Assessing the Potential Benefits of the Colorectal Cancer Program

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Colorectal Cancer

In his 1971 State of the Union address, President Nixon promised to ask Congress for funds for an "intensive campaign to find a cure for cancer" and asked for a commitment for "conquering this dread disease". This led to a large increase in budget for the National Cancer Institute, and the identification of the research effort with a "War on Cancer", a concept developed by the American Cancer Society and its predecessors. In the ensuing years, progress has been made in "defeating" cancer. But cures for cancer remain illusive; there has been progress in three areas: understanding the behavioral and environmental causes of cancer leading to prevention, developing screening tests leading to earlier diagnosis, and improved therapy.(1) For many cancers, including colorectal cancer, the greatest gains have come from prevention. The decline in smoking is the leading example here, but with colorectal cancer, prevention primarily has been through screening.(2) Most colorectal cancers arise out of polyps that grow on the walls of the colon or rectum. Screening can detect and remove these polyps before they become cancerous. Screening also leads to early detection of cancer, and since the standard treatment for early colorectal cancer is surgery, early detection leads to surgery when tumors and smaller and the surgery is more successful. Acceptance of colorectal cancer screening, however, has come slowly.

The most widely used screening methods are fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy. The most effective form of the FOBT is one in which individuals at home collect two or three stool samples and place a smear of stool on a special paper that is then sent to a lab for analysis. The analysis looks for blood in the stool. Sigmoidoscopy and colonoscopy are done in a health care facility, usually by a doctor, but sometimes by skilled technicians. The doctor inserts a flexible instrument with a camera into one's rectum. Through this instrument the doctor can inspect the walls of the rectum and colon. The differences between sigmoidoscopy and colonoscopy are in the preparation for the test and in how much of the colon is examined. For sigmoidoscopy you may be asked to alter your diet before the test and usually you will clean out your colon with an enema before the exam. During the exam the rectum and lower portion of the colon are inspected. For colonoscopy the preparation is more extreme, people have to alter their diets for 3 or 4 days and then clean out their colons with laxatives and enemas, and the examination covers the entire colon. Obviously, these screening tests are rather burdensome. As a result, the proportion of the population participating in screening is low, about 64 percent.(3)

The U.S. Preventive Services Task Force recommends that people aged 50 to 75 years have a FOBT every year, or sigmoidoscopy every 5 years with a FOBT every 3 years, or a colonoscopy every 10 years.(4) The American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology make a similar recommendation.(5) Compared to sigmoidoscopy and colonoscopy, FOBTs are inexpensive, but they are less sensitive, that is less likely to detect a

cancer. Sensitivity of FOBT has been variously reported to be between 36 and 79 percent for the best tests properly administered.(6) Even lower rates have been reported when the testing procedures are not optimal. It is both because the FOBT is less sensitive and because it detects cancer, not the polyps our of which cancer grows, that annual testing is recommended.(5) Sigmoidoscopy is 60 to 70 percent as sensitive at detecting cancer as colonoscopy, and colonoscopy in turn detects about 90 percent of the large adenomatous polyps out of which colorectal cancer develops.(5) Thus, although these screening tests have been shown to reduce mortality from colorectal cancer, they are both burdensome and imperfect.

In calling for an "intensive campaign" Nixon compared the effort to find a cure for cancer to the efforts to split the atom and send a man to the moon. The goal of curing cancer has proved to be both more vague and more elusive and the effort thus more diffuse than in these other two programs. Perhaps Nixon was hoping for a breakthrough discovery. These have been rare, although advances in genomic science are transforming the effort. Still, they are possible. A recent article by a group of Japanese researchers reported that they followed up reports that dogs could be could be trained to identify breast and lung cancer patients by their breath with a study of colonoscopy patients.(7) They trained a dog that then correctly identified 33 out of 36 breath samples from colorectal cancer patients, 91 percent, when these were presented with 4 control samples. The dog did even better with watery stool samples, 37 out of 38 samples, or 97 percent. With breath samples the dog was about as good as a colonoscopy. With watery stool samples, he was much better. These results hold out the possibility that much less burdensome and less costly tests that would be much more accurate could be developed. Until these tests are developed, however, progress with colorectal cancer is made with incremental improvements.

Colorectal cancer background

Colorectal cancer arises in the cells that line the walls of the colon and rectum. Almost all of these cancers grow out of polyps, which are quite common in older people. But some colorectal cancer does not grow out of polyps; it occurs in people with genetic defects, which have only been partially described.(8) There are also some other rare kinds of colorectal cancers that together are about 2.5 percent of all cases.(9)

Colorectal cancer grows slowly. It is estimated that two-thirds of colorectal polyps have the potential to become cancers, but few do so. And, it takes over 5 years for large polyps and over 10 years for the smallest polyps to convert to cancer.(8) This is the basis for the recommended intervals for colorectal screening and the advantage of colonoscopy. In colonoscopy suspicious polyps can be removed, thus preventing the emergence of cancer. With FOBTs and sigmoidoscopy, if there are negative results, colonoscopy is recommended as a follow-up.(4, 5)

New cases of colorectal cancer are classified by the size of the tumor when it is surgically removed and whether or not the cancer has spread.(10) There are two systems for classifications. In a clinical system, small tumors that are confined within the wall of the colon or rectum are stage I. If the tumor has grown outside the wall but has not spread, it is stage II. The spreading of

cancer is determined by examining lymph nodes adjacent to the tumor. With colorectal cancer it is recommended that 12 nodes by removed and examined. If the cancer has spread to some lymph nodes, then it is classified stage III. If it has spread beyond the lymph nodes to other organs, such as the liver or lungs, than it is stage IV, or distant disease. For statistical purposes, cancer cases are staged as in situ, local, regional, and distal.(11) In situ means present only in the layer of cells in which it began. Local means the cancer is limited to the organ in which it began. Regional means the cancer has spread to nearby lymph nodes, organs or tissues. Distant means cancer has spread to distant organs or distant lymph nodes. A residual category, unstaged, is provided for cases for which there is not enough information to determine a stage. Although there are clear parallels between the clinical and statistical staging definitions at there are some overlaps so that there is not complete correspondence.

The significance of staging is that survival rates and costs vary dramatically by stage. Table 1 gives the distribution new cases of colorectal cancer, survival, and cost by two systems of staging. The basic principle is that the more local the cancer, the more successful, in terms of survival, surgical removal of the tumor is. This is the logic behind screening and early detection. Only 15 to 40 percent of colorectal cancers are discovered while they are still stage I or local when the treatment is most successful.

Table 1. Distribution of new cases, survival and cost of treating colorectal cancer			
Stage	Percent distribution of new cases (12)	Percent surviving 5 years (12), (11)	Average cost of treatment (13)
I	15	95	
II	36	82	
III	28	61	
IV	22	8	
Local	39	90	51,000
Regional	37	70	98,000
Distal	19	12	200,000
Unstaged	4	38	

Risk factors

The most significant risk factor for colorectal cancer is age. Among those in their early forties there are only 15 cases per hundred thousand. The rate rises so that for those in their early sixties there are 111 cases per hundred thousand, and for those in their early eighties 339 cases.(11) Only 13 percent of cases occur before age 55 and 70 percent occur at age 65 or older.(14) The lifetime risk is between 5 and 6 per cent.(15)

After age, the next most significant risk factor is family history. Persons with a first-degree relative, a parent or sibling, with colorectal cancer have

about twice the risk of getting colorectal cancer themselves as other people. Persons with more than one relative with colorectal cancer have even higher risk.(16) Family history is a crude measure of genetic susceptibility. The genetics of cancer is an area of intense research in which progress is being made, but the genetics of colorectal cancer is still largely to be worked out.(17) Perhaps 20 percent of all colorectal cancer patients have one or more close relatives who also have colorectal cancer, and about 5 percent of colorectal cancer patients have genetic mutations that are associated with the disease. (17)

Race/ethnicity and sex are lesser risk factors for colorectal cancer. Men have higher rates of colorectal cancer than women and African-Americans have higher rates than non-Hispanic whites. Hispanics have lower rates than non-Hispanic whites.(11)

Life-style also plays a role in colorectal cancer.(18) Persons with diets high in red meat, potatoes and refined grains appear to be at higher risk and persons with diets high in fruits and vegetables appear to be a lower risk of developing colorectal cancer.(19) Certain micro-nutrients may be important, too; some studies have shown that persons with low intakes of folic acid and calcium and vitamin D are at higher risk.(15, 20) Obesity appears to put one at increased risk; exercise lowers risk. Cigarette smoking and alcohol consumption may increase risk.(15)

Finally the incidence of colorectal cancer varies geographically. Some of this variation is associated with differences in the distribution of the population by age and race/ethnicity and regional differences in life-style factors such as diet, smoking and obesity. Some of it is undoubtably due to varying socio-economic conditions. At the individual level being screened for colorectal cancer is associated with higher education, higher income, and having health insurance coverage and a regular source of care,(21, 22) and education, poverty, and health insurance coverage all vary geographically. There are regional differences in health care systems, too, with differences in the rates at which physicians conform to the recommendations for screening for colorectal cancer in referring their patients or prescribing tests, which is a critical step in the process of getting people screened.(23)

Prevention with calcium supplements

The first study reviewed here is an observational follow-up to a clinical trial.(24) The clinical trial was designed to test whether or not calcium supplements were effective at preventing the occurrence of the adenomatous polyps out of which most colorectal cancers develop. Patients who had had at least one adenomatous polyp were recruited to the trial if they had had a screening colonoscopy show that they were free of polyps. Those who agreed to participate were randomly assigned to receive either a placebo or 1200 mg a day of calcium supplements. The treatment lasted, on average, 45 months. The result of the trial was that calcium reduced the rate of recurrence of adenomas in these patients. In this study the researchers extended the period of surveillance for the study participants to determine how long the effect lasted. They found that in the 5 years after treatment the effect was even stronger than during the trial, but that after 5 years the effect diminished, except among those who continued to take calcium supplements on their own.

To estimate the potential benefits of having all similar patients take calcium supplements, we begin by estimating in Table 2 how many similar patients there might be by estimating the number being screened for polyps and how many might have polyps. Screening rates and adenomas vary by age, so in Table 2 the population is estimated for 3 age groups. The youngest group is aged 50-59 years because it is recommended that persons first be screened at age 50. The oldest group is 70-80 years old because the recommendations are to stop screening after age 75.

The first column of Table 2 is population estimates from the US Census Bureau. The second column is derived from peoples' answers to questions in a population survey.(21) The third column is derived from a model projecting the effects of screening from colorectal cancer.(13) The last column is the estimated number of persons with an adenoma that would be found by screening. It is the result of multiplying the population in column 1 by the percents in columns 2 and 3 and also multiplying by 85 percent because not all adenomas are detected by screening. The total population with an adenoma, the sum of the estimates in the last column of Table 2, is 11,109,393.

Table 2. Estimating the number of persons with an adenoma				
Age group	2008 population(25)	Percent screened(21)	Percent with an adenoma	Population with an adenoma
50 - 59	40,075,636	49.7	18.1	3,064,321
60 - 69	26,451,418	66.7	27.6	4,139,070
70 - 80	17,347,678	71.4	37.1	3,906,001

The next step is to estimate how many of these people would benefit if they were to take the daily calcium supplements. In the research study the authors report that 31.5 percent of those who took calcium had a recurrence of polyps compared with 43.2 to percent of those in the trial control group.(24) That is an 11.7 percent difference and 11.7 percent of those with an adenoma is 1,299,799.

Because these people have already had an adenomatous polyp we can assume that they will be referred for screening, and if they were screened, that most of them would have their polyps removed. Referral, however, is not being screened and the compliance rate is surely less than 100%. Two studies suggest that surveillance rates after cancer surgery are no higher than screening rates,(26, 27) so, absent better estimates, we use surveillance rates to estimate how many of these people might have had polyps removed. The calculate is shown in Table 3. The last column of the table shows the estimated number of persons whose polyps would not have been removed because they did not have a surveillance colonoscopy; the total of this column is 472,303 people with polyps that might be prevented were all persons with adenomatous polyps removed to take calcium supplements, even taking into account that surveillance colonoscopy with polyp removal is an alternative method of prevention.

Table 3. Estimating the number of cancers prevented by calcium supplements				
Age group	Number with potentially prevented polyp	Rate of surveillance(2 1)	Number that would have been removed in screening	Number remaining
50 - 59	358,526	49.7	178,187	180,338
60 - 69	484,271	66.7	323,009	161,262
70 - 80	457,002	71.4	326,300	130,703

Adenomatous polyps are not cancer; large polyps become cancer at a rate of about 5 percent per year. This implies a rate of .7 percent of all polyps becoming cancerous each year. Seven-tenths percent of the total of the last column of Table 3 is 3,320 cases of cancer. If we assume that they are distributed as cancer cases are in general (see Table 1 and column 1 of Table 4), then the 3,320 cases are distributed as in column 2 of Table 3.

Table 4. Estimating the cost of treating cancers prevented by calcium supplements				
Stage	Percent distribution of cases	Distribution of cases	Cost of treating 1 case(13)	Cost of treating cases (in millions)
Local	39	1,295	51,000	66.031
Regional	39	1,295	98,000	126.884
Distal	22	730	200,000	146.072

The last step is to estimate the costs and lives saved. The costs of treating cases of colorectal cancer are given in column 3 of Table 4. Treating the cases in column 2 would cost the amounts in column 4.

But treatment costs are not the only costs that would be saved. For those who did get a surveillance colonoscopy, for those who did not have polyps to remove, the colonoscopy would be less expensive. Colonoscopy with polyp removal is estimated to cost $1,350 while if there are no polyps, the cost is only $920, a difference of $430. Furthermore, in rare instances, about 1 in 1,000 cases, there are complications in removing polyps. Caring for those who experience complications is expensive, about $29,000 per case. Applying these costs to the total of column 3 in Table 3, we estimate the potential savings at $355.823 million for not having to remove polyps and $23.997 in avoided complications. Adding these to the total of column 4 in Table 4, which is $338.987 million, the total potentially avoided costs are $718.807 million.

These potential cost savings must be reduced by the cost of the calcium supplements, which might be about 9 cents a day. Assuming that these people are motivated to avoid cancer and there is no cost to getting them to buy and take the calcium supplements, it would cost $336.022 million for the 11,109,393 people with an adenomatous polyp to take calcium supplements for a year. Subtracting this cost from the estimated potential

benefit gives a potential net benefit of $336.022 million.

The five-year survival of persons with local, regional, and distant colorectal cancer are 90.4, 69.5, and 11.6 percent, respectively (Table 1). Given the number of cancers that might be prevented were those with adenomatous polyps to take calcium supplements, this implies that 124 deaths from local colorectal cancer might be postponed, 395 from regional disease, and another 646 from distant disease. That is, each year an additional 1,165 cancer patients' deaths might be postponed so that they survived for 5 years.

Prevention with aspirin

This study is very similar to the previous one; that is, it is a follow-up study of a clinical trial with persons who had a surgically removed adenomatous polyp and the outcome studied is the recurrence of a polyp. In this trial, however, the tested treatment was taking a low-dose aspirin daily. In the trial regular use of low-dose aspirin reduced the risk of additional adenomas by 16%. This follow-up was designed to determine if the effect persisted.(28) Patients were sent annual questionnaires for 5 years to measure the occurrence of significant medical events and the use of medications, vitamins and other dietary supplements, including aspirin. The result of the study was that the effect of taking low-dose aspirin not only persisted in those who continued to take the aspirin but was even stronger than during the trial.

The procedure for estimating the potential benefit of all persons having adenomatous polyps removed take low-dose aspirin is very similar to the one in the previous section. The relevant population is the same, so we begin with the 11,109,393 persons estimated in the previous section to have an adenomatous polyp discovered in screening.

The main result of this follow-up study was that among those taking aspirin 26.8 percent had a recurrence of an adenoma while among those that did not 39.9 percent did, a 13.1 percent difference. This suggests that 1,455,330 adenomas might be prevented. These might be distributed by age as in column 1 of Table 5. In surveillance colonoscopies many of these patients would have their polyps removed, leaving those in column 4 of Table 5 with their polyps; the total of this column is 528,818.

Table 5. Estimating the number of cancers prevented by regular aspirin use				
Age group	Number with potentially prevented polyp	Rate of surveillance(21)	Number that would have been removed in screening	Number remaining
50 - 59	401,426	49.7	199,509	201,917
60 - 69	542,218	66.7	361,660	180,559
70 - 80	511,686	71.4	365,344	146,342

Again, as in the previous section, we estimate health care costs that

might be avoided by preventing the recurrence of polyps in this many people. With 0.7 percent of the polyps becoming cancer each year we would expect 3,737 cases with the distribution in column 1 of Table 6, or as in column 2 of that table. Using the costs for each case in column 3 of Table 6 gives the costs in column 4 for treating these cancers.

Table 6. Estimating the number of treating cancers prevented by regular aspirin use				
Stage	Percent distribution of cases	Distribution of cases	Cost of treating 1 case(13)	Cost of treating cases (in millions)
Local	39	1,450	51,000	73.932
Regional	39	1,450	98,000	142.066
Distal	22	818	200,000	163.551

Surveillance colonoscopy is an effective strategy for preventing cancer by removing polyps and minimizing treatment costs by detecting cancer early. However, colonoscopy without polyp removal is less expensive than with polyp removal and has fewer complications. Applying the $430 reduction in the costs of colonoscopy to the total of column 3 of Table 5 gives a saving in costs of $298.400 million. The avoided costs of treating complications would be $26.869 million. These health care cost savings sum to $804.818 million.

These potential savings must be offset by the cost of the aspirin. Low-dose aspirin tablets cost about 3 cents each or $10.99 per year. To treat all those with polyps detected on screening would cost $122.092 million. The net cost savings to this preventive therapy is therefore $682.726 million.

Again, as in the previous section, 139 people would avoid death following local colorectal cancer, 442 would avoid death from regional cancer and 723 would avoid death from distant disease; these total 1,304 deaths postponed by preventing polyps with regular use of low doses of aspirin.

Prevention with diet

This study of the effects of diet on the recurrence of cancer and survival took place within the context of a clinical trial testing one regime of chemotherapy for colon cancer against another.(29) All the patients in this trial had stage III cancer, which was surgically removed. Patients were given an extensive questionnaire on diet, use of supplements, and life style. The diet portion of the questionnaire measured serving size and frequency of eating 131 different foods. This is called a semi-quantitative food frequency questionnaire. The diet was measured 4 and 14 months after surgery. This is in the middle and after the end of chemotherapy treatment. 1009 patients were included in this study.

In their analysis, the authors of this study identified to two dietary patterns with a statistical technique called factor analysis. (29) With this technique they assigned each person a score on each of the dietary patterns. They called these patterns Western and prudent diet. The Western diet is high in dairy products, red and processed meat, and sweets, sweet drinks and

dessert. The prudent diet is high in vegetables, legumes, fruit, fish, and poultry. The diet scores are independent of each other, meaning that any one person can be high or low on neither, both or either one of these type diets. The results of the study were that reporting a diet that scored high on prudence had no effect of the recurrence of cancer or survival, but those reporting a diet that scored high on the Western pattern more often had a recurrence of cancer and more of them died during the period of observation than those reporting diets that scored low on the Western pattern.

The application of this finding is getting those who have had stage III colorectal tumors surgically removed to change their diets to lower their scores on a Western diet. We begin be estimating the annual number of persons with stage III colorectal cancer, and then work through how changes in their diet might change their expected outcomes.

The American Cancer Institute projects that there will be 142,570 new cases of colorectal cancer in the United States in 2010. (11, Table 1.1) Of these, 27.6 percent might be stage III tumors.(12) It is too much to hope for that all of these tumors can be successfully removed surgically, but we optimistically make that assumption here. Thus, there are potentially 39,349 persons for whom the results of this study might be relevant.

In their analysis, the authors of this study divided their study group in quintiles, (five equal groups) ranked according to their score on a Western diet. The results that they report are odds ratios comparing the mortality in quintiles 2 through 5 to mortality in the first quintile, the one with the lowest score on a Western diet.(29, Table 4) Of those in the first quintile, the five-year survival rate was 68.9 percent. Compared to those in the first quintile, those in the second had even lower mortality. Compared to those in the first quintile, those in the third quintile were about 1.4 times more likely to die. This difference, although substantial, is not, by itself, statistically significant, but it is very close to being significant; the confidence interval for the odds ratio is from .90 to 2.11, where 1 represents no difference. To proceed, we need to establish a target for change. To select 1.4 as a standard seems to be to accept too high a level of risk, so arbitrarily, we select to reduce the risk of mortality due to a Western diet in this quintile by half, to 1.2 times that in the quintile with the lowest score on a Western diet; that is, a survival rate of 67.06 percent. We also use this target for quintiles 4 and 5. These calculations are displayed in Table 7.

Table 7. Estimating lives potentially saved by reducing risk due to a Western diet			
	Quintile of Western Diet		
	3	**4**	**5**
Persons with stage III colorectal cancer	7870	7870	7870
Percent surviving	66.32	63.30	59.58
Difference from 67.06 percent	0.74	3.76	7.48
Lives potentially saved	58	296	589

The first row of Table 7 is the number of persons with stage III colorectal cancer in each quintile. The second row is the survival rate estimated from the reported results of the research.(29, Table 4) The third row subtracts these rates from the standard of 67.06. The fourth row is the product of the first and third rows. The total of the last row is 943 lives that might be alive five years after surgery for stage III cancer were those with higher scores on a Western diet able to change their diets sufficiently to reduce their risk of mortality relative those with low scores on a Western diet to 1.2.

Postponing death is achieved through a reduction in the recurrence of disease, and preventing the recurrence of disease has the potential of reducing costs. We can estimate the magnitude of these possible savings by calculating a number of cases that might be prevented and estimating the costs of treating those cases. The calculation of the number of cases is detailed in Table 8.

Table 8. Estimating cases of colorectal cancer potentially prevented by reducing risk due to a Western diet			
	Quintile of Western Diet		
	3	4	5
Persons with stage III colorectal cancer	7870	7870	7870
Percent surviving disease free	55.22	54.32	40.94
Difference from 58.84 percent	6.62	4.52	17.90
Cancer cases potentially averted	521	356	1409

Row 1 of Table 8 is the number of persons in each quintile of distribution of scores on a Western diet. Row 2 is the percent surviving disease free estimated from the research report. (29, Table 4). Row 3 is the difference between the percent surviving disease free in the higher quintiles and the standard of 58.84. This standard is again estimated to be the rate of survival disease free that is 1.2 times the survival rate in the quintile with the lowest scores on a Western diet and represents a reduction in excess risk in the third quintile by about one-half. The last row is the product of the first and third rows and represents the number of recurrent cancer cases that might not occur where those in the higher quintiles of Western diet score able to change their diets and reduce their risk to only 1.2 times that of those with the lowest Western diet scores. The total of the last row is 2,285 cases.

To estimate what it might cost to treat this number of cases we have to make some assumptions. FIrst, we assume that all of these patients are going to be regularly screened so that should the cancer recur there is a high probability it will be detected early. Second, screening detects about 85% of polyps, so we assume that 85% of these cases will be detected as local disease, leaving the other 15% to be regional disease. This is an optimistic assumption because some proportion of these recurrent cases will be

metastatic disease occurring distant from the original site. The costs of treating distant cancers is even greater than that of treating regional cases. Dividing the cases in this proportion gives 1,943 cases of local cancer and 343 or regional. Treating a local case costs about $51,000 and a regional case about $98,000. Treating the local cases would then cost about $99.072 million and treating the regional cases would cost about $33.596 million, for a total of about $132.668 million.

These savings would not be achieved without some investment. As a beginning at estimating the cost of getting those at higher risk due to a more Western diet, we assume that it would cost $20 to measure these patients' Western diet scores, which could be done with a self-administered questionnaire, $10 to determine each persons level of risk, and then $100 for a one-hour consultation with a dietitian for those with higher risk. The would thus be $30 for each patient plus $100 for the three-fifths at elevated risk. These costs would amount to about $3.541 million. The net potential cost savings then might be about $129.127 million per year.

Rehabilitation through diet and exercise

As cancer treatment improves, more people are surviving cancer and living into old-age. However, older cancer survivors are more likely than others to have a second malignancy, other chronic diseases, and functional limitations. Older cancer survivors are less likely than others to practice healthy life-style behaviors.(30) The research described in this section tests an intervention to promote healthy behaviors -- an improved diet and exercise -- among older cancer survivors as an effort to improve their health, functioning and quality of life.(31)

Participants in the study were recruited from a pool of about 20,000 survivors of breast, prostate or colorectal cancer. These were people whose cancer had been diagnosed more than 5 years before the study began. Ultimately 641 over-weight or obese but moderately healthy individuals volunteered to participate in the study and 558 completed the study. Their mean age was 73.0 years, and they were randomly divided within categories of race, cancer type, and gender into intervention and control groups. The intervention was a personally-tailored workbook, 4 news letters, a program of telephone counseling and automated reminders, a pedometer, exercise bands, educational material on diet and exercise, and personalized record logs to self-monitor dietary intake and exercise.(31) The materials prompted the participants each day to perform 30 minutes of endurance training and to consume 7 or 9 servings of fruits and vegetables (for women and men, respectively) and every other day to do 15 minutes of strength training exercise. The materials encouraged reducing consumption of fats to less than 10 percent of energy intake and reducing weight by 10 percent by the end of the year-long program. The program of telephone counseling began with one session in each of the first 3 weeks, 2 sessions in the next month, and 1 session in each of the next 10 months. Sessions were 15 to 30 minutes in length.

The outcomes of interest were physical functioning, health behaviors, and quality of life. The primary outcome, physical functioning, was measured with a subscale of the SF-36 and scales measuring basic and advanced lower

extremity function. The SF stands for "Short Form" and 36 is the number of questions in the questionnaire. This questionnaire was designed to be a self-administered measure of general health and has subscales covering both physical and mental health. It has been very widely used.(32) The physical functioning subscale asks respondents 10 questions on limitations in physical activities ranging from vigorous exercise to walking to bathing with response categories of none, a little, or a lot. The basic and advanced lower extremity function scales are similar, but more detailed. The basic scale has 14 questions asking how much difficulty one has doing activities ranging from washing dishes while standing to making a bed to standing up from a low sofa couch with five answer categories: none, a little, some, quite a lot, and cannot do. The advanced scale is similar and asks about 11 activities ranging from walk several block to carry while climbing stairs to run one-half mile. (33)

Scores on the SF-36 declined over the course of the year that this study lasted. However, scores for the intervention group declined less than scores in the control group, -2.15 compared to -4.84. On the more detailed lower extremity scores, there was no change in the score for the intervention group, but the scores for the control group declined, although the decline on the advanced scale was not statistically significant.

There were changes in health behaviors in both the intervention and control groups, but the changes were much larger and in the direction of the intervention in the intervention group. The length of strength training exercise increased by 18.7 minutes in the intervention group while there was no change in the control group. The length of endurance exercise increased increased by 36.3 minutes in the intervention group and 23.4 in the control group. Mean intake of fruits and vegetables increased by 1.24 daily servings in the intervention group and did not change in the control group while saturated fat consumption decreased by 3.06 grams per day in the intervention group but only decreased by 1.07 grams in the control group. Finally, the intervention group lost and average of 2.06 kg (4.5 lbs) compared to .92 kg (2.0 lbs) in the control group. In both the intervention and control groups, the percentage meeting recommended levels of strength and endurance training and guidelines for servings of fruits and vegetables and calories from saturated fat increased, but the increase was greater in the intervention group.

Finally, the researchers examined the change in health quality of life as measured by the SF-36. In addition to the physical functioning subscale discussed above, they looked at the total score and subscales for pain, vitality, social functioning, and mental health. In the intervention group there was no change in general health and mental health and there were declines in pain, vitality, and social functioning. In contrast, in the control group the general health and mental health scores declined, and the pain, vitality and social functioning scores declined even more.(29, Table 2)

The participants in this study are a highly selected group. Overweight and obese cancer survivors in moderate health were recruited and those who participated volunteered. It is hard to generalize from this group, and while it might be possible to relate the changes on the widely used SF-36 to the experience of other groups who have responded to this questionnaire, the

comparison is questionable. Nevertheless, it is clear that the intervention was successful in helping the participants make modest changes in their diet and exercise patterns resulting in modest weight loss. The changes in the outcome measures were modest, but substantively significant in these aging people.

Other studies

We identified several other studies that have the potential for changing patient care and outcomes, but we have not estimated the potential benefits of these studies because we were unable to find critical pieces of information required to quantify the outcomes or because the study subjects were too few in number or too highly selected to confidently generalize the results.

Three studies of the effects of diet on colorectal cancer help to refine or focus the general conclusion that diet may influence the occurrence of colorectal cancer. These studies analyze data from the Nurses Health Study and the Health Professionals Follow-up Study. The Nurses study began in 1976 and the Health Professionals study began in 1986. The nurses in the former study were all women, and the professionals in the latter are all men. Both of these studies are on-going; the participants are surveyed every two years. When they started there were over 120,000 women and over 50,000 men. The biannual questionnaires included a food-frequency questionnaire to measure diet and questions on screening and cancer. Those who reported diagnoses of colorectal cancer were contacted for permission to review their medical records.

The first of these studies examines the effect of folate on adanomatous polyps and colorectal cancer.(20) Folate is one of the micronutrients that has been identified as possibly related to colorectal cancer. In this study the authors found that the strongest association between folate consumption and colorectal cancer was found when folate consumption was lagged 12 to 16 years. With this lag, when the participants were divided into 5 groups according to their consumption of folate, those with the highest consumption were 31 percent less likely to have colorectal cancer than those with the lowest consumption. The strongest association between folate consumption and colorectal adenoma was found at a 4 to 8 year lag. With this lag, those in highest consumption group were about 32 percent less likely to have a colorectal adenoma than those in the highest group. These results are from a multivariate statistical model that adjusts for differences in age, smoking, alcohol consumption, weight, exercise, family history of colorectal cancer, and other factors. These lag times are consistent with the time it takes for cancer to develop out of adenomatous polyps, so the researchers conclude that low folate consumption is a risk factor for the development of these polyps.

In this study the researchers also examined consumption of multivitamins. Consumption of vitamins for more than 5 years was associated with about a 25% reduction in risk for colorectal adenomas and for more that 15 years with about a 25% reduction in risk for colorectal cancer. (20)

In 1998 the US Food and Drug Administration required that food manufacturers fortify cereal-grain products with folic acid. This was primarily to prevent spina bifida and other neural tube defects in new-born infants. The effect, however, has been to raise population level folate intakes and is

expected to contribute to a reduction in colorectal cancer.(34)

The second study using the Nurses Health Study and the Health Professionals Follow-up Study uses only a small subgroup of the total participants. This group includes those in whom a colorectal adenoma was discovered. They were invited to participate in a trial to see if folate supplementation would prevent the development of subsequent polyps.(35) The study began with 672 participants and 475 completed endoscopic exams and are included in the analysis. This study began in 1966 continued until 2004. Thus the potential effects of the supplement were muted by the mandated fortification of manufactured foods; folate consumption increased in the control group, but it increased more in the intervention group. The average length of participation was a little over 5 years. Given the results presented in the previous paragraphs, it is not surprising that this study produced few significant results. It was observed, however, that folate supplements reduced the risk of recurrent polyps in those who consumed the least folate and the most alcohol. This is the most vulnerable group because alcohol interferes with the absorption of folate.

The third study of the consequences of diet goes deeper into the nature of colorectal cancer. In this study the researchers analyzed tissue samples from 399 cases of colorectal cancer.(36) These were the cases of colorectal cancer between 1980 and 2001 in the Nurses Health Study for which tissue samples were available. The analysis was designed to detect mutation in a gene called p53. Thirty-six percent of the tumors had mutated p53 genes. For their analysis the researchers used the measure of folate derived from the food frequency questionnaire the first time it was given, in 1980. They found that low consumption of folate was associated with cancers with mutated p53 genes, but not with cancers with normal genes. These results suggest that adequate folate consumption is protective from certain kinds of colorectal cancer.

Another study of p53 mutations looked at the expression of p53 along with another gene, Bcl-2, in colorectal cancers and in adjacent adenomatous tissues. (37) The outcome they studied was survival in 90 patients from a single hospital for whom suitable tissue samples were available. This selected study group is thus not necessarily representative of any population and to generalize these results requires assuming that at the biological level these patients are similar to others. The researchers found that patients with p53 mutations had shorter survival times than those without p53 mutations. They also found that there was an interaction between p53 and Bcl-2 expression. Those patients, there were only 7 of them, who had both p53 mutations and low Bcl-2 expression had especially poor survival, a median of only 15.7 months. The median survival of those without p53 mutations and with increased Bcl-2 expression was 71.8 months.

The effect of Bcl-2 may be specific to earlier stages of colorectal cancer. Another study from the same hospital of non-hispanic white patients with stage II and III colorectal cancer reported that decreased expression of Bcl-2 was associated with increased disease recurrence and decreased survival in stage II patients but not in stage III patients.(38) It seems likely that some of the patients in this study were also in the previous study.

Another genetic mutation that is significant in colorectal cancer is in mismatch repair genes. These genes are involved in repairing chromosonal defects that arise in cell division. The genetic defect leads to microsatelite instability (MSI). Microsatelites are short segments of DNA that have repeated sequences of nucleotides. Variations, or instability, in these nucleotides can be detected and indicate a defect in the mismatch repair genes. MSI is characteristic of hereditary colorectal cancer but is found in 15 to 20 percent of non-hereditary colorectal cancers. Patients with MSI respond to chemotherapy and survive longer than patients with microsatellite stability. (39, 40) Two studies that we reviewed found associations between risk factors and MSI. These are case control studies. The cases are cancer patients selected from registries that have been established to facilitate research. The controls were recruited from among their siblings who did not have cancer.(40) In one study overweight and obesity were found to be associated with colorectal cancers with little or no MSI. The other study, which probably included many of the same patients, found weak associations between alcohol consumption and colorectal cancer with little or no MSI and between cigarette smoking and colorectal cancer with high MSI. (41)

The potential benefits of these studies are the lives and costs that could be saved by preventing cases by modifying consumer behavior to ensure adequate amounts of dietary folate, reduce overweight and obesity, and reduce smoking, and changes in clinical practice following from better understanding the prognosis of patients with tumors having differing genetic characters. The latter possibility is expanded in another study which begins to integrate these genetic findings into a more general description of colorectal cancer. In this study the authors analyzed tissue samples from 97 colorectal cancers for genetic and epigenetic alterations. In addition to p53 and MSI they looked for changes in KRAS and BRAF genes and in the methylation status of 27 promoter-associated CpG islands. They analyzed these data with clustering algorithms and identified 3 distinct patterns in the colorectal cancers.(42) In one pattern MSI and BRAF mutations are prevalent while the other patterns are characterized by KRAS and p53 mutations, respectively.

Disparities

One way in which the costs and burdens of colorectal cancer could be reduced is to reduce the social inequalities and disparities in colorectal cancer. The best documented of these are racial and ethnic differences. Each year both the rate of new cases and the mortality rate are higher among African-Americans (Blacks) than among non-Hispanic whites. Furthermore, for Blacks these rates are declining more slowly than those for whites. These rates for Hispanics are lower than those for non-Hispanic whites.(11) Blacks who are diagnosed with colorectal cancer are more likely than whites to have distant disease and less likely to have the less serious local or regional disease.(43) And, for each stage of disease, whites are likely to survive longer than Blacks.(11, 44)

There are many possible reasons for these racial and ethnic differences including differences in education and income, life-style factors like diet and exercise, access to and use of health services, residence, and possibly even genetic differences. These differences have not been

thoroughly researched, but there is evidence that screening plays an important role. Non-Hispanic whites are more likely to be screened for colorectal cancer than those of other races and there are also differences between those with and without health insurance, and by education and income, all attributes on which Blacks and whites differ in directions that would tend to explain the racial difference. (3) In a clinical trial for which participants were screened with sigmoidoscopy and those with polyps or masses were referred to their physicians for follow-up, more whites than Blacks received colonoscopies. Among those who did receive colonoscopies, there were no differences between Blacks and whites in the findings, suggesting that differing outcomes from Blacks and whites are due more to the care received than to biological differences.(45)

There are also geographic differences in colorectal cancer and screening that may be associated with characteristics of local health care systems. The proportion of physicians who report recommending screening consistent with guidelines increased somewhat in the first decade of this century while the tests recommended also changed; physicians have been increasingly recommending colonoscopy.(46) Consistent with this, the proportion of people reporting that they have been screened has increased.(22) The odds of being screened are influenced by health insurance and contact with a physician.(3, 22) There is variation among the states in the colorectal cancer screening, some of which is associated with state poverty rates.(3) In one study of the survival of patients in New Jersey after diagnosis with colorectal cancer, there were areas with unexpectedly short and unexpectedly long survival after adjusting for the age, sex, race and ethnicity of the patients. Those areas with poorer outcomes were areas where the population was disproportionately poor and minority. Those areas with better outcomes were disproportionately higher income with predominantly white populations. Low Census tract poverty rates seemed to explain the advantage of those areas with better outcomes, but only reduced in size the areas with unexpectedly poor outcomes.(47) In another study using SEER data for cancer patients aged 66 years and older, there are significant differences in patients' survival according to the poverty level of the Census tract where they live.(48)

Several of the studies that we reviewed develop these issues, primarily trying to understand and increase low screening rates. One study explores geographic variation.(23) This study linked data from a survey of physicians on their practice of recommending screening with data on from the National Health Interview Survey on individual characteristics and self-reports of screening. The data from the survey of physicians was aggregated to the level of hospital referral region, which in turn were defined by aggregating counties. The authors find variation among the hospital referral regions in the rates at which physicians refer patients for screening and show that even after controlling for individual characteristics that affect screening the proportion of physicians in the regional health care system recommending screening affects the likelihood that a person is screened. They conclude that screening could be increased through interventions in local health care system.

Another study tested such an intervention.(49) This study took place in

a large multispeciality group practice with 14 health centers. Patients who had not been screened for colorectal cancer were randomly assigned to a treatment group receiving a mailing with educational material, a FOBT, and a request to call to make an appointment for a sigmoidoscopy or a colonoscopy. Half of participating physicians were randomly chosen to receive reminders in their system of electronic medical records to advise their patients to get screened. In this practice 63 percent of patients had already been screened, so this study only included the 27 percent who had not been screened. After 15 months the mailing was effective in getting 44 percent of patients screened compared to 38 percent in the control group; most of this increase was additional patients screened with the FOBT. The difference in screening rates between those seeing physicians with and without reminders was a substantive 6 percent among those with 3 or more visits, but this difference only approached statistical significance. A survey of the physicians found that only about half of them thought that the reminders accurately reflected their patient's screening status or were effective. The authors conclude that while physicians are recommending colonoscopy as the preferred mode of screening, patients prefer FOBT and suggest that in order to raise screening rates patient preferences will have to be considered. The patient participation that was requested with the educational material and the FOBT in the mailing was effective, however.

Pursuing this idea of reaching out to patients, another study applied a psychological model of decision making to having a colonoscopy. In this model there are five stages to the decision to have a colonoscopy. For this study these five stages were collapsed to two: pre-contemplation and contemplation or preparation. Persons in the former stage have varying amounts of knowledge of colorectal cancer, their level of risk, and colonoscopy screening and have either never considered or have decided not to be screened. Persons in the contemplation or preparation stage are considering a colonoscopy sometime in the next year or have made an appointment for one. This study was conducted at the internal medicine clinics of two New York City hospitals and participants who had not been screened were recruited from their African-American patients as they made appointments to see their primary care physicians. Participants were low-income and disproportionately female. In this study participants' knowledge of colorectal cancer and screening, perceived pros and cons of screening, and their level of fear or worry about cancer and degree fatalism regarding cancer were measured in interviews at the beginning and end of the study. At the beginning of the study those with more education were more likely to be contemplating colonoscopy, but the difference was not statistically significant. The factors that differentiated the two groups were having a provider that they saw most often and having received a recommendation from a health professional that they be screened.(50) These patients were interviewed immediately before their doctor visits and then at the doctor visit they were given educational material and advised to have a colonoscopy.
After 3 months these patients were reinterviewed. Nearly 25 percent of them had had colonoscopy screening. Those who were screened were distinguished from those who were not by a significant reduction in fatalistic

beliefs and a shift toward a more positive assessment of the balance between pros and cons of screening. Both the screened and the unscreened reported less worry about having a colonoscopy and getting the results.(51) This study thus shows again that providing patients with educational materials and having physicians recommend screening can be effective at increasing screening rates.

Assessment

In this chapter we have estimated the potential benefits flowing from four research projects. For three of these projects there were potential cost savings and potential reduction in loss of life. Adding these three projects together yields a potential benefit of $1.147 billion and 3,412 more people annually surviving their fifth year after receiving a diagnosis of colorectal cancer. These numbers can be compared to the estimated $14.14 billion that is spent annually on colorectal cancer care(52) and the 51,370 deaths attributed to the disease(43). That is, the potential benefits flowing from the research represent a saving of 8.12 percent of the cost of care and 6.64 percent of the mortality. They can also be compared to the $776.8 million that NIH spent to support the research reviewed here.

The first two studies discussed in this chapter look at using calcium and aspirin to prevent the recurrence of polyps in people who have had adenomatous polyps removed. The potential benefits that were estimated thus are limited by the size of this subset of the population 50 to 80 years old. In clinical trials on physicians, nurses, women, and other more general populations regular aspirin use has been shown to reduces heart attacks and strokes, and its use is sometimes recommended for people with elevated risks for these events.(53) A recent analysis of some of the clinical trials of daily aspirin use for preventing heart attack and strokes has shown that long-term use of aspirin reduces colorectal and some other cancers, suggesting that aspirin use might be beneficial to many more people than just those who have had an adenomatous polyp removed.(54) In this study benefit was unrelated to dose, suggesting that even small doses are beneficial. However, in another study of two different trials among male health professionals the authors concluded there was a dose-response relationship to taking aspirin long-term, meaning that the benefit was proportional to the amount of aspirin taken and the greatest benefit came from the largest doses.(55) There is some hesitancy in recommending that people take aspirin, however, because daily aspirin use also elevates the risk of gastrointestinal bleeding, especially at higher doses. In contrast with aspirin, a recent review of studies of calcium concluded that the benefit of calcium was limited to those who had previously had an adanomatous polyp, although they did report two studies of populations not at increased risk with a similar benefit, but the difference was not statistically significant in these studies.(56)

Because these first two studies examined in this chapter involve two different interventions in the same population, there is an issue of double-counting the benefit. In the first paragraph of this section the benefits of the two studies are simply added together, but one cannot tell from these studies whether the two interventions produce the benefit in the same or different people, or what would happen if people were to take both aspirin and calcium.

This latter question, however, is one that the authors addressed in an earlier study; they reported that there was evidence for a synergistic effect.(57) That is, the benefit of the two interventions together is greater than simply the sum of the two separately.

The existence of this earlier study reminds us of the frame that we defined for our analysis, that of research that was supported in the years 2006-2008. If our analysis were to be repeated on a regular schedule, double counting from one frame to another would also have to be considered. As the study just mentioned illustrates, the studies that we analyzed were not the first to provide evidence that aspirin and calcium prevent polyps, and as already mentioned, there may still be issues to be resolved before physicians are ready to recommend that innovations be adopted generally, so these studies are probably not the last word either.

The third and fourth studies discussed in this chapter require that people change their diets in order to obtain the benefits. The modest results of the fourth study show how difficult this change can be. Even when people have the motivation to prevent a recurrence of cancer, they change only modestly. Other studies have shown that the benefits of dietary change extend beyond reduced risk of colorectal cancer to reduced risk of heart disease, cancer in general, and reduced mortality. (58) The US Departments of Agriculture and Health and Human Services have issued dietary guidelines pushing Americans in the direction of the changes suggested by these studies, but the increasing obesity of the American population is a sign of forces working against this change toward a healthier diet.(59)

The studies cited in the last section suggest that the medical profession is moving toward consensus that colonoscopy is the preferred screening test and that this test is slowly gaining acceptance in the population. These studies also emphasize, however, that reducing disparities in screening and colorectal cancer requires good access to health care, which requires insurance, and insurance because the test is expensive. As one wit suggested, the best screening test is the one that gets done.(Sidney Winawer cited in 60) A breath test, as suggested by the Japanese study with the trained dog, may someday offer a cheaper, more acceptable screening test, but that will require further research.

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