
1: Does lifestyle cause colorectal cancer?

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Introduction

Can lifestyle cause colorectal cancer (CRC)? To answer this it is best first to get an idea of the magnitude of the risk.

Suppose you wanted to get CRC, not by rechoosing your parents and therefore opting to be born with a genetic defect that might make the likelihood of getting cancer as high as 50%, but exclusively through diet/lifestyle alteration or toxic exposure after birth. Could you do it? Not with very much reliability, not even by moving to the highest risk locale, with a population with habits that maximize the chances of getting CRC, whatever they might be. This would only result in a probability of getting the disease of maybe 5–7% and even that in your dotage [1]. These are not very good odds if you are a betting man.

Well, perhaps there is a bit more that you could do, such as burdening yourself with a few chronic illnesses, like inflammatory bowel disease. The risk of cancer is certainly increased here but mostly at a younger age. But no one knows how to contract ulcerative colitis or Crohn's disease, and chronic infectious enteritides have not been reliably connected with cancer risk [2].

The risk of anal cancer can certainly be augmented by lifestyle decisions. Neglected chronic perianal disease, such as hemorrhoids, fissure, and fistula, and acquisition of sexually transmitted disease, especially related to human papilloma virus, can greatly increase the risk of anal cancer over the general population, perhaps as much as 10-fold for some factors [3]. But this type of cancer is much rarer than more proximal colon and rectal cancer, so even this great augmentation would not have a large overall effect on the chances of getting combined colorectal and anal cancer. No matter what you do, the chances are quite strong that you will never get CRC in your lifetime – better than 90%.

Okay, let's be a bit more realistic. You've seen enough CRC in your life and you want to minimize the risk of ever getting it, or of any of your loved ones ever getting it. First of all, how early is the die cast – again limiting our discussion to average risk individuals? Modification of risk in people with obvious familial syndromes has little to do with lifestyle – except for the role screening has in one's style of life. But more about that later. And, since inflammatory bowel disease tends to cluster in families, for whatever reason, screening may have an enhanced role here as well. But when you can or should do something about your life is an important point. For instance, it seems that risk is determined at quite an early age for breast cancer. This adds a new facet to parental responsibility, with the uncertainty of effect decades away. If there is going to be any good news in this discussion, it is that CRC risk seems to be determined at a much older age than with breast cancer or gastric cancer. So it may be possible to change one's ways at an age when motivation is there to do so, compared with an adolescent [4].

So, more fiber, less fat, and don't get constipated, right? Well, maybe. But the trouble is that, though there is some experimental evidence that these factors might diminish risk, what is needed to achieve a material change in the incidence of CRC through public health intervention is evidence that these or other recommendations actually work in the real world. And that is where things get interesting.

Since the establishment of the SEER (Surveillance, Epidemiology and End Results) program in 1973 by the National Cancer Institute in the United States, there has been a continual decline in CRC *mortality* in the United States. During much of the same period, however, CRC *incidence* rose rapidly [1]. In addition, underdeveloped countries, which once had vanishingly small rates of CRC, and whose lifestyles we hoped, in some degree, to emulate in order to reduce CRC incidence, were playing a rapid game of catch-up in CRC. Whereas there was in 1978 a 50-fold difference between mortality in high-risk and lowest-risk countries, by 1992 this had narrowed to only a 12-fold difference [5,6].

Numerous case/control and cohort studies generated apparently useful hypotheses for CRC prevention [7]. But, what had been conspicuous in its absence was any natural population in which CRC incidence had declined. It seemed that only social cataclysm could create such a population; that is, a rising risk of CRC was an inevitable result of peace and prosperity. Yet such a population did appear where it was least expected, in the United States. SEER reported that the rapidly rising incidence of CRC in the United

States suddenly reversed in 1986 and incidence has declined since then at a rate greater than 1% per year up to 2002 [1].

It seems reasonable to suppose that this sudden reversal of incidence, after a long period of rising risk, was preceded by a change in exposure to one or more environmental factors. Investigation of the evolution of suspected risk factors for CRC before and during this period of declining incidence offers a very different and unique perspective in the determination of causation and prevention of CRC. The precise time period of greatest interest in this investigation is uncertain, since there is considerable lag time between exposure to a risk modifier and clinical onset of CRC, but it might be assumed to be anywhere from 5 to 15 years before 1986. Fortunately it is in this period, from 1970 to 1980, in which data became available to allow trending of most risk factors in the United States.

Presented herein first is therefore an analysis of the pattern of change in CRC incidence by anatomic subsite, gender, and race, then a time-trend analysis of exposure to all suspected risk factors for CRC in the United States from 1970 to 1986. This broad focus is necessary because no proven paradigm of CRC prevention yet exists despite 50 years of intensive research. Therefore it would be premature to exclude any risk factor from consideration for being responsible for the declining incidence of CRC in the United States. Finally a summary of the randomized trials of diet interventions will be presented – the natural and necessary next steps to establish the effectiveness of a change in lifestyle in CRC prevention. Some of these trials investigated only single components and others attempted to diminish risk by a more global dietary change.

Incidence and dietary trends

The incidence of CRC is shown over the period from 1973 to 1994 in Figs 1.1 and 1.2. The colorectum is divided anatomically in those graphs into proximal (cecum, ascending, transverse, and descending) and distal (sigmoid and rectum) colorectum. This anatomic division of the colorectum was as a result of an analysis of race, gender, and age issues in CRC subsite location [8]. In that work, it became apparent that grouping the sigmoid, rectosigmoid, and rectum together as distal and all tumors proximal to that as proximal was a more rational point of division than the traditional division of the large bowel into colon and rectum (with further subdivision into the right and left colon). Pathologic misclassification became less likely than when for instance tumors had to be classified as either rectal or recto-sigmoid (a left

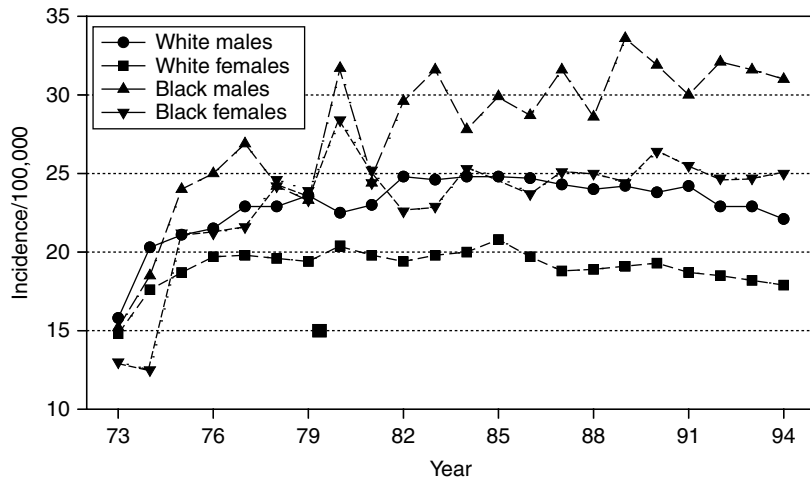


Fig. 1.1 SEER age adjusted proximal colon cancer incidence: 1973–94. Proximal colon extends from the cecum to the junction of the descending and sigmoid colon. (Reproduced from Nelson RL *et al. Dis Colon Rectum* 1999; 42: 741–52, with permission from Springer-Verlag.)

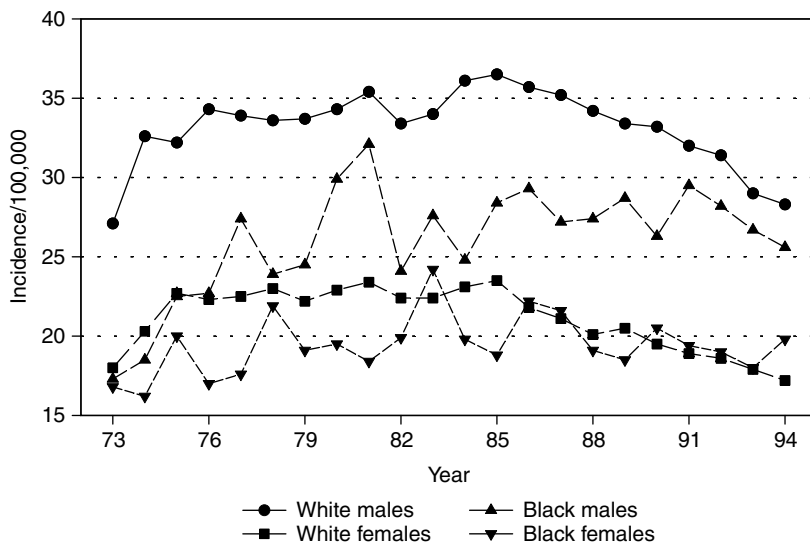


Fig. 1.2 SEER age adjusted distal CRC incidence: 1973–94. Distal colorectum includes the sigmoid, rectosigmoid, and rectum above the anorectal ring. (Reproduced from Nelson RL *et al. Dis Colon Rectum* 1999; 42: 741–52, with permission from Springer-Verlag.)

colon subsite) [9]. The division is more rational on embryologic (division is made at the border of the midgut and hindgut), physiologic, and anatomic grounds.

As mentioned earlier, the incidence of CRC began to decline in 1986 and has continued to drop ever since. The decline in age adjusted incidence of cancer is 24% in the distal colorectum in white men, 26% in the distal colorectum in white women, 12% in the proximal colon in white men and 14% in the proximal colon in white women. Rates among blacks are more variable from year to year but show no consistent pattern of decline in SEER, with an increase in the proximal colon in both genders, but especially in men, since 1986. Thus the decline in incidence is most apparent in both white men and white women in the distal colorectum. The lifestyle factor that had changed the most but was also gender neutral and race specific was therefore the one most likely to be associated with the sudden decline in CRC incidence.

Energy related factors. Though dietary fat has long been suspected to be the major risk factor for CRC, the time-trend data do not support this association in any aspect of energy measurement: fat intake, energy intake, obesity, physical activity, or serum cholesterol. Americans eat about the same amount of fat, exercise less, and weigh more than they did in 1970 [4].

Alcoholic beverages. National Health and Nutrition Examination Survey (NHANES) data show a decrease in ethanol intake in men. World Health Organization data show however an increase in all forms of alcoholic beverage intake [10], including the form most associated with distal CRC, beer [4]. It is interesting to note that the method of manufacture of beer in many breweries generated very high concentrations of nitrosamines, up to 50 times that found in smoked meats. The discovery of this and the delineation of the specific step in the brewing process responsible for these nitrosamines resulted in an industry-wide modification of their procedures in 1980 and the subsequent near disappearance of nitrosamines from all commercial beers [11]. But this is not a gender neutral and race-specific risk factor.

Dietary fiber and related measures. Changes in definition of fiber and instruments that measure fiber intake have made this among the most difficult dietary items to trend over time. Quantitative estimates of changes in fiber intake therefore may not be very precise but the trend appears to be upward in consumption in NHANES, though less so in the National Food Consumption Survey (see Table 1.1). Surrogates of fiber intake

Table 1.1 Time trends of non-energy related risk factors for CRC.

Risk factor	Time period	Data source	Direction + or -
Alcoholic beverages	1960-85	World Health Organization: US Consumption	+54% +61% beer +43% spirits +426% wine
	1971-88	NHANES	-10% men +28% women
Iron intake	1971-88	NHANES	+22% men +27% women
Body iron stores	1971-88	NHANES	-7.8%
Calcium intake	1971-88	NHANES	+0.5%
Constipation	1958-86	NDTI	-33%
Dietary fiber	1976-88	NHANES	+29%
Cholecystectomy	1972-90	US Hospital Discharge Survey	-1.5%
Vitamin A	1971-88	NHANES	+8%
Vitamin C	1971-88	NHANES	+18%
Parity	1960-88	NSFG	-33%
Oral contraception	1971-80	NHANES	-2%
Postmenopausal estrogen	1980-85	Ambulatory Care Survey	+22%
Cigarettes	1950-91	National Cancer Inst.	-60%
Polypectomy	1970-93	HCFA & Wisc. Hospital Assoc.	+ from negligible to >830,000 indiv.
Aspirin	1985-90	Minnesota Heart	+300%
General diet score	1965-90	National Food Consumption Survey	-10.5% (improved) (see text)

NHANES, National Health and Nutrition Examination Survey; NDTI, National Disease and Therapeutic Index; NSFG, National Survey of Family Growth; HCFA, Health Cost Finance Administration. (Reproduced from Nelson RL *et al. Dis Colon Rectum* 1999; 42: 741-52, with permission from Springer-Verlag.)

described below may more accurately reflect the trend in fiber consumption. These include constipation, vitamin A and C intake, and a combination of iron intake and body iron stores (which if diminished, imply chelation of oral iron by fiber-related phytic acid). Each of these suggest an increase in fiber ingestion from 1970 to 1985. On the other hand, data from the National Food Consumption Surveys, which report specific food groups, show an increase in these foods only in higher socioeconomic classes of both blacks and whites from 1965 to 1991. In addition there is little difference between blacks and whites in the trend for the foods, though throughout the study period whites had slightly higher fruit and vegetable (but not fiber) consumption. Neither fiber nor anti-oxidant

vitamins have been associated previously with protection against specific CRC subsites.

Calcium. There seems to have been little change in dietary calcium intake over the study period. The number of people ingesting calcium supplements is however large, though skewed towards female gender. The randomized trials of calcium (see below) are more informative.

Estrogen. Parity has declined, oral contraception use has changed very little, and the use of postmenopausal estrogen has increased and then recently again declined. Again, the randomized trials described below have been more informative for this factor, which is hardly gender neutral.

Aspirin. Chronic aspirin use for the disease prophylaxis, either coronary or neoplastic, has been difficult to track before 1985, though it is unlikely to have been prominent before that date. Aspirin use may, therefore, be a cause for further decline in CRC incidence in the future, though mostly in men, since they are the principal consumers of aspirin for prophylaxis. Even if aspirin-induced bleeding resulted in polypectomy, the effect on CRC incidence should only become apparent about now (see below).

Cigarettes. Cigarette use has been consistently associated with benign colorectal adenoma risk and only recently in a study for CRC risk as well. The use of cigarettes has declined progressively in all age/race/gender cohorts in the United States since 1951.

Cholecystectomy. Cholecystectomy has been extensively investigated as a risk factor for CRC and may increase risk of proximal CRC many years after the operation [12]. The rate of cholecystectomy in the United States dropped less than 1% between 1972 (212/100,000) and 1980 (211/100,000) in data from the Hospital Discharge Survey of the National Center for Health Statistics (NCHS). From 1972 to 1990 (209/100,000) the rate dropped 1.5% [13]. In Sweden, from 1970 to 1980 the rate of cholecystectomy dropped by 25% [14].

Polypectomy. Polypectomy has grown from an occasional procedure in 1970, performed either through a rigid proctoscope or through colectomy (a huge intervention when the adenoma–carcinoma sequence was still controversial) to one performed upon almost one million individuals in the United States in 1993. It has been estimated that risk of CRC could be reduced by 70% by polypectomy [15]. If there is a 10-year lag time from polyp detection to cancer formation, which is a broadly accepted conservative estimate [16], then the rapid growth of polypectomy would be first seen in reduced CRC incidence around the mid-1980s. The National Polyp Study demonstrated that colonoscopy was most effective in preventing distal

CRC [17], which fits with SEER data (Figs 1.1 and 1.2). If population-based data could show that both white genders have had equal exposure to colonoscopy and blacks have had less access than whites to polypectomy, and even if the 70% risk reduction for CRC is wildly optimistic, polypectomy may be the most likely explanation for the declining incidence of CRC.

Indirect evidence in support of less access to polypectomy among blacks and equal access in white genders can be found in SEER CRC stage data in which whites of both genders had discovery of CRC at an earlier stage than blacks. This implies that discovery was more likely to have been made during screening of asymptomatic individuals, the same type of individuals who would be getting polypectomy.

Summary of observational epidemiology

Because this time trend review does not contain a specific experiment in a defined cohort, it might seem that the findings carry less weight than would such an experiment. However the individual findings of this report in most cases carry the weight of being derived from populations and data weightings that make them more representative of the entire American population than any other available data. Any degree of direction of change in exposure over time is therefore significant. Time trending also is a powerful tool in the determination of disease causation, especially when the trending covers a disease that has undergone such an abrupt change in incidence as CRC has in the mid-1980s. These analyses therefore have important implications related to screening for CRC. The apparent success of polypectomy in reducing CRC incidence in the general population suggests that cancer control might be more effectively achieved if the emphasis in screening would shift towards technologies that are effective in detecting adenomas [18].

Most importantly, the feasibility of incidence reduction has also been established and should encourage further attempts to accelerate this through primary prevention. Increased fiber consumption and changes in alcoholic beverages may already have played a role in this reduction and current trends in the use of estrogen, aspirin, and calcium and may accelerate this decline in CRC risk over the next decade. Altered caloric balance (eating less fat and more exercise), so heavily emphasized in recent reports, is apparently more difficult to achieve in this society than CRC reduction [4].

Randomized clinical trials in risk modification and prevention

Vegetable *fiber* has been assessed in at least four randomized clinical trials [19–23]. Amongst these trials, none so far have shown a diminished risk of adenoma recurrence with increased fiber consumption. Indeed one large trial actually showed an increased risk in the high fiber group that quite alarmed its investigators [23]. Does this translate into increased cancer risk with dietary fiber? There is statistical evidence presented below which would argue against this, and decades of observational epidemiology would be negated by such a conclusion.

Dietary *calcium* was also hoped to be a significant contributor to risk reduction and has been looked at in two relatively large trials and two much smaller cancer-prone groups, that is, individuals either with familial adenomatous polyposis or hereditary non-polyposis CRC. Similar to the results regarding dietary fiber, none of these intervention trials has shown a protective effect related to calcium [19,23–26].

Two trials, one in Australia and one in the United States, assessed more *global dietary change*, feeling that no single dietary component would obtain significant protection [19,20]. Both of these trials have unfortunately shown no benefit to a program that increased fiber, fruits, vegetable, and beta carotene and decreased fat intake. The resolution of these disappointing results with prior descriptive epidemiology, which had suggested significant dietary modification of colon cancer risk, has not been achieved.

On the other hand, several items have emerged as significant, though modest, risk modifiers in randomized trials. One is *selenium* status in the Polyp Prevention Trial [27]. Another pharmacologic intervention that appears to provide benefit in randomized controlled trials is supplementation or ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) [28]. This has been demonstrated both in cancer-prone individuals, that is, individuals with hereditary polyposis, and in the randomized trials amongst intermediate-risk individuals with prior histories of either cancer or adenoma, looking at adenoma recurrence. Unlike hormone replacement therapy (HRT) in women, in whom significant harmful effects of HRT may have been found, there seems to be little risk of harm in low-dose NSAID ingestion.

These trials did not use CRC as an end point of effect, but adenoma recurrence. This was chosen for several reasons. First is that it occurs soon enough and frequently enough to make these randomized trials economically feasible. It also, being a non-lethal surrogate for CRC, allays the ethical conundrum of allocation of study participants into a research arm that one

may feel could be deleterious, whether it is the intervention or the control. There is however no perfect correlation between either adenoma risk or adenoma recurrence risk and subsequent incidence of or mortality from CRC. Many patients with adenomas never get cancer. Yet, there is no other intermediate end point or usable study outcome measure that correlates as well with cancer risk as this. The suitability of this as a surrogate for population-wide reduction in CRC risk must be called into question because of the failure of these trials. Cogent statistical arguments against the use of even more perfect surrogate end points have been raised [29]. Also, the use of high-risk groups in dietary intervention trials as economic surrogates for the general population has been shown to be unwise [30].

Hormone replacement therapy, that is, postmenopausal estrogen either opposed or unopposed by progestin [31], is unique amongst these randomized intervention trials, using colon cancer as an end point. Despite some of the alarming effects noted in the Women's Health Initiative related to estrogen supplementation, there still remains one significant health benefit to HRT in addition to reduction of osteoporosis and postmenopausal symptoms, and that is the diminished risk of CRC.

Analyses of more recent novel risk factors in non-randomized trials

Novel risk factors have also been sought with interesting though preliminary data. None of these have yet achieved significant enough evidence to rationalize their assessment in randomized trials. One of the most thoroughly investigated is *iron* status, either measured as dietary iron intake, body iron stores, or as genetic carriers of a disease known to increase iron exposure, hereditary hemochromatosis. The *hemochromatosis* population is the most interesting of these because it is, first of all, the most prevalent genetic disease in the United States. Second, evidence of increased risk of cancer or adenoma in this population bypasses some of the biases inherent to etiologic studies in observational epidemiology, almost giving the strength of randomized trials. Several trials have shown a positive association even in hemochromatosis heterozygosity and colorectal neoplastic risk [32,33].

Dietary *magnesium* has recently been found to be a significant protective factor in women for colon tumors [34] and *black tea* has not [35]. No relation has been found in a meta-analysis of prior *gastric surgery* and CRC risk [36]. Looking at what is perhaps this country's most prevalent disease, *obesity*, there is also a significant risk for CRC amongst these individuals, especially

in men [37]. In a loosely related vein, cholesterol lowering with *statins* may have the added advantage of diminishing CRC incidence as well [38]. This comes from a case/control study; no randomized trials of statin use have reported this as yet. *C reactive protein* has received much recent publicity as a marker of heart disease risk and it has similarly been found to correlate with colon cancer risk [39].

So, in summary, what is the most important lifestyle decision one can make to avoid getting CRC?

Get screened. There is no dietary practice that comes close to the effectiveness of this measure in disease prevention [4]. Eating healthy, being active, staying slim may help and will certainly make each day more enjoyable. Adding aspirin, a statin, or estrogen if you dare may have an incremental effect but always at some cost [40].

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