon cancer mortality rates for 35 countries are plotted against calories derived from vegetable products as a fraction of total calories, there is a very high correlation [Grant, 1999]. In 1970, Americans obtained 34% of their calories from animal products [FAO, 1996]. This places the U.S. near the top of colon cancer mortality rates, with northern European countries having higher rates. The lowest rates are in Southeast Asian countries.

Figure 1. Colon cancer mortality rates for males aged 75+ years in 1986 vs. vegetable product calories/total calories. The adjusted r^2 was greater than 0.90.



A recent study in the U.S. found that the “Western” diet was positively associated with colorectal cancer incidence while a “prudent” diet was inversely associated (protective) [Fung et al., 2003]. The prudent diet was characterized by higher intakes of fruits, vegetables, legumes, fish, poultry, and whole grains, while the Western pattern was characterized by higher intakes of red and processed meats, sweets, French fries, and refined grains [Fung et al., 2001]. Dietary sugar and high glycemic index foods are also risk factors for colorectal cancer [Slattery et al., 1997; Giovannucci 2001, 2002, 2003].

There are several reasons why animal products are a high risk factor for colorectal cancer, as well as breast and prostate cancer [Grant, 2002a; Grant, 2004]. One reason is that fat and protein increase the production of insulin like growth factor-I (IGF-I) [Holmes et al., 2002; Giovannucci et al., 2003]. IGF-I is strongly implicated in the etiology of colon cancer [Giovannucci, 2001, 2002; Kaaks and Lukanova, 2002; Reinmuth et al., 2002]. IGF-I plays an important role in stimulating cell growth and, hence, tumor growth.

In a multi-factor cohort study, age, gender, family history of colon or rectal cancer, height, body mass index, physical activity, folate, intake of red meat as a main dish, intake of processed meat and alcohol were significantly associated with colon cancer risk. However, only age and gender were associated with rectal cancer [Wei et al., 2004].

Exercise and colorectal cancer

Exercise is often found associated with reduced risk of colorectal and other cancers. There are several potential mechanisms for the association between physical activity and reduced risk for breast and colon cancer. One such mechanism is simply the bias due to the strong correlation between physical activity and other health factors. For example, people who exercise regularly are less likely to smoke, drink heavily, or use medications. Other mechanisms include the direct effects of exercise on the body, such as reduced obesity, hormonal and reproductive effects, mechanical effects, and enhancement of the immune system [McTiernan et al., 1998].

Geographical variation in colorectal cancer

When one inspects the geographic variation of colon and rectal cancer mortality rates in the U.S. [Devesa et al., 1999], one is struck by the large variation. For white males for the period 1970-94, the rates in the northeastern states are 2-3 times higher than in the southwestern states. For example, there were 23-30 deaths/100,000/year in New Jersey and New York, but only 9-15 deaths/100,000/year in New Mexico, western Texas, and Utah. For rectal cancer, the rates in New York were 5.8-8.6 deaths/100,000/year vs. 1.5-2.6 in western Texas. If one were to try to link diet to these data, one would predict a Scandinavian, high-animal product diet in the northeast, and the Southeast Asian, high-carbohydrate, high-vegetable product diet in the southwest. As anyone knows who has traveled much, this just isn't the case.

Sunlight, vitamin D, and colorectal cancer

More than two decades ago, Garland and Garland [1980] first suggested that sunlight, through the production of vitamin D, could explain the geographic distribution of colon cancer mortality rates in the U.S. They also showed that people who had higher levels of serum 25-hydroxyvitamin D (25(OH)D), the circulating metabolite of vitamin D, 10-20 years prior to the study had lower rates of colon cancer [Garland et al., 1989]. Their ecologic study has been confirmed in a number of subsequent studies [Freedman et al., 2002; Grant, 2002b; Grant submitted]. To approximate UVB radiation (290-315 nm), the data for July 1992 obtained using the Total Ozone Mapping Spectrometer (TOMS) [Herman et al., 1999] were used in ecologic studies by Grant [2002b; submitted]. In the most recent study [Grant, submitted], a number of factors were added to the analysis such as degree of urbanization, lung cancer as an index for smoking, the fraction of white Americans with Hispanic heritage, and the fraction of those living below the poverty level, all state-averaged values. The results for the period 1970-94 are given in Tables 1 and 2. UVB had the strongest (inverse) association with both colon and rectal cancer in general, with degree of urbanization being an important risk factor for males. Six types of cancer (breast, colon, endometrial, esophageal, ovarian, and non-Hodgkin's lymphoma) were inversely correlated to solar UVB radiation and rural residence in combination. Thus, living in an urban region is considered an additional risk factor due to reduced exposure to solar UVB radiation. Those who live in urban regions spend more time indoors than those living in rural regions, and even when they are outside, tall buildings block direct sunlight. Smoking is also a risk factor for colorectal cancer, as supported by other papers in the literature [Terry et al., 2001; Giovannucci, 2002]. It is also interesting that a recent study in North Carolina did not find any dietary or other factors to explain why colon cancer rates are much higher for African-Americans than for white Americans; however, the study did not consider racial differences in absorption of UVB or serum vitamin D levels [Satia-Abouta et al., 2003].

Table 1. Regression results for cancer mortality rates, 1970-94, for white Americans in the 48 contiguous states plus DC. The fraction of the variance explained by each factor is approximately proportional to the adjusted r^2 times

t² divided by the sum of the t².

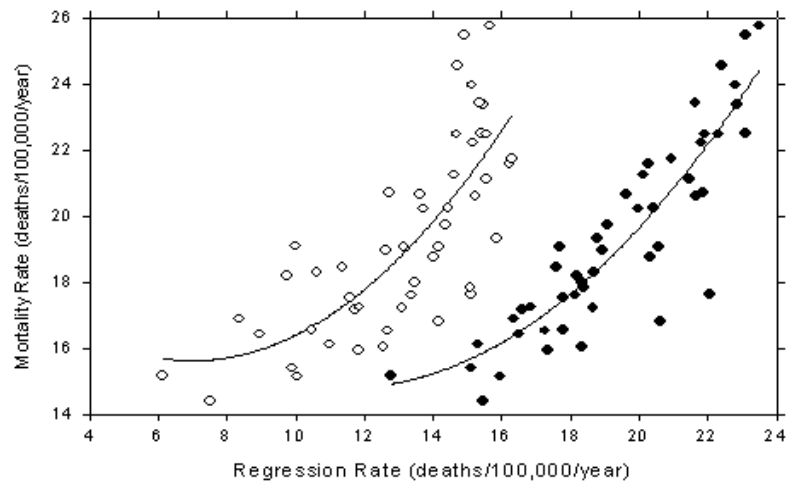
Cancer	Sex	Adjusted r ² , F, *	1 st Term (t, p)	2 nd Term (t, p)	3 rd Term (t, p)	4 th Term (t, p)
Colon	M	0.73, 44	UVB -10.3, *	Urban 6.7, *	LungCanM 4.1, *	
	F	0.59, 24	UVB -6.8, *	LungCanF 2.7, 0.009	Poverty -2.1, 0.039	
Rectal	M	0.76, 39	UVB -10.2, *	Hispanic 4.9, *	Poverty -4.3, *	LungCanM 3.0, 0.005
	F	0.60, 25 fail CV	UVB -6.4, *	Poverty -3.5, 0.001	Hispanic 2.8, 0.008	

Table 2. Multivariate regression results for cancer mortality rates for African-Americans. Terms and abbreviations are as in Table 1.

Cancer Site	Sex	n, adj. r ² , F, p	1 st Term (t, p)	2 nd Term (t, p)	3 rd Term (t, p)	4 th Term (t, p)
Colon	M	41, 0.41, 10, *	UVB -2.7, 0.011	Urban 2.4, 0.024	LungCanM 1.9, 0.063	
	F	41, 0.46, 36, *	LungCanF 6.0, *			
Rectal	M	38, 0.37, 8.1, *	Urban 2.5, 0.016	UVB -2.0, 0.051	LungCanM 2.0, 0.058	
	F	32, 0.20, 8.6, 0.006	UVB -2.9, 0.006			

Figure 2. Colon cancer mortality rates for white males in the U.S., 1970-94 vs. a regression based on UVB, degree of urbanization, smoking, and poverty level.

Colon Cancer Mortality Rates for Males, 1970-94, vs. a Regression Based on UVB, Urbanization, Lung Cancer, and Poverty (dots) and with Degree of Urbanization Set Equal to Zero (circles)



Despite the strong evidence that UVB reduces the risk of colorectal cancer, the other epidemiologic data are not as strong. Part of the reason for this is that many of the case-control and cohort studies, which are the models preferred by the health community, have considered only dietary vitamin D. Of the 11 cohort studies of dietary vitamin D and colon, rectal, or colorectal cancer, only 1 [Garland et al., 1985] found a statistically significant risk reduction associated with dietary vitamin D ($p < 0.05$). For case-control studies, only 1 of 6 studies found a statistically significant risk reduction associated with dietary vitamin D [LaVeccia et al., 1997]. However, when total ingested vitamin D (diet plus supplements) was considered, most studies found a significant risk reduction (Table 3).

Table 3. Studies of total ingested vitamin D (diet and supplements) and colon, rectal or colorectal cancer [Grant and Garland, in press].

Outcome	Type of Study, Location	Vitamin D Range (IU/day)	Study Period (years)	OR or RR* Highest to lowest, with 95% C.I.	P for Trend	Reference
Colon cancer	Cohort, Iowa, USA	<159 - >618 (quintiles)	4	RR = 0.54 (0.35-0.84)	0.02	Bostick et al., 1993
Colon cancer	Cohort, USA	<161 - >613 (quintiles)	6	RR = 0.66 (0.42-1.05)	0.02	Kearney et al., 1996
Colorectal cancer	Cohort, USA	<120 - >550 (septiles)	12	RR = 0.42 (0.19-0.91)	0.04	Martinez et al., 1996
Rectal cancer	Cohort, postmenopausal women, Iowa	<224 - >476 (tertiles)	7	RR = 0.76 (0.50-1.16)	0.20 (F)	Zheng et al., 1998
Colorectal cancer	Cohort, USA	<110 - >525 (quintiles)	5	RR = 0.71 (0.51-0.98) (M) 1.00 (0.68-	0.02 (M) 0.62 (F)	McCullough et al., 2003

				1.47) (F)		
Colon cancer	Case-control, Wisconsin, USA	<148->557 (quintiles)	--	OR = 0.7 (0.4-1.1)	0.05	Marcus et al., 1998
Colon cancer	Case-control, N. Calif., Minn., Utah	Supplements Never vs. ever	--	OR = 0.5 (0.2-1.1) (M) 0.6 (0.4-1.1) (F)	0.01 (M) 0.21 (F)	Kampman et al., 2000

*Odds ratio (OR) or relative risk (RR), highest compared to lowest group. 95% confidence limits are provided when available; M = males; F = females

The evidence for UVB and vitamin D as risk reduction factors for colorectal cancer is tabulated in Table 4. The criteria for causality in a biological system were used in making the determination. These criteria were originally proposed in a somewhat different form as postulates by Koch in the 19th century when he was making the case that bacteria were the cause of tuberculosis [Ligon, 2002]. Hill [1965] codified them in modern form, and they have been prioritized more recently [Potischman and Weed, 1999; Weed, 2000]. As can be seen, different approaches have different levels of confidence in whether the association can be considered causal, but when taken together, the case for the risk reduction role of vitamin D is unmistakable (see Table 4).

Table 4. Evaluation of the various approaches for determining the effect of UVB and vitamin D on colorectal cancer based on Hill's criteria for causality [Hill, 1965] [Grant and Garland, in press].

Factor Approach:	Strength	Consistency	Biologic Gradient	Biologic Plausibility	Temporality	Confounding Factors Included	Analogy
Ecologic	High	High	High	High	High	High	High
In Vitro	High	High	High	High	High	High	High
Cohort Diet	Low	Low	Low	Medium	High	Low	Medium
Diet plus Supplements	High	High	High	High	High	Medium	Medium
CC* Diet	High	High	High	High	High	Medium	High
CC: Diet, Supplements	High	High	High	High	High	Medium	High
CC: Serum	Medium	Medium	Medium	High	High	Medium	High
Summary	High	High	High	High	High	High	High

* CC = case-control

The mechanisms whereby vitamin D reduces the risk of colorectal cancer are well known. These mechanisms include increasing the absorption of calcium (for colorectal cancer) [Lamprecht and Lipkin, 2003], attenuating growth signals and metastasis, inducing cell death (apoptosis) and cell differentiation, and reducing the sprouting of blood vessels (a requirement for tumor growth) [Holt et al., 2002; van den Bemd and Chang, 2002].

Colorectal cancer is considered an epithelial cancer. Epithelia are the cell layers that cover all internal and external surfaces of the body. These cell layers can support rapid growth, and are most often the cells involved in cancers of all organs. UVB, through the production of vitamin D, has been identified as a risk reduction factor for 14 types of epithelial cancers [Grant, 2002b; Grant, submitted].

It should also be noted that colorectal cancer has a long incubation period, approximately 20 years. As the Japanese diet changed from the traditional high-fiber, low-fat one in 1947 to a more Western low-fiber, high-fat diet by 1963, a time lag of 23 years was identified between dietary changes and increased colon cancer mortality [Tsuji et al., 1996]. Cancer goes through lengthy initiation and development stages before it is detected [Weisburger, 1997; 2000].

Conclusions

In summary, colorectal cancer risk is related to diet, with animal products, especially meat, animal fat, and sugar as high risk factors. Alcohol consumption, smoking, and lack of exercise also contribute. Vegetable products, especially high-fiber ones, and calcium are generally risk reduction factors. UVB and vitamin D are also important risk reduction factors. Table 5 summarizes the information available in the literature regarding the risk and risk reduction factors for colorectal cancer. For optimal protection against colorectal cancer, one should adopt a diet and lifestyle that minimize the risk factors and maximize the risk reduction factors, consistent with other goals and objectives.

Table 5. A summary of risk and risk reduction factors for colorectal, colon, and/or rectal cancer and colorectal adenomas along with estimates of the degree of risk or protection.

Factor	Mechanism	Hazard Ratio (HR) Odds Ratio (OR) Risk Ratio (RR)	Reference
Risk		(larger numbers mean more risk)	
Animal product energy/total energy	Insulin-like growth factor-I	RR = 6-10	Grant, 1999 Giovannucci, 2001
Dietary glycemic load		RR = 2.85	Higginbotham et al., 2004
Non-prudent diet (prudent diet is high in fruits, vegetables, whole grains, fish and poultry)		OR = 2.8	Slattery et al., 2003b
Smoking		RR = 1.9 for >20 cigarettes/day vs. none for those <50 years of age	Colangelo et al., 2004
Overweight	Insulin, insulin-like growth factor-I	RR = 1.9 for males, 1.2 for females with BMI >32.5 vs. BMI 22 - 23.5	Murphy et al., 2000
Refined cereals	Insulin	OR = 1.5 for	Slattery et al.,

and grains		amounts in tertiles	1997b Chatenoud et al., 1999
Risk reduction		(smaller numbers mean less risk)	
Allium family vegetables (garlic, onions, leeks)	Sulfur compounds are anticarcinogenic	OR = 0.32	Levi et al., 1999 Knowles and Milner, 2001
Vitamin D	Attenuate tumor growth signals, induce cell differentiation, death, reduce angiogenesis, increase calcium absorption	RR = 0.4 for max UVB in U.S., rural residence	Van den Bermd and Chang, 2002; Lamprecht and Lipkin, 2003 Grant, submitted
Aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs)	Reduction in inflammation? (side effects include GI tract bleeding)	RR = 0.49 for adenomas for >14 tablets/week OR = 0.66 for use of NSAIDs	van Leerdam et al., 2003; Lieberman et al., 2003 Chan et al., 2004
Fiber		OR = 0.5	Slattery et al., 1997b
Legumes (beans)		RR = 0.53 for >2 times/week vs. <1 time/week	Singh and Fraser, 1998
Exercise	Plausible: changes in endogenous sexual & metabolic hormone levels & growth factors, decreased obesity & central adiposity, possibly changes in immune function	OR = 0.55-0.60 for vigorous exercise	Friedenreich and Orenstein, 2002 Slattery et al., 2003
Rural vs. urban residence	UVB/vitamin D production	RR = 0.6	Grant, submitted
Folate	suppress the development of tumors	OR = 0.6	Harnack et al., 2002 Kim, 2003 Crott et al., 2004
Fish	n-3 oils reduce inflammation	OR = 0.6-0.7 for frequent consumption	Yang et al., 2003
Whole grains	Antioxidant properties of phytochemicals	OR = 0.6 OR = 0.85	Slattery et al., 1997b Levi et al., 1999 Adom and Liu, 2002
UVB irradiance in U.S.	Vitamin D production	RR = 0.64	Grant, 2002b; Grant, submitted
Hormone replacement		RR = 0.67 for current; = 0.92 for	Nanda et al., 1999

therapy		ever use	
Calcium	Inhibits dietary haem-induced colonic cytotoxicity and epithelial hyperproliferation	OR = 0.65 for distal colon cancer, >1.25 vs. <0.5 g/day	Sesink et al., 2001 Wu et al., 2002 Lamprecht and Lipkin, 2003
Vegetables		OR = 0.7 for higher intake	Slattery et al., 1997b
Calcium		OR = 0.74 for 1.2 g/day	Lamprecht and Lipkin, 2003 Weingarten et al., 2004
Vegetarian diet		RR = 0.85 in U.K. vs. non-vegetarian	Sanjoaquin et al., 2004

While the risk and risk reduction factors discussed here are the findings of observational studies, and are likely generally correct, they have not necessarily been accepted or endorsed by the health community. Once they think the observational evidence is strong enough, they like to do carefully controlled double blind cross over studies to make sure that there is a causal relationship. Some observational studies, such as that finding that women who used hormone replacement therapy (HRT) after menopause, generally had better health habits, which was overlooked in the earlier studies. However, it was realized in more recent studies that the risk factors for various diseases such as breast cancer and strokes from HRT outweighed any long-term health advantages [Chlebowski et al., 2003; Rossouw et al., 2003; Wassertheil-Smoller et al., 2003], although HRT is still used by women trying to reduce menopausal symptoms. Therefore, anyone considering changing his or her diet or lifestyle in order to reduce the risk of colorectal cancer, or any other disease for that matter, should read the referenced papers as well as others that can be found for example at PubMed by clicking the “related articles” button associated with the reference paper. Note that it can take decades for the health system to fully accept and endorse new scientific methods, and that the American health care system is much more interested in secondary (examinations and prescription drugs) and tertiary (surgery and chemotherapy) prevention approaches than primary (diet and lifestyle), so it does behoove people to be more proactive in protecting their own health and well being.

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(Note – abstracts for most of these papers can be found at PubMed:
<http://www.ncbi.nlm.nih.gov/pubmed/>)

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