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# Primary and Secondary Prevention of Colorectal Cancer

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**ABSTRACT**

**INTRODUCTION:** Cancer is a worldwide problem as it will affect one in three men and one in four women during their lifetime. Colorectal cancer (CRC) is the third most frequent cancer in men, after lung and prostate cancer, and is the second most frequent cancer in women after breast cancer. It is also the third cause of death in men and women separately, and is the second most frequent cause of death by cancer if both genders are considered together. CRC represents approximately 10% of deaths by cancer. Modifiable risk factors of CRC include smoking, physical inactivity, being overweight and obesity, eating processed meat, and drinking alcohol excessively. CRC screening programs are possible only in economically developed countries. However, attention should be paid in the future to geographical areas with ageing populations and a western lifestyle.[19,20] Sigmoidoscopy screening done with people aged 55–64 years has been demonstrated to reduce the incidence of CRC by 33% and mortality by CRC by 43%.

**OBJECTIVE:** To assess the effect on the incidence and mortality of CRC diet and lifestyle and to determine the effect of secondary prevention through early diagnosis of CRC.

**METHODOLOGY:** A comprehensive search of Medline and Pubmed articles related to primary and secondary prevention of CRC and subsequently, a meta-analysis of the same blocks are performed.

**RESULTS:** 225 articles related to primary or secondary prevention of CRC were retrieved. Of these 145 were considered valid on meta-analysis: 12 on epidemiology, 56 on diet and lifestyle, and over 77 different screenings for early detection of CRC. Cancer is a worldwide problem as it will affect one in three men and one in four women during their lifetime. There is no doubt whatsoever which environmental factors, probably diet, may account for these cancer rates. Excessive alcohol consumption and cholesterol-rich diet are associated with a high risk of colon cancer. A diet poor in folic acid and vitamin B6 is also associated with a higher risk of developing colon cancer with an overexpression of p53. Eating pulses at least three times a week lowers the risk of developing colon cancer by 33%, after eating less meat, while eating brown rice at least once a week cuts the risk of CRC by 40%. These associations suggest a dose–response effect. Frequently eating cooked green vegetables, nuts, dried fruit, pulses, and brown rice has been associated with a lower risk of colorectal polyps. High calcium intake offers a protector effect against distal colon and rectal tumors as compared with the proximal colon. Higher intake of dairy products and calcium reduces the risk of colon cancer. Taking an aspirin (ASA) regularly after being diagnosed with colon cancer is associated with less risk of dying from this cancer, especially among people who have tumors with COX-2 overexpression.[16] Nonetheless, these data do not contradict the data obtained on a possible genetic predisposition, even in sporadic or non-hereditary CRC. CRC is susceptible to screening because it is a serious health problem given its high incidence and its associated high morbidity/mortality.

**CONCLUSIONS:** (1) Cancer is a worldwide problem. (2) A modification of diet and lifestyle could reduce morbidity and mortality. (3) Early detection through screening improves prognosis and reduces mortality.

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## Colorectal Cancer (CRC): Descriptive Epidemiology, Risk Factors, and Mortality

Cancer is a worldwide problem as it will affect one in three men and one in four women during their lifetime.[1] Currently, cancer accounts for one in eight deaths around the world. The global cancer rate has doubled in the last 30 years of the 20th century, and will almost triple by 2030, a year in which it is foreseen that 20.3 million people will be diagnosed with cancer and 13.2 million will die as a result of this disease.[2]

CRC is the third most frequent cancer in men, after lung and prostate cancer, and is the second most frequent cancer in women after breast cancer. It is also the third cause of death in men and women separately, and is the second most frequent cause of death by cancer if both genders are considered together. CRC represents approximately 10% of deaths by cancer. The incidence of CRC is low up to the age of 45–50 years, but progressively increases with age, and men are at more risk than women. In the USA, 136,717 people were diagnosed with CRC in 2009; of these, 70,223 were men and 66,494 were women, and it has been estimated that 142,820 adults will be diagnosed with CRC in 2013. These figures include 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer.[3] In 2009, 51,848 people died from CRC, of whom 26,806 were men and 25,042 were women, and it is calculated that there will be 50,830 deaths by this pathology in 2013 (26,300 men and 24,530 women).[3] In Europe, CRC is the second cause of death from all cancer types in both men and women. In 2012, 447,000 new cases of CRC causing 215,000 deaths were estimated.[4]

Around the world, especially in more industrialized countries, high CRC rates continue, whereas they are lower in East Europe, Asia, Africa, and South America. In 2008, the highest incidence rates were found in Australia and New Zealand, Europe, and North America, whereas the lowest incidence rates were recorded in Africa and Central Asia, and were markedly higher in men than in women.[5] The incidence of CRC has increased in several geographical areas where its incidence has been traditionally low: Spain (29,000 new cases every year), and countries of East Asia and Central and East Europe[6,7]—Slovakia (92 per 100,000), Hungary (87), and the Czech Republic (81) in men, and Norway (54), Denmark (53), and Holland (50) in women, with lower rates in the Balkan countries of Bosnia and Herzegovina (30 in men, 19 in women), Greece (25 and 17), and Albania (13 and 11). Mortality partly follows the geography of incidence, but is also high in some countries with a relatively low incidence (Moldavia, Russia, Montenegro, Poland, and Lithuania).[4] Interestingly, the rates found for women from the Czech Republic and Japan have exceeded the incidence peak observed in the USA, Canada, and Australia, where these rates are diminishing or becoming stable (6, 7). This unfavorable trend reflects a combination of factors, which include changes in diet, obesity, and heavy smoking.[7,8] The USA is the only country where the incidence of CRC has lowered significantly in both men and women during the 1975–2006[9] period, due to the beneficial effect of early diagnosis and exeresis of precancerous lesions by CRC screening.[7,9] Although CRC mortality rates have lowered in several western countries thanks to improved treatments and early detection, rates continue to increase in other countries with fewer economic resources and limited healthcare infrastructures, particularly in South and Central America and East Europe (Table 1).

Studies done on Japanese immigrants in the USA, Asian Jewish immigrants in Israel, and East European immigrants in Australia have revealed that they acquire the common CRC rates in the country of their adoption. There is no doubt whatsoever which environmental factors, probably diet,[10] may account for these cancer rates. Excessive alcohol consumption and cholesterol-rich diet are associated with a high risk of colon cancer.[11,12] A diet poor in folic acid and vitamin B6 is also associated with a higher risk of developing colon cancer with an overexpression of p53.[13] Eating pulses at least three times a week lowers the risk of developing colon cancer by 33%, after eating less meat, while eating brown rice at least once a week cuts the risk of CRC by 40%. These associations suggest a dose–response effect. Frequently eating cooked green vegetables, nuts, dried fruit, pulses, and brown rice has been associated with a lower risk of colorectal polyps.[14] High calcium intake offers a protector effect against distal colon and rectal tumors as compared with the proximal colon. Higher intake of dairy products and calcium reduces the risk of colon cancer.[15] Taking an ASA regularly after being diagnosed with colon cancer is associated with lower risk of dying from this cancer, especially among people who have tumors with COX-2 overexpression.[16] Nonetheless, these data do not contradict the data obtained on a possible genetic predisposition, even in sporadic or non-hereditary CRC.

Modifiable risk factors of CRC include smoking, physical inactivity, being overweight and obesity, eating processed meat, and drinking alcohol excessively.[6,17,18] CRC screening programs are possible only in economically developed countries. However, attention should be paid in the future to geographical areas with aging populations and a western lifestyle.[19,20] Sigmoidoscopy screening done on people aged 55–64 years has been demonstrated to reduce the incidence of CRC by 33% and mortality by CRC by 43%.[21]

The vast majority of CRCs are sporadic and the rest occur in patients who are considered to be at high risk. Some patients are predisposed to develop CRC, including patients with hereditary afflictions, such as familial adenomatous polyposis (FAP), hereditary non-polyposis CRC, and ulcerative colitis.[22] The presence of polyps considerably increases the risk of CRC, which depends on the size, histology, and degree of dysplasia; almost half of polyps of >2 cm present malignant degeneration, while 5% of tubular adenomas become malignant as opposed to 40% of the villous types, and 20% of those with mixed forms. FAP patients have an almost 100% risk of developing CRC. Ulcerative colitis and Crohn's disease also raise the risk of CRC, with a risk 5 to 11 times higher than the general population for the former, and 20 times higher for the latter. Approximately 20–30% of CRCs occur among the patient's first-degree family members; indeed several studies have demonstrated the high risk among first-degree family members of patients diagnosed with CRC and adenomas.[23–25] Between 5 and 10% of CRCs occur in people with genetic syndromes, such as FAP and the syndromes of Gardner, Turcot,

**Table 1.** Colorectum—estimlated incidence and prevalence, adult population: both sexes.

| POPULATION | INCIDENCE | 1-YEAR (PROP.%) | 3-YEAR (PROP.%) | 5-YEAR (PROP.%) |
|---|---|---|---|---|
| World | 1,360,056 | 957,110 (18.4) | 2,409,465 (46.4) | 3,543,582 (68.2) |
| Eastern Africa | 12,357 | 8,193 (4.1) | 18,487 (9.2) | 24,926 (12.4) |
| Middle Africa | 3,281 | 2,230 (3.0) | 4,966 (6.7) | 6,598 (8.9) |
| Northern Africa | 12,859 | 8,217 (5.7) | 19,920 (13.9) | 28,740 (20.1) |
| Southern Africa | 4,871 | 2,913 (7.1) | 7,034 (17.3) | 10,151 (24.9) |
| Western Africa | 7,638 | 5,280 (2.9) | 11,749 (6.4) | 15,622 (8.5) |
| Latin America and Caribbean | 87,438<br>8,400 | 58,403 (13.3)<br>5,369 (17.2) | 147,279 (33.5)<br>13,489 (43.1) | 217,906 (49.5)<br>19,916 (63.7) |
| Central America | 11,600 | 7,696 (6.9) | 19,532 (17.4) | 29,042 (25.9) |
| South America | 67,438 | 45,338 (15.3) | 114,258 (38.5) | 168,948 (57.0) |
| Northern America | 158,149 | 124,444 (44.2) | 325,208 (115.5) | 486,650 (172.9) |
| Asia | 606,840 | 290,230 (22.4) | 751,280 (57.9) | 1,130,066 (87.0) |
| Eastern Asia | 421,250 | 154,468 (14.0) | 390,901 (35.3) | 583,054 (52.7) |
| South-Eastern Asia | 68,951 | 45,192 (10.1) | 109,953 (24.7) | 158,845 (35.7) |
| South-Central Asia | 89,522 | 50,661 (4.0) | 108,052 (8.5) | 142,447 (11.3) |
| Western Asia | 27,117 | 17,425 (10.5) | 42,745 (25.8) | 62,162 (37.5) |
| Europe | 447,090 | 330,779 (52.8) | 827,131 (132.1) | 1,203,943 (192.3) |
| European Union (EU-28) | 345,309 | 258,161 (60.2) | 650,872 (151.8) | 953,097 (222.3) |
| Central and Eastern Europe | 139,845 | 98,467 (39.5) | 235,016 (94.3) | 330,603 (132.6) |
| Northern Europe | 65,159 | 46,972 (56.7) | 117,447 (141.7) | 171,237 (206.6) |
| Southern Europe | 104,995 | 79,202 (59.2) | 202,262 (151.1) | 298,884 (223.3) |
| Western Europe | 137,091 | 106,138 (66.4) | 272,406 (170.3) | 403,219 (252.1) |
| Oceania | 19,533 | 13,143 (45.8) | 35,661 (124.2) | 55,526 (193.4) |
| Australia/New Zealand | 18,886 | 12,776 (57.8) | 34,792 (157.4) | 54,266 (245.4) |
| Melanesia | 484 | 310 (5.4) | 739 (12.9) | 1,073 (18.7) |
| Micronesia/Polynesia | 163 | 57 (6.6) | 130 (15.2) | 187 (21.8) |

Incidence data from: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 25/2/2014.
Prevalence data from: Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133–45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.
Proportions by 100,000.

and Lynch. Furthermore, radiotherapy, former abdominal surgery, and having a personal medical background of CRC can also increase the frequency of CRC. Patients with Peutz–Jegher syndrome or juvenile polyposis coli are not at a particularly high risk of CRC.[22] Occupational exposure to asbestos triples the risk of colon cancer when compared to the rest of the general population.

Being diagnosed with colon cancer is almost three times more frequent than rectal cancer. The total incidence and mortality rates of colon cancer have lowered in both men and women since the mid-1980s,[26] unlike previous decades; this lower mortality rate is probably due to the better treatments currently available and diagnosis being made generally earlier as survival depends basically on the tumor stage at the time of diagnosis. Notwithstanding, the accumulated risk during one's lifetime of developing colon cancer in the USA is 5.1%, and this risk is lower in women than in men. However it is 3.5%, for example, in Spain. The possibility of developing this disease clearly increases with age and is higher in men than in women. In the USA, 1.40% of men who are now 60 years of age will contract CRC at some time over the next 10 years; this means that 1 or 2 per 100 men who are now 60 years of age will develop CRC by the time they are 70. Save some hereditary forms, onset of this disease before the age of 40 is not a frequent occurrence, so it is advisable to start screening in people as of 50 years. When CRC is diagnosed, the disease is localized in 37% of patients, 37% have CRC with regional extension, 20% present distance metastasis, and 6% have not been staged. The 5-year survival rate for local, regional, and distance neoplastic colon disease is 90, 70, and 12%, respectively.[27] Thus, early colon cancer diagnosis is important as it offers a high cure rate (60%) when localized in the intestine alone. However in patients with only one or some tumors that have disseminated from the colon to the lungs or liver, the surgical

removal of these tumors can eliminate the cancer, which notably improves survival rates.

Care must be taken when interpreting CRC survival statistics because estimations are based on data that originate from thousands of people with this cancer type in only the USA each year for instance, while a given individual's actual risk can vary. It is impossible to tell people how long they will live with CRC. As survival statistics measure in five-year intervals, it is quite possible that they do not represent the advances made in treating or diagnosing this cancer type.[3]

## Primary Prevention of CRC

Many factors may influence the appearance of CRC. Although it is not possible to accurately determine the exact foods or nutrients that are the main causes of it, we can take an approach, and even offer a list of these factors which, according to studies, influence CRC:

- High fat content in food
- High calorie intake
- High raw meat intake
- Very low fiber intake
- Very low vitamin C content
- Low calcium content
- Low selenium content
- High alcohol intake and smoking
- Very low salt intake, among others.

**Macronutrients.** An excessive intake of the various macronutrients making up a diet can increase the risk of CRC. Nonetheless, there are studies that present limitations because isolating different diet components is not easy. The food type that independently contributes to the risk of CRC, or whether there is a relation between it and excessive dietary intake of several macronutrients, is also unknown.[28]

*Fats.* Observational studies offer contradictory results of the effect that a low-fat diet has on the risk of CRC. The randomized clinical trial (RCT) of the Women's Health Initiative (WHI) (48,835 postmenopausal women aged 50–75 years, selected between 1993 and 1998) does not reveal that low-fat diet cuts the risk of CRC after an eight-year follow-up.[28]

In an at-risk population, the ECA Polyp Prevention RCT[7,8] (2,079 men and women aged over 35 years with a background of colorectal adenomas) does not reveal that low-fat, high-fiber diet with fruit and vegetables modifies the recurrence rate of colorectal adenomas after an eight-year follow-up (relative risk [RR] = 0.98; 95% confidence interval (CI): 0.88–1.09). Nevertheless, the study design does not definitely conclude that changes in diet are ineffective to lower the risk of CRC.[28]

*Meat.* Observational studies present contradictory results on the effect of red meat as a factor of CRC. However, several meta-analyses reveal that eating red meat and processed meat can increase the risk of CRC.[29–33]

The most recent review done, which included 15 cohort studies on eating red meat (7,367 cases) and 14 observational studies on consuming processed meat (7,903 cases) published up to 2006 show an RR of 1.28 (95% CI: 1.15–1.42) for red meat and an RR of 1.20 (95% CI: 1.11–1.31) for processed meat.[33]

Another review demonstrates a higher association with processed meat than with red meat.[12] Eating red and processed meats is positively associated with a high risk of developing colon and rectal cancer. However, the association with red meat is higher for rectal cancer.[33]

Several pyrolysis products, such as heterocyclic amines, aromatic polycyclic carbohydrates, and nitro compounds, which form when meat is very well-done or comes into direct contact with flames, can increase the risk of CRC, especially in people who are genetically predisposed to transform these components into more active intermediate products. Genetic predisposition can also influence the risk associated with eating red or processed meat.[33]

*Fiber, vegetables, and fruit.* Several studies conducted with cases and controls show an inverse association between fiber intake and the risk of CRC, which most studies do not confirm.[17] The result obtained in a systematic review, which included 13 prospective studies (725,628 men and women) and follow-ups of between 6 and 20 years, reveals that fiber intake is inversely associated with the risk of CRC according to an analysis adjusted for age (RR = 0.84; 95% CI: 0.77–0.92). However, this protective effect disappears when other diet-related risk factors are taken into account (RR = 0.94; 95% CI: 0.86–1.03).[21] Nonetheless, the prospective study done in the NIH-AARP Diet and Health Study reveals that total dietary fiber is not associated with a change in the risk of CRC, but with a slight reduction in this risk with cereals.[34]

The result of a meta-analysis, which included 14 prospective studies (756,217 men and women) and with follow-ups lasting 6–20 years, shows that eating fruit and vegetables is associated with a non-significant reduction in the risk of CRC: fruit and vegetables (RR = 0.91; 95% CI: 0.82–1.01), fruit (RR = 0.93; 95% CI: 0.85–1.02), and vegetables (RR = 0.94; 95% CI: 0.86–1.02).[24] Notwithstanding, when the analysis was done by taking tumor location into account, eating fruit and vegetables is significantly associated with a reduced risk of distal cancer (RR = 0.74; 95% CI: 0.57–0.95), but not of proximal cancer (RR = 1.02; 95% CI: 0.82–1.27).[35]

In a high-risk population of a Cochrane review, which evaluated the effect of dietary fiber on the incidence or recurrence of colorectal adenomas and the incidence of CRC (including 5 RCTs and 4,349 cases), greater dietary fiber intake did not lower the incidence or the recurrence of adenomatous polyps over a period lasting two to four years (RR = 1.04; 95% CI: 0.95–1.13).[36]

As mentioned earlier, the polyp prevention trial does not demonstrate that low-fat, high-fiber diet with fruits and vegetables modify the recurrence of colorectal adenomas.[37]

The combined analysis of the wheat bran fiber trial and the polyp prevention trial reveals that this risk lowers significantly among men (RR = 0.81; 95% CI: 0.67–0.98), but not among women.[38–41]

*Milk and other dairy products.* Case–control studies do not show that milk and dairy products protect against the risk of CRC, although cohort studies do.[42,43] The result of a systematic review, which included 10 prospective studies (534,536 cases), shows a protector effect for consumption that exceeds 250 g/day (RR = 0.86; 95% CI: 0.78–0.94), but in relation only to neoplasias located in the distal colon.[43]

**Micronutrients.** Several studies have evaluated the effect of administering folate, calcium, and vitamin D supplements, among others, to prevent CRC.

*Folate acid.* The result of a systematic review, including seven prospective studies and nine case–control studies, shows that the association between folic acid intake in diet and CRC (RR = 0.75; 95% CI: 0.64–0.89) is stronger than dietary folic acid plus folic acid supplements (RR = 0.95; 95% CI: 0.81–1.11).[44]

In people with a previous history of adenoma, the United Kingdom Colorectal Adenoma Prevention RCT did not reveal that administering folic acid supplements (0.5 mg/day) amends the risk of recurrent adenoma (RR = 1.07; 95% CI: 0.85–1.34).[45]

Similarly, in the Aspirin/Folate Polyp Prevention Study RCT, administering folic acid supplements (1 mg/day) did not reduce the risk of colorectal adenomas recurring (RR = 1.04; 95% CI: 0.90–1.20), and an increase in this risk was even detected in relation to preneoplastic lesions after a three to five year follow-up.[46]

*Calcium.* The result obtained with a systematic review including 10 prospective studies (534,536 cases) reveals a protector effect of dietary calcium consumption (RR = 0.86; 95% CI: 0.78–0.95) and dietary calcium intake plus supplements (RR = 0.69; 95% CI: 0.69–0.88).[43] Nonetheless, this review does not differentiate the independent effect of diet and calcium. A preliminary analysis of the WHI RCT does not reveal that calcium supplements cut the risk of CRC after a seven-year follow-up.[27] Yet a re-evaluation of these data consistently shows an interaction with estrogens, to the extent that calcium modifies the effect on the relation with a risk of CRC depending on whether estrogens are administered concomitantly or not.[47]

The Cochrane review, which included two TCTs (1,346 subjects), shows that in those people with a history of adenomas, taking calcium supplements can have a protector effect on the development of colorectal adenomas (RR = 0.74; 95% CI: 0.58–0.95).[47]

*Vitamin D.* Two meta-analysis of observational studies show that taking high vitamin D doses (1,000–2,000 U/day) cuts the risk of CRC, but also indicate that taking low doses (200–400 U/day) may not suffice to appreciate such benefits, particularly if sun exposure is low.[48–51] A preliminary analysis of the WHI RCT does not indicate that vitamin D supplements reduce the risk of CRC after a seven-year follow-up period.[51] A re-evaluation of these data consistently shows an interaction with estrogens, to the extent that vitamin D amends the effect in relation to the CRC risk depending on whether estrogens were administered concomitantly or not.[52]

**Antioxidants.** The results of a recently updated Cochrane review, which included 20 RCTs and 211,818 participants, show that administering antioxidants, as compared to placebos, does not modify the incidence of CRC (RR = 0.91; 95% CI: 0.80–1.03). Similar results were obtained for different antioxidants, administered either separately or combined, after a 2–12-year follow-up period: beta-carotenes (RR = 1.09; 95% CI: 0.79–1.51), vitamin E (RR = 1.10; 95% CI: 0.87–1.9), selenium (RR = 0.8; 95% CI: 0.22–1.05), beta-carotene + vitamin A (RR = 0.97; 95% CI: 0.76–1.25), beta-carotene + vitamin E (RR = 1.20; 95% CI: 0.89–1.63), beta-carotene + vitamins C and E (RR = 0.84; 95% CI: 0.65–1.07), and beta-carotene + vitamins C and E + selenium (RR = 0.88; 95% CI: 0.49–1.58).[53]

The results of a recent meta-analysis, which included 11 cohort studies (702,647 participants with follow-up lasting 6–20 years, on carotenes also confirm that carotenes do not modify the risk of CRC (RR = 1.04; 95% CI: 0.84–1.00).[54]

The results of another meta-analysis indicate that antioxidants do not seem to have a beneficial effect on preventing the recurrence of colorectal adenomas.[55]

**Other factors.** Several risk factors related with lifestyle and economic development in western countries are associated with a higher incidence of CRC.

**Physical activity, obesity, and energy balance.** More than 50 observational studies estimate that regular physical exercise cuts the risk of CRC by around 40%, independently of body mass index (BMI).[56] The level of activity, intensity, frequency, and duration of physical activity, and maintaining this activity over time, seem to be associated with a greater reduction in this risk. The results of a systematic review reveal a significant reduction in this risk in men as regards to both occupational (RR = 0.79; 95% CI: 0.72–0.87) and recreational (RR = 0.78; 95% CI: 0.68–0.91) activity, but only for recreational activities in women (RR = 0.71; 95% CI: 0.57–0.88).[57]

Cohort and case–control studies have shown an association between body fat content and the risk of CRC41. The results of a meta-analysis, which included 23 cohort studies and 8 case–control studies, show that obesity, when comparing people with a BMI of >30 with those who have a BMI = 20–25, presents a direct and independent association with the risk of CRC, be it weaker than previously assumed (RR = 1.19; 95% CI: 1.11–129). The risk for men is higher (RR = 1.41; 95% CI: 1.30–1.54) than for women (RR = 1.08; 95% CI: 0.98–1.18).[58] The other meta-analyses confirm that the association between BMI and CRC is higher in men.[56–59] The European Prospective Investigation into Cancer and Nutrition Study shows the

distribution of the waist–hip index and waist perimeter as indicators of abdominal obesity, both associated with the risk of CRC in both genders.[55] Another meta-analysis confirms this association.[57]

The consistency of the results obtained on diet, obesity, central obesity, physical inactivity, and the risk of CRC, corroborates the hypothesis that high concentrations of circulating insulin are a risk factor. In a meta-analysis of cohort studies, an excessive risk of CRC is shown to be associated with high C-peptide, circulating insulin, and blood sugar marker values.[60–62]

**Alcohol.** In a joint analysis of eight cohort studies, a positive association is revealed between drinking alcohol and developing CRC,[63] showing that the more alcohol drunk, the greater the association. Alcohol intake of 30–45 g/day implies a risk of 1.16 (95% CI: 0.99–1.36) and a risk of 1.41 (95% CI: 1.16–1.72) for >45 g/day. Nevertheless, it is important to point out that the results of these studies are inconsistent because of their different study designs and possible confounding factors (diet, gender). In a more recent meta-analysis based on data from 16 cohort studies, alcohol intake was associated with both the risk of developing colon cancer (RR = 1.50; 95% CI: 1.25–1.79) and rectal cancer (RR = 1.63; 95% CI: 1.35–1.97).[64]

**Smoking.** In the various reviews that have been conducted[65,66] on studies done before the 1970s, no association was found between smoking and CRC. However, the more long-term follow-ups of some these studies (30 and 40 years) reveal an increased risk of CRC. The results of a meta-analysis, which included[67] observational studies, unveils an association between cigarette smoking and developing colorectal adenomas, with differentiated risks for active smokers (RR = 2.14; 95% CI: 1.86–2.46), former smokers (RR = 1.47; 95% CI: 1.29–1.67), and occasional smokers (RR = 1.82; 95% CI: 1.55–2.01).[68] Some recent studies show that active smokers are at higher risk of rectal cancer (RR = 1.95; 95% CI: 1.10–3.47) but not for colon cancer.[69]

**Age.** Younger adults can suffer CRC, although the likelihood of developing it increases significantly after the age of 50. There are reports that more than 9 of every 10 people diagnosed with CRC are at least 50 years old.

**Evidence of chemoprevention.** Several case–control and cohort studies and phase II/III RCTs have been done to evaluate the potential use of various chemoprevention agents.

These include ASA, NSAIDs, five aminosalicylates, 5-ASAs, statins, and ursodeoxycholic acid, as well as vitamins and micronutrients (calcium, selenium, folic acid, etc.), which have all been reviewed in other sections.

**Acetylsalicylic acid and non-steroidal anti-inflammatory drugs.** The results of a Cochrane review, which included three RCTs, showed that ASA significantly lowers the recurrence of adenomas after a three-year follow-up (RR = 0.77; 95% CI: 0.61–0.96).[70] The joint analysis of the British doctors aspirin trial and the UK-TIA aspirin trial indicates that taking ASA in doses of ≥300 mg/day for at least five years is an effective primary prevention method against CRC with a 10-year latency period.[71] The same authors did a systematic review, which included 19 case–control studies (20,815 cases) and 11 cohort studies (1,136,110 individuals), and demonstrated that regular use of ASA and NSAIDs is associated with a reduced risk of CRC, particularly after 10 years or more. However, it is noted that this association is consistent only for ASA taken in doses of ≥300 mg/day, and this association decreases and is more inconsistent with lower doses if not taken on a daily basis.[16] This association has also been found in a recent observational prospective study, which included men treated with a dose of 325 mg/day for at least six years.[72]

**Table 2.** Relationship factors of diet and exercise with colorectal cancer.

| FACTOR | PREVENTION OR NO EVIDENCE |
|---|---|
| Fat | + |
| Meat | ++ |
| Fiber, fruit and vegetables | ++ |
| Protector milk | ++ |
| Folate protector | + |
| Calcium protector | + |
| High dose vitamin D | + |
| Antioxidants | No evidence |
| Physical activity | ++ |
| Obesity | ++ |
| Alcohol | ++ |
| Tobaco | ++ |
| Age | +++ |
| Acetylsalicylic | ++ |
| NSAIDs | ++ |
| Statins | No evidence |
| Hormone Therapy | + |
| Others | + |

The results of two systematic reviews of RCTs on the role of NSAIDs in preventing colorectal adenomas in patients with FAP show that, in the short term, treatment with sulindac or celecoxib favors the regression of adenomas, but not their elimination or prevention.[16,72] Subsequent RCTs confirm that selective inhibitors of cyclo-oxygenase-2, celecoxib,[73,74] and rofecoxib[75] help reduce the recurrence of colorectal adenomas.[76]

**Statins.** The results of a meta-analysis with six RCTs (RR = 0.95; 95% CI: 0.80–1.13) and three cohort studies (RR = 0.96; 95% CI: 0.84–1.11) reveal that statins have no significant beneficial effect on preventing CRC, although nine case–control studies do (RR = 0.91; 95% CI: 0.87–0.96).[77]

**Hormone treatment in postmenopausal women.** Several observational meta-analysis studies show an inverse association between hormone treatment and the risk of

CRC in postmenopausal women. Nonetheless, RCTs that have evaluated the incidence of cancer as a secondary variable do not confirm a protector effect. The preliminary results of the Women's Health Initiative indicate this association (RR = 0.63; 95% CI: 0.43–0.92), which is not statistically significant, after adjusting (RR = 0.63; 95% CI: 0.32–1.24).[78] A more recent analysis reveals that this effect disappears three years after dropping off treatment, and that the incidence of colorectal adenomas and the risk of CRC even increase.[79] The results of the Heart and Estrogen/Progestin Replacement Study show a non-significant protector effect (RR = 0.81; 95% CI: 0.46–1.45).[80–85]

## CRC: Secondary Prevention

CRC is susceptible to screening because it is a serious health problem given its high incidence and its associated high morbidity/mortality. Its natural history is known, there are screening tests that allow the disease to be detected at early stages, and treatment is more effective when the lesion is diagnosed early. The aim of CRC screening is to reduce its incidence (by detecting and resectioning precursor lesions, basically colorectal adenomas) and mortality by this cause.

Different screening strategies exist for the medium-risk population (individuals aged ≥50 years with no other risk factors for developing CRC). Traditional CRC screening tests include the detection of fecal occult blood (FOB) using the guaiac test, sigmoidoscopy, and colonoscopy. The new screening tests include immunological FOB detection, a fecal DNA analysis, and virtual colonoscopy.

The various tests were evaluated and compared in intervention efficiency terms (lower morbidity/mortality) after considering risks and adverse factors. Validity, acceptability, and participation rate were evaluated for all the tests.

**Screenings with feces occult blood tests by the guaiac method.** The meta-analysis of four RCTs, which examined screening by FOB detection with Hemoccult II®, reveals reduced mortality by CRC, and included 327,043 participants in Denmark (Funen), Sweden (Gothenburg), the USA (Minnesota), and the UK (Nottingham). A recently updated Cochrane review estimates a reduction in the mortality of the intervention group of 16% (RR = 0.84; 95% CI: 0.78–0.90). In the three RCTs that used a two-yearly detection system (Funen, Minnesota, Nottingham), the reduction in the risk of death by CRC was 15% (RR = 0.85; 95% CI: 0.78–0.92).[86] The reduction in estimated mortality rises to 25% (RR = 0.75; 95% CI: 0.66–0.84) when adjusting for participation in at least one round. No differences were found in either overall mortality (RR = 1.00; 95% CI: 0.99–1.02) or overall mortality with CRC excluded (RR = 1.01; 95% CI: 1.00–1.03).[87]

In the Minnesota RCT, which included a group examined after a one-year interval and another after a two-year interval, initially no significant reduction in mortality was found in the group that was submitted to the two-year examination, but a significant reduction was seen after an 18-year follow-up (RR = 0.79; 95% CI: 0.62–0.97).[88]

The Minnesota RCT used the FOB test with fecal rehydration and shows a 33% reduction in mortality (RR = 0.67; 95% CI: 0.50–0.87).

The Minnessota RCT results also indicate a reduction in the incidence of CRC of 20% with annual screening (RR = 0.80; 95% CI: 0.70–0.90) and of 17% with two-yearly screening (RR = 0.83; 95% CI: 0.73–0.94).[89]

The sensitivity of the FOB tests to detect any colorectal neoplasia (nine cohort studies) was 6–46% (with specificity at 80–89%) for Hemoccult II® and 43% (with specificity at 91%) for Hemoccult Sensa®. When comparing the rehydrated vs. the non-rehydrated FOB studies, sensitivity was 10–14% (with specificity at 90–94%) for rehydrated samples and 6–45% (with specificity at 94–98%) for non-rehydrated samples.[90]

Sensitivity to detect adenomas of ≥10 mm (seven cohort studies) was estimated to be 16–33% (with specificity at 94–98%) for Hemoccult II® and 21–27% (with specificity at 90–99%) for Hemoccult Sensa®. Sensitivity was greater for CRC detection (19 cohort studies),[91] which was estimated at 25–96% (with specificity at 80–99%) for Hemoccult II® and at 62–79% (with specificity at 87–96%) for Hemoccult Sensa®. When comparing the rehydrated and non-rehydrated FOB studies done, sensitivity was 25–89% (with specificity at 80–99%) for rehydrated samples and 25–89% (with specificity at 92–96%) for non-rehydrated samples.[91]

The systematic review carried out by the US Preventive Services Task Force (USPSTF),[91] which included studies until 2007 and was based on two cohort studies (106,107 cases), point out that the sensitivity of Hemoccult Sensa® was higher for CRC than Hemoccult II® (64–80%), but specificity was lower (87–90%). Nonetheless, both the systematic CRC review and the USPSTF show that reference Hemoccult Sensa® data are scarce.[91,92] When specificity lowers, there are more false positives, which increase the risk of having to do further research (colonoscopy).

**Immunological feces occult blood detection tests.** No RCT has been performed to evaluate the efficacy of FOB tests in terms of incidence or mortality, but some have assessed them in terms of intermediate results (rate of detecting colorectal neoplasias). One RCT compared FOB (Hemoccult II®) with iFOB (OC-Sensor® test) in a population sample of 20,623 individuals in the 50–75 year age group. It reveals that the latter is significantly more efficacious than the former to detect CRC and advanced adenomas, although its specificity is lower.[93] In this study, participation in and fulfillment of the iFOB test are significantly higher (a 12.7% increase) than those obtained with the FOB test.[94]

In the systematic CRD review on the diagnostic validity of qualitative iFOB tests, which included studies done until December 2004 (more than 50% of them were case–control studies), it is estimated that the sensitivity of these tests to detect colorec-

tal neoplasias (6 cohort studies) is 5–63%, while their specificity is 89–99%.[94,95] Moreover, their sensitivity to detect: CRC (15 cohort studies) is 2–98%; any adenoma (5 cohort studies) is 4–63%; and adenomas of >1 cm (4 cohort studies) are 28–67%. Specificity is estimated at: 89–99% to detect CRC; 89–98% to detect any adenoma; 93–97% to detect advanced adenomas.[96]

The systematic review done by the USPSTF, which included studies done until 2007, centers on nine cohort studies. It concludes that the iFOB test is more sensitive for detecting CRC (61–69%) than Hemoccult II® for a FOB test with non-rehydrated samples (25–38%), and that it is less specific (91–98% as opposed to 98–99%, respectively).[93–97]

**Fecal DNA detection.** By analyzing fecal DNA, it is possible to identify the molecular alterations present in cells of adenomas and CRC.[98,99]

No RCT has been done to evaluate the efficacy of a fecal DNA analysis in CRC screening in terms of incidence or mortality.[98–106]

A multicentre cohort study done in a medium-risk population, made up of 5,486 individuals aged over 50 years, shows that a multitarget fecal DNA test, which included the detection of 21 mutations in genes *TP53*, *KRAS*, and *APC*, these being markers of the instability of microsatellites and the analysis of DNA integrity, offers higher sensitivity than the FOB test to detect CRC (52 vs. 13%), CRC and adenomas with a high degree of dysplasia (41 vs. 14%), as well as advanced colorectal neoplasias (18 vs. 11%), but their specificity is similar (94 vs. 95%).[106]

Other studies done with less objective reference standards, in several age groups, and using various molecular markers, show that the validity of the fecal DNA test is lower than that of colonoscopy. These studies estimate that FOB DNA test sensitivity and specificity to detect CRC are 52–91 and 82–97%, respectively, and that its sensitivity to detect adenomas is lower (15–82%).[99,104–106]

The FOB DNA test is not invasive and entails no adverse effects, no restrictions to diet or medicine, or colon preparation. Its acceptability is greater than that of other CRC screening techniques and is just as acceptable as a guaiac-based (gFOB) test.[99,103–106] The clinical relevance of a positive result obtained in a patient with a negative colonoscopy is currently unknown. However, its high cost and low cost-effective ratio, as compared with other screening strategies, limits its applicability.[107] Finally, scientific tests to determine the suitable interval between performing two determinations are not available.

**Sigmoidoscopy.** Flexible sigmoidoscopy is done using an endoscope that allows the examination of the mucous surface up to 60 cm from the anal verge (rectum, sigmoid colon, and part of the descending colon). This examination is done before colon lavage using enema or administering laxatives, and sedation is not necessary. The procedure lasts 10–15 minutes. A positive result means having to completely examine the colon by colonoscopy.

Currently, three RCTs are underway: two European ones, the UK flexible sigmoidoscopy screening trial,[108] and the Italian SCORE trial,[109] which evaluate the efficiency of performing a single sigmoidoscopy in people in the 55–64 age group with 170,432 and 34,292 people randomly selected, respectively. The US RCT, called the PLCO cancer screening trial, assesses the efficacy of sigmoidoscopy done at five-year intervals (with three-year intervals between the first two sigmoidoscopies) in 154,000 people aged 55–74 years. The mortality data of the European RCTs are still not available, and those of the US RCT go up to 2010–2012.

The detection rate in these RCTs for CRC (0.3–0.5%) and distal adenomas (7.2–12.1%) in the first screening round is higher than that obtained in the RCTs done on gFOB-based detection (0.2 and 8%, respectively).[110–112] Nonetheless, the detection of advanced adenomas performed by sigmoidoscopy screening is significantly lower than that observed in colonoscopy screening.[111]

A Norwegian non-randomized controlled study—the Telemark Polyp Study—assessed the effect of polypectomy on the incidence of CRC in a screening program context, with 400 people (50–59 years) that formed a study group, and 399 controls. It shows that sigmoidoscopy reduces the incidence of CRC, adenomas of ≥5 mm (RR = 0.7; 95% CI: 0.5–0.95), and high-risk adenomas (RR = 0.6; 95% CI: 0.3–1.0) after a 13-year follow-up.[109–111] Sigmoidoscopy sensitivity for CRC is estimated to be 58–75% for small-sized lesions and 72–86% for more advanced neoplasias. These variations are likely accounted for by the differences in examiners' experience and skills, and by the risk of proximal lesions in the unexplored colon.[109]

When sigmoidoscopy detects a carcinoma or an adenoma of ≥10 mm, conducting a complete study of the colon is mandatory given the major incidence of synchronic lesions proximal to the tract explored. It has been estimated that 5–16% of colonoscopies are performed after sigmoidoscopy.[112,113]

In the clinical practice, there is some controversy as to the need to explore the whole colon when distal lesions of <10 mm have been detected. A meta-analysis estimates that the RR of presenting a proximal neoplasia is 2.68 (95% CI: 1.93–3.73) for any distal adenoma and 2.36 (95% CI: 1.30–4.29) for adenomas of <10 mm. The meta-analysis that evaluated the meaning of distal hyperplasic polyps offers a series of estimations. One meta-analysis reveals that these polyps are associated with the presence of a proximal neoplasia (RR = 1.44; 95% CI: 0.79–2.62), but are not statistically significant. Another meta-analysis indicates that distal hyperplasic polyps are associated non-significantly with the presence of a proximal neoplasia (RR = 1.3; 95% CI: 0.9–1.8), but significantly with an advanced proximal neoplasia (RR = 2.6; 95% CI: 1.1–5.9). Another more recent meta-analysis shows that the RR of proximal neoplasia for patients with distal hyperplasic polyps is 1.81 (95% CI: 1.20–2.73). However when including only quality studies, this increased risk disappears. In this meta-analysis, distal

hyperplasic polyps present an RR of proximal neoplasia of 0.69 (95% CI: 0.60–0.80)[114,115] as compared with distal adenomas.

Case–control studies estimate that sigmoidoscopy has a protector effect over a period lasting 9–10 years.[116] Based on this, a five-year interval between screening sigmoidoscopies was conservatively established.[113,117–120] This interval is shorter than that employed in colonoscopy screening because sigmoidoscopy sensitivity is lower owing to the technique itself, colon preparation, and variability in examiners' experience.[116]

The results available to date reveal that sigmoidoscopy is well-accepted by the general public and is feasible and safe.[121–124] Compared to colonoscopy, sigmoidoscopy is a safer test, although it is not completely risk-free. According to some estimations made in the UK Flexible Sigmoidoscopy RCT, 0.3 cases of hemorrhages associated with sigmoidoscopy, 0.15 perforations, and 0.025 deaths per 1,000 examinations occur. The results of an RCT indicate that 14% of individuals complain of pain (which is strong in 1%) after having been submitted to sigmoidoscopy. If we compare it to colonoscopy, lack of sedation is associated with more discomfort and less adhesion to future sigmoidoscopies.[125]

*Feces occult blood detection and sigmoidoscopy.* The combination of two screening tests can overcome the limitations that each has separately.[123] No RCT has been found which evaluates the efficacy of the screening strategy in terms of reduced mortality by CRC.[123–125]

The Danish Funen-2 RCT provides limited data about the incidence and mortality of CRC. It included 5,495 people to whom it offered a FOB test and a single sigmoidoscopy, and 5,483 people were invited to undergo only a FOB test.[123,126] An RCT done in Norway evaluated this same intervention in 20,780 men and women in the 50–64 age group, but it also provides limited data. Both studies conclude that the combination of FOB and sigmoidoscopy does not exceed sigmoidoscopy in terms of the number of CRC and advanced adenomas identified.[123–127]

The sensitivity of the combined strategy does not improve that of sigmoidoscopy. Thus, in one study with a large number of individuals, the rehydrated FOB and sigmoidoscopy combination gives sensitivity of 76%, which is similar to that achieved with sigmoidoscopy alone. Indeed the positive predictive value of the combined strategy (2.8%) is lower than that of the FOB (5.4%).[126]

The adverse effects of the combined strategy are the sum of those derived from each strategy separately. These drawbacks may condition their acceptability. Along these lines, one study reveals that adhesion to the combined strategy is less than that to each separate test (47% with sigmoidoscopy, 32% with gFOB, and 30% for the combination). In the RCTs of Norway and Demark, participation was higher in the sigmoidoscopy or the gFOB groups than it was for the combined strategy.[113–117,128,129]

*Colonoscopy.* Colonoscopy is done using an endoscope, which allows an examination of the mucous surface of the whole colon. For it to be considered complete, it must reach the blind gut (by visualizing the ileocecal valve or appendicular orifice), which is done in 80–95% of explorations.[130] Colonoscopy must be done under sedation using intravenous drugs. It also requires being on a low-residue diet on the days before the test, antegrade colon lavage, administrating laxatives, and drinking plenty of water. A thorough exploration must be done during withdrawal, which must last at least six to eight minutes. This examination takes between 20 and 40 minutes. Most people fully recover after one hour of rest.

No RCT has evaluated the efficacy of colonoscopy in CRC screening in reduced mortality terms. However, several studies indirectly corroborate its efficiency and show that this test not only favors CRC detection in early stages, but also reduces the incidence of CRC as it identifies and resects polyps. Therefore in the Minnessota detection FOB RCT, the major reduction in mortality as compared with the European RCTs is attributed to the fact that more colonoscopies were performed.[130–132] Likewise, several cohort studies demonstrate that polyp removal lowers the incidence of CRC by 76–90%, and that colonoscopy detects the majority of these lesions.[130]

Colonoscopy could be advantageous over other non-invasive tests like FOB and iFOB. Currently some RCTs evaluating if colonoscopy is superior to the FOB test in CRC screening are underway. The National Cancer Institute of the United States began a multicentre RCT in May 2000 and it invited 5,000 healthy people aged 40–69 years to participate. The Spanish Gastroenterology Association (AEG, in Spanish) set up a multicentre RCT in a medium-risk population to be carried out in eight Spanish Autonomous Communities (SACs) (Aragon, Canary Islands, Catalonia, the Valencian Community, the Basque Country, Galicia, Madrid, and Murcia) to assess the efficiency of colonoscopy as compared to the iFOB detection test.

As it is a reference test, colonoscopy validity is difficult to analyze. The results of a meta-analysis (nine studies), which compared conventional colonoscopy and virtual colonoscopy, estimates greater sensitivity for the virtual test, 98% (95% CI: 96–100%) for polyps of ≥10 mm, and 97% (95% CI: 94–100%) for polyps of ≥5 mm.[131]

Narrow band colonoscopy imaging, which allows images of submucous vascularization by a digital chromoendoscopy technique, does not appear to significantly improve the rate of adenomas detected by conventional colonoscopy. However, the available RCTs do not offer consistent scientific tests.[132,133]

The colonoscopy employed in screening imposes the risk of adverse effects for healthy patients. The mortality associated with colonoscopy is 0.3 cases per 1,000 examinations. The rate of intestinal perforation or hemorrhaging is one to five cases per 1,000 examinations.[118,127,130–136]

Other described complications include infections and those relating to sedation, particularly among the elderly with cardiovascular problems. Nonetheless, the results obtained with a systematic review, which included 36 studies and

**Table 3.** Relation of screening with evidence and cost effectiveness.

| SCREENING | EVIDENCE | COST/EFFECTIVENESS |
|---|---|---|
| Guaiac fecal occult blood | ++ | ++++ |
| Immunological FOB | ++ | ++ |
| ADN fecal | +++ | + |
| Sigmoidoscopy | +++ | +++ |
| FOB + sigmoidoscopy | +++ | ++++ |
| Colonoscopy | ++++ | + |
| CT colonography | +++ | ++ |

3,918 patients, reveal that superficial sedation provides a high degree of patient and doctor satisfaction, with a low risk of adverse effects.[137] Complications basically occur when therapeutic procedures are carried out.

*Computed tomography (CT) colonography.* CT colonography or virtual colonoscopy consists in obtaining tomographical images after colon insufflation using air or carbon dioxide, and their subsequent 2D or 3D construction in a computer. This test requires the same preparation required for a colonoscopy, but without sedation.[126,127] Currently, the efficiency of performing CT colonography, without colon lavage, but with fecal marking using an oral contrast is being evaluated. Images can be captured in 5–10 minutes, although a further period lasting 20–30 minutes is required to reconstruct and interpret them. If the result is positive, performing a colonoscopy is mandatory, ideally on the same day or the next day in order to avoid further intestinal preparation.[130–132,134,135]

No RCT has been done to assess the efficacy of screening by CT colonography in terms of the incidence of or mortality by CRC.

The efficacy of detecting adenomas and CRC has been evaluated in several comparative studies. In them, CT colonography reveals a similar rate for detecting polyps of ≥10 mm and advanced neoplasias to that of colonoscopy.[134]

The systematic review done by the US Prevention Services Task Force concludes that variations in the validity parameters of CT colonography can be attributed to not only the size, but also to the shape, of the lesion (polypoid vs. flat), and also to the radiologist's experience, the technique being used, and colon preparation.

CT colonography is a non-invasive test and barely entails serious complications. The rate of symtomatic colon perforations is 0.05%, which lowers if carbon dioxide is employed instead of air. Patients complain about abdominal discomfort when the colon is insufflated. The potential risks of periodical exposure to low radiation doses are not clear. Another CT colonography value is the detection of significant extracolon disease in 4.5–16% of all assessed individuals. However, its consequences in terms of potential benefits, risks and costs remain unknown. There are no scientific tests available on determing the suitable internval between screening CR colonographies.

**Cost-effectiveness of CRC screening.** The results of two systematic reviews[126] reveal that CRC screening is cost-effective when compared to no screening.

In the US, the cost-effective ratio of the various screening strategies available ranges between 10,000 and 25,000 dollars per life gained.

One- or two-year screening with FOB offers the most consistent and favorable scientific tests on the cost-effectiveness ratio, as well as information about costs obtained directly from RCTs. The limited information available on the effectiveness and costs of screening with iFOB or sigmoidoscopy means that it is difficult to consistently establish which strategy offers the best cost-effective ratio and the optimum age to start and finish screening.

Cost-effectiveness studies must be valued in each context and merely represent approaches to the clinical practice in each setting. In Spain, a Markov decision model and some conservative assumptions concluded that CRC screening is cost-effective and that the screening strategy with a better cost-effective ratio is an iFOB done yearly, with an incremental cost of $2,154 per year of life adjusted by quality gained. Yet other screening strategies present similar incremental costs: 1-yearly FOB, $2,211; 2-yearly FOB, $2,322; 2-yearly iFOB, $2,233; 5-yearly sigmoidoscopy, $2,305, and 10-yearly colonoscopy, $2,369, per year of life adjusted by quality gained.

**Other aspects related with CRC screening.** In some health systems, primary care doctors actively participate in CRC screening programs. An RCT conducted in Italy shows that if primary care doctors actively participate in screening programs, the aim of this practice is significantly enhanced. In the UK, preparing informative materials for primary care doctors has become a priority, as have regular information exchanges to guarantee their support. The results of a recent narrative review assign several possible roles to primary care doctors in screening programs, such as facilitators, advisors, and educators. In these roles, communication among primary care and specialist care, if a consultation is located in an urban or rural area, and other individual factors, are all influences.[138]

Some studies have evaluated other strategies to raise participation rates. A descriptive study done in Australia indicates a statistically significant increase when FOB tests are collected in chemists.

Other experiments performed in France reveal that the participation rates increase when there is coordination between all health areas, including primary care and chemists. Finally, an RCT evaluated the effect of two different contact methods with the target population and shows that the direct contact made by a trained non-healthcare professional was much more effective than sending a letter of invitation.

A study done in Albacete (Spain) in 1996 by Tárraga[138] shows that participation rose to almost 76% after sending a letter of invitation and running an awareness campaign.

**Populational CRC screening strategies and implementation in our setting.** Despite scientific tests indicating that CRC screening lowers the incidence of and mortality by this neoplasia, these measures have been poorly introduced into usual clinical practice. This is most probably because of the characteristics of the screening test, the fact that it is barely perceived as being beneficial, and its low social pressure.

Doctors should be familiar with the various screening options available and know their potential risks, offer them to participants, and identify those individuals who belong to high-risk CRC groups, who can benefit from screening or specific monitoring measures.

Despite there being no gold-standard screening test, any one of them is much better than none at all. Although the FOB detection test is not ideal, it is justified by the scientific tests resulting from RCTs, and their cost-effective ratio and greater feasibility as far as resources are concerned. iFOB detection methods avoid drawbacks relating to dietary and pharmacological restrictions, improve fulfillment, favor better standardization and quality control of the process, and allow a more efficient fecal hemoglobin detection cut-off point to be selected in accordance with the resources available. Colonoscopy is the most sensitive and specific test, but is associated with a higher rate of complications, requires more resources (trained staff and suitable facilities), and is not as well-accepted by the population as FOB or sigmoidoscopy detection. Flexible sigmoidoscopy seems to be more effective than FOB and must be considered an alternative. It is also safer than a colonoscopy, patient preparation is easier, and requires neither sedation nor monitoring. Applied as a screening method, it involves considerable investments in facilities and training professionals. CT colonography efficacy is similar to that of colonoscopy to detect advanced neoplasias, but entails milder adverse effects, but its application as a screening test requires better quality and consistent scientific tests, as well as considerable technological resources and specialized professionals. Fecal DNA tests are not currently backed by direct scientific tests to confirm their efficiency, and they are still expensive.

In 2003, the International Colorectal Cancer Screening Network (ICRCSN) was created for the purpose of promoting quality CRC screening programs. This international group did a descriptive survey-based study of the various initiatives before 2004 to identify, share, and promote the best strategies to carry out screening programs. In all, 35 screening initiatives in 17 countries were identified: 10 were populational screening programs, 9 were pilot-phase programs, and 16 were research projects. The most widely employed screening test was FOB, although one program included colonoscopy. Most invited people aged 50–64 years to participate, although some included patients of 40 years of age, while others did not set an age limit.

European Union Council Directives, the NHS Cancer Strategy, and various Health Plans of SACs recommend applying populational CRC screening with FOB in men and women within the 50–74 age range. Currently, only three SACs (Catalonia, Murcia, and the Valencian Community) have a CRC screening program, although most SACs are proposing them. Indeed, the *Interterritorial* Board of the Spanish Ministry of Health has approved CR screening.

The participation and follow-up rates of the programs that are underway are low and lower than those of other cancer prevention programs. The NHS Cancer Strategy establishes the need to conduct preliminary population pilot studies that evaluate all these aspects, particularly the acceptance of the various strategies by the population, their effectiveness, the human and material resources required for screening, diagnosis, and treatment in any detected cases, and the cost-effective ratio in our setting. The efforts made to reduce mortality by CRC must concentrate on developing programs that maximize participation. For this purpose, when setting up a population program, it is essential to run awareness campaigns for the general population and health professionals about the benefits, risks, and limitations of CRC screening to control this disease.

A population screening program will be beneficial if it is systematically applied, covers the whole target population, and is of good quality. To set it up, organizing an adequate summoning system and one that provides a suitable diagnosis, treatment, and follow-up for patients is essential. Managing a screening program means that information systems that include the target population and data on screening tests, evaluation, and diagnostics must be available. A quality program includes an analysis of the process and its results, and also notifying them quickly. A screening program evaluation is easier if the program's database is linked to cancer and mortality registries. The European Guidelines for Quality Assurance of Colorectal Cancer Screening are being prepared in Europe. These guidelines will cover the entire screening process, from inviting participants to treating detected lesions, and will include a series of recommendations on standardizing processes, program follow-up, program evaluation, and future CRC screening perspectives.

The various experiments and accomplishments to reduce mortality by breast cancer must serve as experience in implementing CRC screening in forthcoming years. Primary care and specialized care professionals must be a clear reference for the population. Coordination and team work among SACs are essential to design and organize such programs. Screening alternatives may vary in the future if the RCTs underway, which evaluate colonoscopy efficiency, confirm a reduction in the incidence of and/or mortality by CRC.

## Author Contributions

Analyzed the data: PJTL, JSA, JARM. Wrote the first draft of the manuscript: PJTL, JSA, JARM. Contributed to the writing of the manuscript: PJTL, JSA, JARM. Jointly developed the structure and arguments for the paper: PJTL, JSA, JARM. Made critical revisions and approved final version: PJTL, JSA, JARM. All authors reviewed and approved of the final manuscript.

### DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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