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COLORECTAL CANCER AND HYPERCHOLESTEROLEMIA: REVIEW OF CURRENT RESEARCH

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Aim: **In spite of ample research about a high level of cholesterol in the blood of patients with colorectal cancer (CRC), the relationship between factors causing hypercholesterolemia and factors leading to CRC development is not fully investigated. The purpose of this article is to provide a review of the current research about the risk factors leading to the development of hypercholesterolemia and CRC, and to show the relationship between these factors, hypercholesterolemia and CRC with the implication for CRC preventive and treatment practices.** ***Methods:*** **A systematic search of MEDLINE and PUBMED databases between 1990 and 2005 was conducted to locate the studies that investigated the risk factors causing CRC and hypercholesterolemia. From among 255 studies found, 66 were selected that matched the following criteria for selection: (1) reported original research; (2) discussed at least one of the listed eight factors; (3) discussed hypercholesterolemia; and/or (4) discussed colon or rectum cancer.** ***Results:*** **The studies were grouped according to four areas of research: (1) studies that explored the relationship between different factors and CRC incidences; (2) studies that investigated the relationship between different factors and CRC incidences and the role of mutations in causing CRC; (3) studies that looked at the factors causing hypercholesterolemia; and (4) studies that explored the relationship among the factors, hypercholesterolemia, and CRC development. A discussion of the studies is presented and the details related to the studies major aspects are summarized in 4 tables.** ***Conclusion:*** **The review has revealed a relationship between factors that can lead to the development of CRC and those that lead to hypercholesterolemia. Although the role of many individual risk factors is still controversial the analysis of their significance in combination might be important for diagnostic and development of the models for prediction of cancer occurrence.**

Key Words: **colorectal cancer, factors, hypercholesterolemia, ademato us polyp, mutations.**

Colorectal cancer (CRC) is one of the most common neoplasms of the digestive system in the world [6, 24]. Worldwide, CRC is the third leading cause of cancer in males and the fourth leading cause in females [11]. In 2002, an estimated 1 million new cases of CRC were diagnosed, which accounted for more than 9% of all new cases of cancer diseases [9]. It is also predicted to be increasing with time: in 2005–2009, the number of predicted value for colon cancer for 100,000 women is 41.5 and for 100,000 men is 104.9; for rectum cancer, it is 22.9 for 100,000 women and 37.2 for 100,000 men [18].

The frequency of CRC occurrences varies around the world. CRC is common in the Western countries, but it is much rare in Asia and Africa [9, 11]. The highest rates of CRC are observed in highly industrialized countries, especially in North America, Australia, and to a lesser extent in Northern and Western Europe [6]. Examination of time trends during the last decades reveals a sharp increase in CRC incidences in Japan and in eastern and southern Europe [6]. In the United States, CRC accounts for most of gastrointestinal cancers [12, 52]. In 2004, an estimated 146,940 new cases of CRC, 73,620 men and 73,320 women, were registered that make up 11% of all new cases of cancer diagnosed between men and women in 2004 [12]. Ninety percent of people diagnosed with CRC are over 50 years old. Thirty-seven percent of CRC is diagnosed in its early stages. When diagnosed in early stages, CRC has a five-year survival rate of about 90%. The incidence of CRC is highest among African-American men and women — a rate of 64.3 per 100,000 as compared to a 55.2 per 100,000 among Caucasians and 41.4 per 100,000 among Hispanic Americans [12]. There is a growing tendency of CRC diseases occurrence among people at younger ages [78].

Nearly 75% of all cases of CRC are diagnosed in people with no known risk factors, including a family history [12]. However, among the studied risk factors causing CRC development are heredity, age, low fiber and high fat food, alcohol, tobacco use, obesity, low physical activity, and environmental pollution, including radiation [20, 40, 43, 52, 59, 76, 78]. All these factors can stimulate the increase of cholesterol level in the blood, which, in its turn, increases the risk of CRC development [33, 39, 45, 69]. Hypercholesterolemia, a higher serum total cholesterol level, causes sclerotic changes in blood vessels, leading to hypoxia of large intestine tissue and changes of the homeostasis of its cells. It was noted that molecular genetic changes in normal epithelium lead to adenomatous polyp, which is associated with a higher serum total cholesterol level, and might result in CRC [50, 62]. This is particularly observed with age due to heredity predisposition, wrong nutrition, sedentary life style, environmental pollution, and/or longitudinal exposure to alcohol and tobacco use.

In spite of ample research about a high level of cholesterol in the blood of CRC patients, the relationship between factors causing hypercholesterolemia

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Abbreviations used: CRC – colorectal cancer; FH – familial hypercholesterolemia; HC – hypercholesterolemic; HDL – high-density lipoprotein; HNPCC – hereditary nonpolyposis colorectal cancer; LDLR – low-density lipoprotein receptor; LOH – loss of heterozigosity; MSI – microsatellite instability.

and factors leading to CRC development is not fully investigated. Studies mostly focused either on the exploration of one or some such factors, the characteristics of single aspects of those factors, or the cholesterol level in CRC patients. The purpose of this article is to provide a review of the current research about the risk factors leading to the development of hypercholesterolemia and CRC, and to show the relationship between these factors, hypercholesterolemia and CRC with the implication for CRC preventive and treatment practices.

Methods. To locate the studies that investigated the risk factors causing hypercholesterolemia and CRC, we conducted a systematic search of the years 1990 to 2005 using MEDLINE and PUBMED databases. We used the key words of "colorectal cancer", "colon cancer", "rectal cancer", "cholesterol", "hypercholesterolemia", and eight factors, such as "heredity", "age", "food", "obesity", "low physical activity", "alcohol", "tobacco", and "environmental pollution". From among 255 studies found, we selected 66 that matched our criteria for selection: (1) reported original research; (2) discussed at least one of the listed eight factors; (3) discussed hypercholesterolemia; and/or (4) discussed colon or rectum cancer.

Results. As a result of the review of 66 studies that investigated risk factors causing CRC and hypercholesterolemia, we identified four areas of research: (1) studies that explored the relationship between risk factors and CRC incidences; (2) studies that investigated the relationship between risk factors and CRC incidences and the role of mutations in causing CRC; (3) studies that looked at the factors causing hypercholesterolemia; and (4) studies that explored the relationship among the risk factors, hypercholesterolemia, and CRC development. Tables 1–4 present the studies organized by these four areas. The description of each study area follows.

Risk factors and CRC. Twenty-six studies explored the relationship between risk factors and CRC incidences (see Table 1). Out of eight listed factors causing CRC the most investigated were food, heredity, age, and environmental pollution. Low physical activity and alcohol consumption were among the least explored, while the role of tobacco use in CRC development was not discussed in any of the studies from this group.

Food. Food was found to be a strong factor leading to CRC incidences [16, 39, 60, 73, 76, 78, 79]. For example, in the study that examined trends of CRC incidence rates among the Japanese and the Caucasians in U.S. [78], consumption of red meat and its heterocyclic amines content was associated with an increased risk for CRC. In Uruguay and Argentina, where the rates for CRC are among the highest in the world, the main type of meat consumed is beef, of which consumption rank first and second, respectively in the world, with about 60 kg per year per capita [43]. Navarro and colleagues [48] assessed the dietary habits of 287 patients with colorectal adenocarcinomas in Argentina and evaluated different meat types. They found that consumption of total meat, red meat, and other types of meat were not related to increased risk of CRC, however, consumption of relatively large amounts of cold cuts and sausages (odds ratio (OR) 1.47; 95% confidence intervals (CI) 1.02–2.15) and bovine viscera (OR 1.73; 95% CI 1.18–2.54) led to an increased risk of CRC. Another population-based, case-control study [8] found moderate positive associations between CRC and increasing intake of red meat, specifically well done and pan-fried.

In Japan, incidences of CRC were also positively associated with fat and oil intake, of both plant and animal types [76]. In this study, incidence data for 1976–1996 and national values for per capita daily food nutrient intake in 1956–1995 were analyzed by first investigating chronological changes of food nutrients and CRC, and then by calculating correlation coefficients with time lags of five, 10, 15, and 20 years. Incidences of colon and rectal cancers gradually increased during 1976–1996 with the highest incidence rates, 25.31 and 13.75 per 100,000, respectively during 1996.

A positive relationship was noted between CRC and animal protein and fat [16, 76, 78, 79]. In You and colleagues' study [79] conducted in China, based on incidence data of 37,000 CRC incidences from 1972–1997, CRC development was associated with vegetable oil, poultry, eggs, and pork consumption. However, in a cohort longitudinal study of 37,547 healthy US women aged more than 45 years old, little evidence was found that intake of dietary fat and major fatty acids was associated with risk of CRC [39]. Instead, for 202 women who developed CRC during an average follow-up period of 8.7 years, there was a positive association between intake of fried foods away from home and CRC development.

Heredity. Heredity as a factor in causing CRC was explored in five studies [3, 27, 28, 34, 38]. Most of this research was conducted on twins from databases registered in Sweden, Denmark, Finland and Norway databases. In the study of 44,788 pairs of twins of cancer affected persons listed in the Swedish, Danish, and Finnish twin registries [38], the statistically significant effects of heritability for CRC for twins was 35%. The heritable component included both dominant genetic effects, as well as additive recessive genetic effects. However, it was found that inherited genetic factors made a minor contribution to susceptibility to most types of neoplasms, as compared to environmental factors. In another study [3] conducted on monozygotic and same-sex dizygotic twins from the same twin registry as in [38], it was revealed that genetic susceptibility made only a small to moderate contribution to the incidence of CRC.

A study conducted on the patients from Swedish Family-Cancer Database examined the risk of familial CRC adenocarcinoma due to environmental or heritable genetic factors [34]. The national database included 10.3 million patients whose invasive cancers were followed up to 2000. A significant risk was observed in the parent-offspring comparison among different subsites (left-sided and right-sided colon,

Table 1. Risk Factors and CRC

Study	Sample	Factors	Findings
Abou-Zeid et al., 2002	177 patients with CRC, 104 males; 73 females aged 19–74	Age	38% of CRC in patients younger than 40 and in 15% of patients aged above 60 (Egypt)
Baker et al., 2005	45, 000 pairs of twins	Heredity, environmental factors	Dominant cancer susceptibility genotype for CRC: 0.08–0.27; genetic susceptibility made a small to moderate contribution to CRC incidences (USA)
Barchana et al., 2004	All Israeli CRC data accumulated during 1970–2001	Obesity, low physical activity, food	Colon cancer increased in males and European-American born; for Israeli-born Jews the lowest incidence and best survival data for stages-2 and -3 CRC (Israel)
Butler et al., 2003	1,658 individuals (701 African-American and 957 White)	Food (meat)	Moderate positive associations between CRC and increasing intake of red meat, specifically well done and pan-fried (USA)
Dirx et al., 2003	62,573 women and 58,279 men aged 55–69 years	Food (energy intake)	Nonsignificant and weak inverse relation between energy restriction during adolescence and the risk of colon carcinoma (Netherlands)
Gulis et al., 1998	Incidences of CRC during 1986–1995 (27.5 per 100,000 inhabitants)	Environmental pollution	Positive and statistically significant correlations between standardized incidence ratio of CRC and waste dump location and surface water (Slovak)
Hemminki et al., 2001	More than 6 million individuals from the Swedish Family-Cancer Databases	Heredity, environmental components	10% of CRC incidences are inherited, shared and childhood environments components equally important in CRC (Sweden)
Hemminki et al., 2004	Data on 10.3 million people	Heredity, age, environmental factors	60% of the CRC variation due to random environmental effects; 35% to heritable factors (Sweden)
Iversen et al., 2001	23,334 twins born in Norway 1905–45	Heredity	Incidences of CRC reduced for both sexes (Norway)
Iwasaki et al., 2004	5,826 death certificates registered during 1999–2001	Obesity, low physical activity, food	No differences in the mortality rates from CRC between the Japan-born residents of Brazil and the native Japanese (Brazil)
Jakobsson et al., 1994	14,564 cement, industrial and workers and fishermen	Environmental polutiuon (radiation)	Increased incidence of cancer in the right part of the colon in cement workers (Sweden)
Lichtenstein et al., 2000	44,788 pairs of twins	Heredity, environmental factors	27–42% of CRC incidences in twins; environmental risk factors played a more important role (Sweden, Denmark and Finland)
Lin et al., 2004	A randomized trial for 39,876 US women aged 45 and more	Food (fried foods)	Positive association between fried food and risk of CRC (USA)
Little et al., 1999	80,206 atomic bomb survivors; 8,613 solid tumor cases	Age, environmental pollution (radiation)	5–7 rate-limiting six stages for colon cancer development were identified (Japan)
Navarro et al., 2002	853 individuals	Food (meat)	Consumption of total meat, red meat, and other types of meat not related to increased risk of CRC; consumption of relatively large amounts of cold cuts and sausages and bovine viscera led to an increased risk of CRC (Argentina)
Pedersen et al., 2003	Randomly selected 15,491 men and 13,641 women aged 23–95 years	Alcohol use	Significantly increased risk of CRC; the risk was reduced when wine was included in alcohol intake (Denmark)
Roy et al., 2002	Multiple intestinal neoplasia mice	Alcohol (ethanol)	Ethanol consumption resulted in a significant increase in tumor number (US)
Slattery et al., 2003	952 individuals with CRC	Food (energy intake), obesity, physical activity	Physical activity significantly reduced (40%) rectal cancer risk; energy intake significantly increases risk of rectal cancer (USA)
Steindorfr et al., 2000	180 patients with CRC	Low physical activity	Low occupational physical activity positively associated with CRC development (Poland)
Thompson et al., 1994	8,613 individuals with first primary solid cancers	Environmental polutiuon (radiation)	For CRC, excess relative risk at 1 Sv for A-bomb survivors 0,72 (Japan)
Tsukuma et al., 2004	Population-based Cancer Registration database	Age	Increase in the age-standardized incidence rate for CRC; cancer incidence highly affected by the generation (Japan)
Tsyb et al., 1996	Solid cancers in 435,000 persons; 152,000 participants in the liquidation of the Chernobyl accident	Environmental pollution (radiation)	Within 20 years after radiation in a cohort of liquidators an attributive risk for solid cancers, including CRC, was estimated 2,8% (Russia)
Walker et al., 2002	126 patients (58 males, 68 females)	Food, age	The proportion of African patients under 40 years was 19,0%, and 4% in the white population; 44/100,000 CRC incidences in white populations in 1993–1995 (South Africa)
Yang et al., 2002	CRC incidences rates for 1976–1996	Food (oil, animal fat, protein)	Incidences of colorectal cancer positively associated with fat, animal protein, and oil intake; 39,6/100,000 CRC rates in 1996 (Japan)
Yiu et al., 2004	Trends of CRC incidence rates among Japanese and US whites during 1959–1992	Age, food	Age-standardized CRC rates increased, similar to US white rates, 50–60/100,000; tendency to increase in younger people (Japan)
You et al., 2002	Incidence data on 37000 colorectal cancers from 1972–1997	Food (vegetable oil, poultry, fresh eggs and pork)	Statistically significant positive associations between CRC and per capita consumption of vegetable oil, poultry, fresh eggs, and pork (China)

rectum, and all CRC), with standardized incidence ratio ranging from 1.74 to 1.84. Overall, the results for among spouses and siblings pointed to the importance of heritable factors in familial CRC. A more recent study [27] that used the data on more than 6 million individuals from the Swedish Family-Cancer Databases concluded that 10% of CRC incidences were inherited, while shared and childhood environment components were equally important in CRC.

Age. Six studies reported increased incidences of CRC with age [1, 34, 40, 70, 73, 78]. Yiu, Whittemore, and Shibata [78] examined trends of CRC incidences rates among Japanese and United States Caucasians between 1959 and 1992. Age-standardized rates in Japan had significantly increased and were similar to US Caucasian rates. Those trends suggested that CRC would become a major source of morbidity and mortality in Japan and the tendency is observed for increased rates of CRC in younger people. Other authors also observed this tendency [1, 34, 73]. For example, in Walker and Segal's study of 126 patients (58 males, 68 females) in South Africa [73], the proportion of African patients under 40 years was 19%, while in [1], which reviewed the age distribution of CRC in Egypt, 38% of the tumors occurred in patients aged less than 40 years old. In another study [70] that used Population-Based Cancer Registration database in Japan a birth cohort analysis revealed that that CRC incidence was highly affected by the generation.

Environmental pollution. Increased incidences of CRC among people in regions with high level of pollution were reported in five studies [25, 30, 40, 66, 72].

Gulis, Fitz, Wittgruber, and Suchanova [25] studied the incidences of the CRC in rural areas of Trnava district (Slovak Republic) during 1986–1995. The standardized incidence ratios (observed/expected cases) (SIR) were calculated for all villages, including statistical parameters. The SIR's were correlated with time of public drinking water supply, surface water quality, location of waste dumps, and time of gas heating using as kind of house heating. Positive and statistically significant correlations were found between SIR of the CRC and waste dump location for females and weaker for surface water and SIR for males.

Jakobsson, Albin and Hagmar [30] investigated associations between exposure to mineral fibers and dust and cancer in subsites within the large bowel for blue collar workers employed for at least one year in different trades: asbestos cement and cement workers (n = 2,507), other industrial workers (n = 3,965), and fishermen (n = 8,092). SIRs were calculated for cause specific cancer morbidity between 1958 and 1989. They found that asbestos cement and cement workers had a slightly increased risk of CRC (SIR 1.5), and it was due only to an increase only in the right part of the colon (SIR 2.5).

Radiation was also argued to lead to increased incidences of solid cancers, including CRC [40, 66]. For example, Little, Muirhead, and Charles [40] evaluated the risks of cancer arising from exposure to ionizing radiation after 45 years of atomic bombings in Japan. They found that a relative risk model could describe the radiation-induced excess risk of solid cancers. Thus, over the period of 1968-1987 tumor cumulative incidences increased about 37% (up to the age of 74) for Japanese males and 29% for females in the Miyagi tumor registry. In another study conducted on 79,972 Japanese atomic bomb survivors [66], 8,613 first primary solid cancers were diagnosed between 1958 and 1987. A standard set of analyses was carried out for each of the organs and organ system considered. A statistically significant excess relative risk at 1 Survival (ERR1Sv) was 0.63; for cancer of the colon, ERR1SV equaled 0.72. Tsyb and Ivanov [12], who studied 152,000 participants in the liquidation of the Chernobyl accident from Russia, found that within 20 years after radiation an attributive risk for solid cancers, including CRC, was estimated 2.8%.

Obesity and low physical activity. Two studies reported energy restriction resulting from obesity and low levels of physical activity as a factor leading to CRC [60, 61]. Misbalance between energy intake and physical activity can lead to increased body mass and consequently ruin the energy balance. In a study [60] conducted to determine how physical inactivity interacts with other components of energy balance (energy intake and body mass) in determining CRC risk in 2,073 first primary cases of colon cancer and 2,466 age- and sex-matched controls, lack of lifetime vigorous leisure-time activity was associated with increased risk of colon cancer (OR 1.63, 95% CI 1.26–2.12 for men, and OR 1.59, 95% CI 1.21–2.10 for women). Those at greatest risk of colon cancer were those who had the most unfavorable energy balance in that they were physically inactive, had high-energy intakes, and had large body mass index (BMI). The study conducted on 180 hospitalized CRC patients in Poland also highlighted the effect of low occupational physical activity on cancer development (OR 0.61, 95% CI 0.29–1.29) [61].

Dietary changes, reductions in physical activity, and increasing obesity in urbanized settings lead to higher risk of CRC incidences. A study that investigated the trends in CRC incidences and mortality in the Israeli Jewish ethnic populations [2] based on all Israeli CRC data accumulated during 1970–2001 found that colon cancer increased in males and European-American born, while Israeli-born Jews had the lowest incidence and best survival data for stages-2 and -3 CRC. However, Iwasaki and colleagues [29] did not find any differences in the mortality rates from CRC between the Japan-born residents of Brazil and the native Japanese.

Alcohol and tobacco use. Alcohol and tobacco use was also associated with increase in the risk of CRC [53, 56], however there is little empirical research on alcohol and tobacco as independent CRC causing factors. Pedersen and colleagues [53] investigated the relationship between amount and type of alcohol and the risk of colon and rectal cancer, using a random sample of 15,491 men and 13,641 women. Drinkers of more than 41 drinks a week had a relative risk of CRC of 2.2 compared with non-drinkers, while drinkers of more than 14 drinks of beer and spirits a week, but not wine, had a risk of 3.5. Those who drank the same amount of alcohol but including more than 30% of wine had a risk of 1.8, which allowed the authors to conclude that CRC risk was reduced when wine was included in the alcohol intake. Alcohol consumption has also been reported as increasing the risk of CRC because ethanol potentates adenomas in a genetic model of carcinogenesis. In the study conducted by Roy and colleagues [56] on multiple intestinal neoplasia mice ethanol supplementation resulted in a significant increase in tumor number.

Risk factors, CRC and mutations. Eight studies investigated the relationship between risk factors and CRC incidences and the specific role of mutations in causing CRC (see Table 2). Most of the factors discussed in this group of studies were heredity and tobacco and alcohol consumptions. One study explored the role of obesity and mutations in CRC development.

Heredity. A few authors [31, 42] suggested that loss of heterozigosity (LOH) in the long arm of chromosome 18 was related to poor survival and possibly to the development of metastases in patients with CRC. In Jernvall, Makinen, and Karttunen's study [31] of 255 Finnish patients, 195 were informative with regards to LOH status when analyzed in primary CRC specimen using the polymerase chain reaction and fragment analysis. LOH at 18q21was significantly associated

Table 2. Risk Factors, Mutations and CRC

Study	Sample	Factors	Mutations	Adenomatous Polyp	Findings
Jernvall et al., 1999	255 patients with CRC	Heredity	LOH 18q21	Not discussed	Increased rate (82%) of CRC recurrence (Finland)
Martinez-Lopez et al., 1998	144 patients with CRC	Heredity	LOH 18q21	Not discussed	Unfavorable outcomes in patients with stage II CRC (Spain)
Morton et al., 2000	56 patients with CRC	Heredity	p53	Not discussed	Decreased survival of patients with CRC; 4-year survival rates for wild-type p53 – 71%, mutant p53% – 54% (USA)
Takeshita et al., 2000	200 individuals (69 with CRC polyps, 131 – without polyps)	Alcohol, tobacco use	*ALDH2* gene	Colorectal polyps	Synergistic effect of smoking and alcohol; increased risk of CRC (Japan)
Takezaki et al., 2001	131 patients with CRC	Obesity	*Beta-3* adrenoceptor gene (*BAR3*) polymorphisms	Not discussed	BAR3 polymorphism might alter susceptibility to CRC risk in obese people (Japan)
Terry et al., 2003	157 cases with early colorectal neoplasia	Alcohol , tobacco use	p53	Adenomatous polyp	p53 overexpression in early CRC neoplasia positively associated with alcohol intake and inversely associated with smoking (USA)
Watson et al., 2004	596 mutation carriers from 62 HNPCC families	Tobacco use	hMLH1; hMLH2	Without adenomatous polyp	Tobacco use, hMLH1 mutation carriage, and male sex with increased risk of nonpolyposis CRC (USA)
Yin et al., 2004	685 incident cases of CRC adenocarcinomas	Alcohol	1298CC	Not discussed	A1298C was associated with statistically significant increase of CRC risk (Japan)

with the development of recurrence ($p = 0.01$) and indicated poor survival in patients with CRC. Another study [42] investigated the frequency of LOH in sporadic CRC and its effect on prognosis for 144 patients. 18q LOH was found to indicate an unfavorable outcome in patients with stage II CRC.

Poor survival from CRC was also associated with p53 mutations. In the study conducted on 56 patients with sporadic colorectal carcinoma [32], with the median follow-up time of 45 months, p53 mutations were detected in 28 of 56 American patients (50%). Thirty-three patients (59%) were alive at last follow-up, but 15 of the 23 patients who died (65%) had p53 mutations and 8 (35%) had wide-type p53. Thirteen patients developed a disease recurrence, 9 of whom (69%) had tumors with p53 mutations. p53 status and stage were found to be independent significant predictors for survival (p53 negative: $p = 0.02$; stage: $p = 0.0002$).

Alcohol and tobacco use. Watson, Ashwathnarayan, Lynch, and Roy [74] researched hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, or Lynch syndrome, and its relationship to cigarette smoking and alcohol consumption by identifying 596 mutation carriers from 62 HNPCC families. The HNPCC syndrome is known to cause 90% of CRC penetrance, but the risk of CRC increases due to tobacco and alcohol use. Thus, cigarette smoking selectively increases the CRC that manifests high microsatellite instability (MSI-high). The MSI-high tumors make up approximately 20% of all CRC and are the molecular hallmark of HNPCC.

Alcohol drinking and cigarette smoking were associated with the development of adenomatous types of colorectal polyps, which is a precursor of CRC. Asian population (Japanese, Chinese and Korean) has high frequency of genetic polymorphism in low Km *aldehyde dehydrogenase* (*ALDH2*) gene, which greatly regulates alcohol intake. Takeshita and colleagues [63] studied 200 Japanese to identify relationship between this polymorphism and lifestyles with colorectal polyps. They found that the frequency of the *ALDH2* genotype was not different between those with colorectal polyps (n = 69) and those without the polyps (n = 131). Smoking was associated with the development of colorectal polyps (OR 4.7, 95% CI 1.9–11.5) in the *ALDH2* proficient genotype. The risk of colorectal polyps was enhanced by drinking alcohol since there was a synergistic effect of smoking and alcohol drinking (> or = 60 ml/day) (OR 9.9, 95% CI 2.9–34.1).

Two other studies [65, 77] also showed the increase of CRC incidences due to alcohol and tobacco consumption. In [77] *1298CC* genotype was associated with a statistically significant increase in the CRC risk when alcohol consumption was high, while [65] reported that p53 overexpression in early CRC neoplasia might be positively associated with alcohol intake and inversely associated with cigarette smoking.

Obesity. One study [64] examined the links between polymorphisms in *beta-2* and *beta-3* adrenoreceptor genes (*BAR2* and *BAR3*) and the risk of CRC in Japan. Mutations of the *BAR2* gene at codon 27 (Glin27GLU) and of the *BAR3* gene at codon 64 (Trp64Arg) were examined in 131 CRC patients. The BAR3 polymorphism was found to have a potential to alter the susceptibility to colon cancer risk in obese patients.

Risk factors and hypercholesterolemia. Twenty-three studies focused on the relationship between risk factors and hypercholesterolemia (see Table 3). All eight factors were found to be leading to hypercholesterolemia, however, food, heredity, obesity together with low physical activity, and age were among the most explored.

Food. Seven studies showed that quality of food together with low physical activity can lead to hypercholesterolemia at early ages [4, 13, 14, 23, 41, 67, 68]. Gonzalez, Ortega, and Moreiras [23] analyzed the influence of the diet on blood cholesterol levels in a group of 156 teen-agers from 14 to 18. The diet cholesterol density was higher than the recommended one of 100 mg/1000 Kcal, and eggs, meat and milk were the most important cholesterol food sources. Women, who had the highest hypercholesterolemia, also had the highest and unbalanced lipid intake when compared to men. Cowin and Emmett [14] investigated a randomly selected group of children (214 boys and 175 girls) in south-west England. At the end of 31 months, non-fasting blood samples from all the participants were analyzed for total and high-density lipoprotein (HDL) cholesterol and triglyceride. Among the boys, total cholesterol concentration was positively associated with the intake of total fat ($r = 0.209$, $p = 0.002$) and saturated fatty acids ($r = 0.211$, $p = 0.002$). Among the girls, HDL cholesterol was positively associated with

Table 3. Risk Factors and Hypercholesterolemia

Study	Sample	Factors	Hypercholesterolemia	Mutations	Findings
Bates et al., 1999	1556 people aged 65 and older	Age, food	Total cholesterol level and high density lipoprotein	Not discussed	Women had significantly better status for plasma alpha- and beta-carotene, ascorbate, HDL-cholesterol and homocysteine, but higher concentrations of total and non-HDL-cholesterol (United Kingdom)
Bernstein et al., 2002	1,708 randomly selected men and women aged 35 to 74	Low physical activity	Apolipoprotein E	Not discussed	Significant protective effects of physical activity on HDL cholesterol in the apoE4 group versus the apoE2 group (Switzerland)
Brown et al., 2000	15,645–16,681 nationally surveyed population for 6 years	Age, obesity, tobacco	Total cholesterol level, high-density lipoprotein-cholesterol (HDL-C) and dyslipidemia	Not discussed	Prevalence of high blood and mean levels of cholesterol higher at body mass index levels over 25; rates of low HDL-C increased and mean levels of HDL-C decreased at levels of BMI increased (USA)
Celermajer et al., 1992	100 (20 cigarette smokers, 10 children with FH, 20 patients with CAD)	Age, tobacco use	Familial hypercholesterolemia	Not discussed	Endothelial dysfunction present in children and adults with FH and smokers (United Kingdom)
Costanza et al., 2005	1,543 men and women aged 35–74	Age, food, obesity, alcohol, tobacco, physical activity	Blood lipid concentrations	ABCA1, APOA1, APOE, CETP, EL, HL, LCAT, LPL, LDLR, PLTP, SR-BI	Obesity and cigarette smoking with higher serum total cholesterol, LDL, and triglycerides but with a lower HDL (Switzerland)
Cowin et al., 2001/140/	Randomly selected children (214 boys and 175 girls)	Age, food (fat, sugar)	HDL cholesterol and triglyceride	Not discussed	Dietary determinants of blood lipid concentrations differed between boys and girls (England)
Descamps et al., 2001	273 patients with severe hypercholesterolemia and family history of early cardiovascular disease	Heredity, age, low physical activity	Low-density lipoprotein (LDL) cholesterol between 240 and 300 mg dL^{-1}	LDL-R gene mutattions, Apo B-R3500Q	Presence of a genetically ascertained FH with a higher degree of atherosclerosis (Belgium)
Drexler et al., 1991	15 patients (8 with hypercholes-terolemia and 7 age-matched controls)	Age	Mean serum cholesterol 7.8 [SE 0.3] mmol/l	Not discussed	Hypercholesterolemia impaired endothelium-dependent dilatation of coronary microcirculation (Germany)
Glowinska et al., 2003	285 children and adolescents aged 14.3 yrs	Heredity, obesity	Lipid metabolism disturbances, total cholesterol	Not discussed	Young patients with obesity had significant lipid metabolism disturbances regarding total cholesterol LDL, and triglycerides (Polish)
Gonzalez et al., 1993	156 teenagers	Food (eggs, meat, milk)	Cholesterol density higher than 100mg/1000 Kcal	Not discussed	Feminine population had the highest cholesterolemia and unbalanced lipid intake when compared to men (Spanish)
Harada-Shiba et al., 2003	Female mice 12–15 weeks of age	Heredity, environmental factors	Plasma total cholesterol level	ARH locus to chromosome 1p35	The function of the hepatic LDLR in the ARH mice *in vivo*, despite its normal function *in vitro*. (Japan)
Kessling et al., 1990	571 children aged 4–19	Age	Familial hypercholesterolemia	*LDL-receptor* gene	Increased cholesterol level in children with FH and selected had defective allele of *LDL-receptor* gene (United Kingdom)
Kotseva, 2000	141 viscose workers (64 men and 77 women)	Environmental pollution (carbon disulfide (CS_2)	Total cholesterol level	Not discussed	Carbon disulfide (CS_2) caused hypercholesterolemia in viscose rayon workers (Bulgaria)
Mansfield et al., 1999	25 active and sedentary males (17–35 years old) with no personal of family history of coronary heart disease	Food, alcohol, low physical activity	HDL- and LDL-cholesterol	Not discussed	Low physical activity with higher levels of HDL-C and lower levels of LDL-C; dietary intake of saturated and monounsaturated fats and alcohol predicted changes in some apolipoprotein and lipoprotein levels (Canada)
Merched et al., 2003	ApoE-deficient mice	Heredity	Familial hypercholesterolemia	p53	A crucial role of p53 in atherosclerosis lesion development and remodeling (USA)
Pakala et al., 2004	New Zealand white rabbits	Environmental pollution (radiation)	Plasma lipid levels	Not discussed	Histological cross sections and quantification of the plaque formation had more pronounced lesions in the radiated segments (USA)
Resnicow et al., 1990	11,389 children aged 5–18	Obesity	Plasma total cholesterol	Not discussed	Children with weight (kg)/height (m^3) values above the 95th percentile had total cholesterol greater than 180 mg/dl (US)
Roest et al., 2005	187 patients with familial hypercholesterolemia	Heredity	Intima media thickness (IMT) of the carotid arterial wall in patients with FH	PON1-activity (L55M, Q192R, T-107C, C-126G, G-162A, G-824A, C-907G)	Genetic variation at the PON1 locus had a strong influence on PON1 activity as well as on carotid IMT (Netherlands)
Salazar et al., 2002	35 unrelated patients with heterozygous familial hypercholesterolemia	Heredity	FH	E92X, C371, R236W, G322S, G352D, A370T, C675W, C677Y, G(20)R, T476P, V503G, D580H, S652R, FsR757, FsS828	Broad spectrum of mutations in the *LDLR* gene in FH patients (Brazil)
Schroder et al., 2002	Cross-sectional population-based survey of 1748 Mediterranean population	Tobacco and alcohol use	Cholesterol and serum triacylglycerol	Not discussed	Worst triacylglycerol levels with heavy smoking and alcohol drinking (European Mediterranean)
Thorogood et al., 1990	208 volunteers (52 selected from each of 4 groups)	Food, alcohol	Plasma high density lipoprotein	Not discussed	Nature rather than quantity of dietary fat was important determinant of cholesterol concentrations (United Kingdom)

Study	Sample	Factors	Hypercholesterolemia	Mutations	Findings
Tonsted et al., 1999	346 patients at a lipid clinic (205 women and 141 men) aged 20–73	Food, obesity, alcohol, tobacco	Total cholesterol level	Not discussed	Low ratio of energy intake to estimated basal metabolic rate with increased energy-adjusted intakes of protein, thiamine, riboflavin, niacin, iron and cholesterol and with decreased intakes of sugar, poly and monounsaturated fats and vitamin E (Norway)
Young et al., 1993	Cohort sample 807 people (men – 380, women – 427, aged 18–74)	Physical activity	Total cholesterol level and HDL	Not discussed	Improvement in the composite physical activity score with an increase in HDL and decreases in body mass index for men, and changes in HDL cholesterol for women (USA)

Table 4. Risk Factors, hypercholesterolemia, and CRC

Study	Sample	Factors	Hypercholesterolemia	Adenomatous Polyp	Findings
Fiorenza et al., 2000	530 patients (103 colon cancer) with newly diagnosed cancer	Body mass index	Total cholesterol level, HDL-cholesterol, LDL-cholesterol, triglycerides	Not discussed	Total cholesterol, LDH cholesterol, HDL cholesterol, serum albumin lower in cancer patients (Italy)
Fujimori et al., 2002	1,349 male patients	Alcohol	Serum total cholesterol level	Colorectal adenoma	Significantly lower levels of serum cholestgerol and triglycerides in daily drinkers with adenoma than in those without (Japan)
Kamiya et al., 2000	283 men aged 40-59 with adenomatous polyp or normal cholesterol	Age, obesity	181 mg/dl and higher 209 mg/dl	Colorectal adenomatous polyp	Risk of CRC adenomatous polyp with a higher serum total cholesterol level in patients aged 40 (Japan)
Kono et al., 1990	88 men with adenoma	Food	Serum total cholesterol, triglycerides, HDL-cholesterol	Colorectal adenoma	No association between serum total cholesterol and colorectal adenoma; an increased risk of adenoma at the highest quartile of triglycerides and at the lowest of HDL-cholesterol (Japan)
Neil et al., 2005	2,871 patient cohort from 21lipid clinics in the UK	Food, tobacco use, physical activity	9.5 mmol/1 for men, 9.9 mmol/1 for women	Not discussed	4,7% deaths from cancer of digestive organs (United Kingdom)
Nomura et al., 1991	7,926 Japanese-American men	Low physical activity	Serum total cholesterol	Not discussed	Increase in serum cholesterol levels associated with decrease in risk for colon cancer, but not for rectal cancer (Japan)
Park et al., 2000	134 male patients	Food	Serum total cholesterol, triglycerides	Colorectal adenomatous polyp	Increased adenomatous polyp risk with the rise in serum cholesterol level and triglyceride (South Korea)
Tsushima et al., 2005	7,619 Japanese-American men	Alcohol and tobacco use, obesity	Serum triglyceride	Not discussed	Strong positive association of alcohol intake and pack-years of cigarette smoking with CRC; no prediction of CRC by Serum triglyceride (Japan)
Yamada et al., 1998	129 patients with CRC	Age, obesity, tobacco use, alcohol consumption	Cholesterol, triglycerode level, fasting plasma glucose	Not discussed	Positive association between serum total cholesterol levels, serum trigleceryde and colorectal carcinoma in situ (Japan)

energy intake ($r = 0.204$, $p = 0.018$) and negatively associated with intakes of polyunsaturated fat, saturated fat and sugar in multivariate analysis.

Another study conducted in England [67] examined a cross sectional sample of 208 people eating four different diets. After controlling for age, sex, and BMI, the correlation between plasma total cholesterol and Keyes score (which includes dietary cholesterol and saturated and polyunsaturated fat) was 0.37 ($p < 0.001$). The mean saturated fat intake in all groups was low (6-14% of energy), but polyunsaturated fat intake was high, so mean total fat intake was generally above that recommended, which allowed the researchers to conclude that the nature rather than quantity of dietary fat was an important determinant of cholesterol concentrations.

Four studies [4, 13, 41, 68] explored the combination of different factors, such as food, age, low physical activity, and alcohol and tobacco in causing hypercholesterolemia, however food was not the dominant factor. These studies are reviewed in further sections.

Heredity. Familial hypercholesterolemia (FH) was found to be related to the presence of mutations [15, 26, 44, 55, 57]. Worldwide, about 700 different mutations in the *low-density lipoprotein receptor (LDLR)* gene have been reported. Different authors pointed out different LDLR mutations observed more frequently in their regions. For example, in Brazil, 35 patients with heterozygous FH were studied to characterize LDLR mutations [57]. Two nonsense (E92X and C371X) and six missense LDLR mutations (R236W, G322S, G352D, A370T, C675W, and C677Y) that had been previously described in FH patients from other populations were found. Five novel missense (G(-20)R, T476P, V503G, D580H, and S652R) and two novel frame shift LDLR mutations (FsR757 and FsS828) were registered. Four patients were found to carry two different mutations in the *LDLR* gene: G352D and A370T (one patient), S652R and C675W (one patient) and T476P and V503G (two patients). Another study [26] reported that LDLR function was also destroyed in patients with autosomal recessive hypercholesterolemia.

In Netherlands, Roest and colleagues [55] studied seven most common single nucleotide polymorphisms (SNPs) in both the coding and promoter sequences of PON1 (L55, Q192R, T-107C, C-126G, G-162A, G-824, and C-907G) in terms of PON 1 activity and intima media thickness (IMT) of the carotid arterial wall in 187 patients with FH. They found that genetic variation at the PON 1 locus had a strong influence on both PON 1 activity and carotid IMT. PON1 was involved in the pathogenesis of atherosclerosis. In another study conducted in Belgium on 273 lipid patients [15], genetically ascertained FH was associated with a higher degree of atherosclerosis. In the research conducted on mice [44], p53 was shown to also play a crucial role in atherosclerosis.

Age. Age is a significant factor causing hypercholesterolemia [4, 7, 10, 13–15, 17, 35]. Elevated total and LDL cholesterol concentrations and low HDL concentrations

are a well-established risk factor for atherosclerosis. The initial stages of atherosclerosis have been shown to occur in children as young as three. In the study that examined the dietary determinants of blood lipid concentrations at 31 months of age on 389 randomly selected children, total cholesterol concentrations were positively associated with the intake of total fat (r = 0.209, p = 0.002) and saturated fatty acids (r = 0.211, p = 0.002) among boys, and HDLC with energy intake (r = 0.204, p = 0.018) among girls [14].

A study that investigated non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis [10] suggested that the latter is present in children with FH as young as 10 years old. It was also reported that a proportion of young children who are at risk for FH (i.e. carriers of a mutation causing FH) may initially present with lipid levels within the normal range [35], and elevated levels may only develop at a later age, however such damage can occur as early as 10 [17].

Obesity and low physical activity. A lot of studies investigated the relationship between obesity, low physical activity and hypercholesterolemia [5, 7, 13, 15, 22, 41, 54, 68, 80]. Obese patients typically would have a pattern of hypercholesterolemia. National Health and Nutrition Examination Survey III of 8,816 men and 10,009 women aged 20 years and older [7] showed that mean serum cholesterol levels increased with increasing BMI from 193 mg/dL among men at the lowest BMI category to 211mg/dL in men at the highest category of BMI. Among women, total cholesterol levels increased from 195 mg/dL at the lowest BMI category to 217 mg/dL at the highest BMI level. Among men, the prevalence of high blood cholesterol ranged from 13% at the lowest BMI level to 22% at the highest BMI level. The prevalence of high blood cholesterol increased from 13% among women at the lowest BMI level to 30% among women with higher BMI levels. Other authors demonstrated the relationship between excess body weight and increase blood level of cholesterol [13, 54].

Low physical activity also leads to hypercholesterolemia development [5, 15, 22, 41]. Bernstein and colleagues [5] conducted a population-based cross-sectional survey of 1,708 randomly selected men and women aged 35 to 74 years. The total energy expenditure and its percentage used in high-intensity activities was measured for each participant. The effects of the high-intensity activity interaction on the lipid profile were investigated by using multiple linear regression models. Among men, increased high-intensity activity had greater protective effects in the apoE4 group regarding (1) HDL cholesterol ($p < 0.001$), compared with either the apoE2 (interaction p = 0.05) or apoE3 (interaction $p < 0.03$) groups, and (2) triglycerides ($p < 0.03$), compared with the apoE3 group (interaction p = 0.07). A 10% increase of high-intensity activity by an apoE4 man would correspond with a 0.07-mmol/L increase in HDL cholesterol and a-0.15 mmol/L decrease in triglycerides. Among women, only the protective effect of physical activity on HDL cholesterol in the apoE4 group versus the apoE2 group was statistically significant. Some other studies pointed out that obese patients typically had a pattern of dyslipidaemia that was refractory to single drug therapy plus weight loss, and increased physical activity [5, 13, 80]. Some studies showed that healthy life styles can prevent hypercholesterolemia and related atherosclerosis development [7, 80].

Alcohol and tobacco use. Six studies reported that smoking and alcohol consumption tended to increase the level of cholesterol in the blood [7, 13, 41, 58, 67, 68]. In the study [13] conducted on 1,543 randomly selected men and women in Geneva, Switzerland, cigarette smoking were individually associated with higher serum total cholesterol, LDL cholesterol, and triglycerides, while alcohol intake was associated with higher serum total cholesterol, HDL cholesterol, and HDL cholesterol/LDL cholesterol ratio. Similar relationships were found in another study [58] that used a cross-sectional population based survey of a southern European Mediterranean population.

While smoking was found to be negatively correlated with hypercholesterolemia, alcohol can differently affect the level of cholesterol. Mansfield, Mcpherson, and Koski [41] studied healthy, young men (17 to 35 years old) to determine the relationship of energy and nutrient intake and physical activity to concentration of plasma cholesterol. They found that dietary intake of saturated and monounsaturated fats and alcohol predicted changes in some apolipoprotein and lipoprotein levels. Because alcohol and waist-to-hip ratio were both important predictors of LDL-L level, even in active young men, the consumption of low levels of alcohol (< 3 drinks per week) might be beneficial only if waist-to-hip ratio was maintained within the healthful range by achieving an appropriate balance of physical activity and macronutrient intake.

Other studies, however, indicated that alcohol could increase the level of cholesterol [58, 67, 68], which was observed in heavy drinkers, confounded by smoking and obesity. For example, Thorogood and colleagues [67] who studied people eating different diets found that plasma HDL values were not associated with any measure of fat intake, but there was a significant correlation of 0.24 between high density lipoprotein values and alcohol intake. Another study [68] reported hypercholesterolemia development in patients with self-reported consumption of alcohol.

Environmental pollution. The relationship between environmental pollution and hypercholesterolemia was investigated in two studies [37, 49]. Kotseva [37] studied the effect of occupational exposure to carbon disulfide (CS_2) concentrations bellow threshold limit value (TLV)-time-weighted average (TWA) (31 mg/m^3) on total cholesterol. The cross-sectional study involved 141 viscose rayon workers (64 men) and 141 age- and gender-matched controls without occupational contact with noxious chemicals. A cumulative exposure index (CS_2) was calculated for each worker by the CS_2 concentrations in that job environment, by

multiplying the number of years held in a particular job. Depending on the job and specific work place the CS_2 concentrations were between 1 and 30 mg/m^3. Cholesterol levels were significantly higher in the exposed group (4.9–0.7) compared with the controls (4.6–0.7). Adjustment for age, smoking, BMI and gender showed the significant effect of the CS_2 index on the total cholesterol ($p < 0.001$). The prevalence of hypercholesterolemia was significantly higher in the exposed group (42.6%), compared with the controls (26.2%).

Pakala and colleagues [49] investigated the effect of ionizing radiation on patients with hypercholesterolaemia. They used animal models (New Zeland White rabbits), after feeding with 1% hypercholesterolemic (HC) diet for 7 days, followed by balloon denudation of both the iliac arteries, and continued on 1% HC diet. After four weeks, in 12 rabbits one of the iliac arteries was radiated (192-Ir, 15 Gy), and in five rabbits both the iliac arteries were sham treated and fed with 0.15% HC diet. Four weeks later in radiated arteries plague area became significantly larger (32%) than in sham. Macrophage-positive area in radiated arteries was 2.4 times greater than the macrophage-positive area in the nonradiated arteries.

Risk factors, hypercholesterolemia, and CRC. Nine studies explored the relationship among the risk factors, hypercholesterolemia and CRC development [19, 21, 33, 36, 47, 48, 51, 71, 75]. Most of these studies were conducted in Japan and Korea and used predominantly male population. Risk factors causing hypercholesterolemia and CRC were food, age, obesity, alcohol and tobacco use, and low physical activity.

In their prospective study of serum cholesterol levels and large-bowel cancer, Nomura and colleagues [48] measured serum cholesterol levels in 7,926 Japanese-Americans for over 20 years. During that period they identified 231 incident cases of colon cancer and 97 cases of rectal cancer. An increase in serum cholesterol was associated with a decrease in risk for colon cancer ($p = 0.01$), but not for rectal cancer. This association appeared stronger as the site of cancer moved from the sigmoid colon to the cecum. In a later study of the serum triglyceride, glucose and CRC that used 7,619 Japanese-American men [71], the same research team found a strong positive relationship between alcohol intake and pack-years of cigarette smoking with CRC. BMI and heart rate were also positively related to colon, but not to rectal cancer. At the same time, they found that serum triglyceride did not predict the development of either colon or rectal cancer. Similar results were found in Kono and colleagues' study [36] that examined serum lipids and colorectal adenoma among 1,143 male Japanese.

In contrast, other studies indicated a positive relationship between serum cholesterol levels and the risk of CRC, rather than an inverse relation [19, 47, 51, 75]. In a case-control study of 129 patients with colorectal carcinoma and 258 matched controls among examinees undergoing a health check-up in Tokyo, there was a significant positive association between serum total cholesterol levels and the risk of colorectal carcinoma *in situ* after adjustment for age, sex, BMI, smoking status and alcohol consumption. A modest increase of colorectal carcinoma *in situ* risk was also observed in the highest category ($\geq$ 116 mg/dl) of fasting plasma glucose levels, which supported the hypothesis that hyperinsulinaemia might play an important role in colorectal carcinogenesis.

Higher serum HDL-cholesterol was observed to lead to the risk of colorectal adenomatous polyp [21, 33, 36, 51]. In the study of 283 Japanese men with and without adenomatous polyp conducted by Kamiya and colleagues [33], the risk of colorectal adenomatous polyp was associated with a higher serum total cholesterol level in the 40s. In another study [36] an increased risk of adenoma at the highest quartile of triglycerides and at the lowest of HDL-cholesterol was found for 88 Japanese men, while in [51] a significant trend of incidences of adenomatous polyp risk was observed with the rise in serum cholesterol level (p trend = 0.07) in 134 Korean male patients. Another study [21] conducted in Japan on 1,349 male patients who underwent both barium enema examination and total colonoscopy confirmed that alcohol intake, which is associated with increased colorectal adenomas, and serum cholesterol levels are closely related.

Conclusion. The present review of current studies on risk factors for CRC development has revealed a relationship between factors that can lead to CRC and those that lead to hypercholesterolemia. Risks of hypercholesterolemia and CRC increase with age, but a tendency is observed for both to occur in younger people, which was also reported in earlier reviews [10, 78]. The risk of hypercholesterolemia and CRC increases in developed countries where the risk factors are most evident. Although the role of many individual risk factors is still controversial the analysis of their significance in combination might be important for diagnostic and development of the models for prediction of cancer occurrence.

The role each factor plays in CRC development depends on patient's predisposition to cancer diseases and the degree of a factor presence. Heredity is an important factor in increasing the probability of CRC and hypercholesterolemia. In 95–100% of cases, when mutations MADH4, SMAD4, BMPR1A, APC, and LKB1 are present, adenomatous polyp acts as a precursor to CRC. However, in some types of mutations, such as MLH1, MSH2, MSH6, and PMS2, CRC can develop without a polyp. Many authors have suggested that for patients with an adenomatous polyp as a precursor to CRC, the role of other factors and their combination in the development of CRC increases significantly. Mutations Chr 18q21 and p53 significantly decrease survival rates of CRC patients.

Heredity and related atherosclerosis can cause hypercholesterolemia that is frequent for many patients with adenomatous polyps. Adenomatous polyps are typically accompanied by hypercholesterolemia and atherosclerosis changes in blood vessels. Paraf and colleagues [50] showed that cholesterol crystal em-

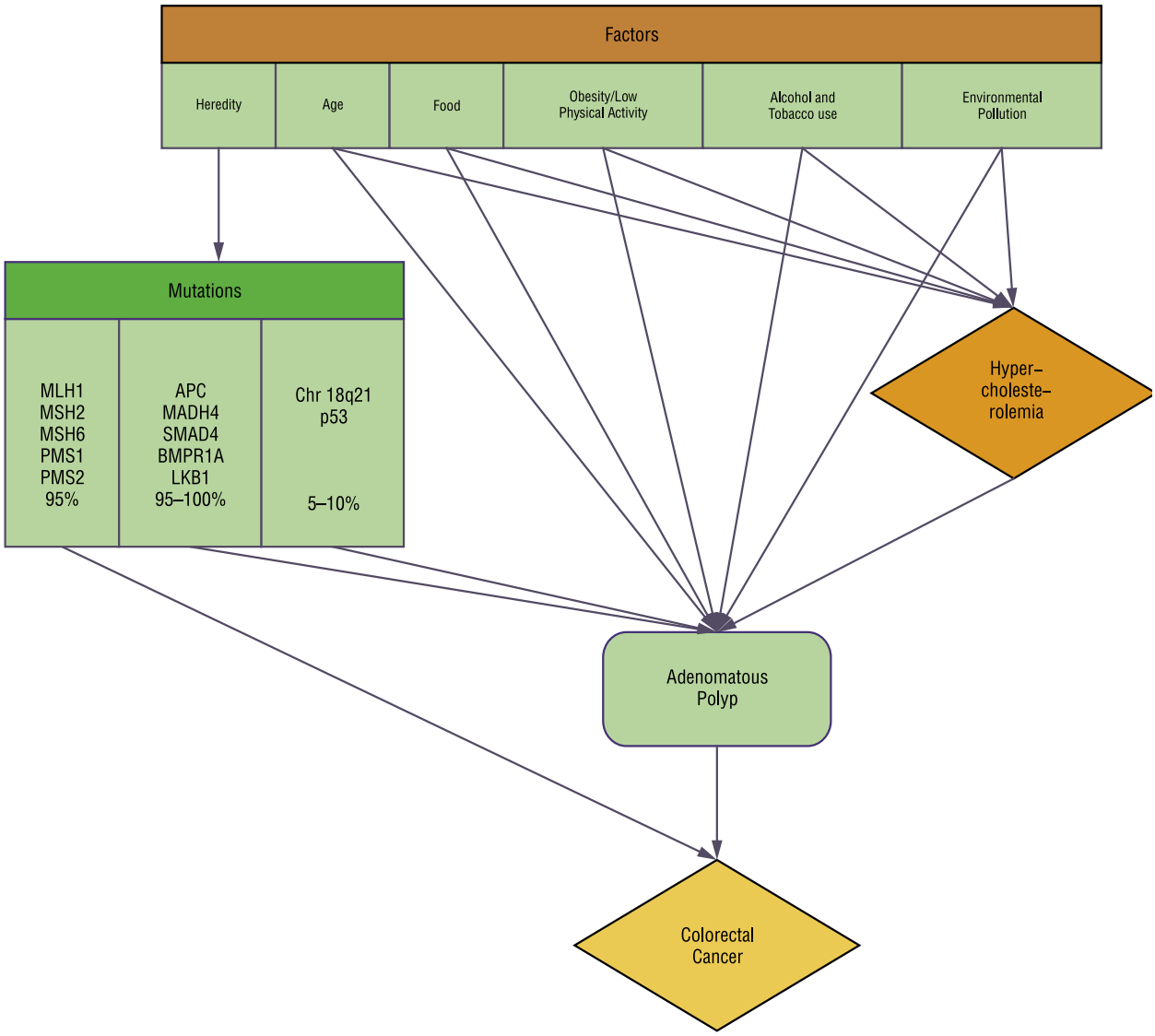

Figure. Relationship between risk factors, hypercholesterolemia, and CRC

bolization was observed in an adenomatous colonic polyp with foci of adenocarcinoma in patients with an abdominal aortic aneurysm. The fact that some patients with CRC had atherosclerosis leads to the conclusion that those patients had an inherited predisposition to hypercholesterolemia that can result in the development of atherosclerosis. In such cases hypercholesterolemia concurrently with atherosclerosis can increase the risk of CRC occurrence. Accordingly, the combination of factors, specifically heredity, tobacco use, dietary intake and low physical activity, increases incidences of hypercholesterolemia and potential CRC development.

The majority of those identified with colorectal adenomas had multiple behavioral risk factors for CRC and hypercholesterolemia. High fat-protein and low fiber food, low physical activity and related obesity, alcohol and tobacco use, as well as environmental pollution, can directly affect colon and rectum causing damage in their cells and leading to the growth of adenomatous polyps. At the same time they increase cholesterol blood level resulting in atherosclerosis and, subsequently, lead to a decreased blood supply in colon and rectum, accordingly, increasing the risk of CRC. Hypercholesterolemia can be viewed as one of the important factors causing the emergence of adenomatous polyps and leading to CRC.

In conclusion, we suggest that there is a relationship between the risk factors causing CRC and hypercholesterolemia. We graphically present this relationship in the Figure. The direction of the arrows reflects direct and indirect relationships that exist between the risk factors, mutations, hypercholesterolemia, adenomatous polyp and CRC.

This model is tentative and serves as a first attempt to understand the relationship between risk factors, CRC and hypercholesterolemia. The limitation of this study is its reliance on a limited number of reviewed studies, bounded by 15 year time period. In addition, the review was not comprehensive and might not have included all the potential studies on the topic. Other than specified eight risk factors might deem important in the development of CRC and hypercholesterolemia. More detailed studies on correlation between hypercholesterolemia and CRC and the role of mutations in the development of hypercholesterolemia and CRC

need to be conducted. Of great importance is to examine the combined effect of risk factors in CRC and hypercholesterolemia development, and the tendency for younger people to develop cancer.

Determining the relationship between hypercholesterolemia and CRC can provide useful information for preventive purposes. Decreasing the damaging effect of environmental factors can lower the risk of CRC incidences. Taking into account that patients with adenomatous polyps had hypercholesterolemia, it is important to closely watch their total cholesterol level after polypectomy, especially in younger patients. Patients with increased total serum cholesterol level and residing and working in polluted areas, overweight patients leading sedentary life, as well as consumers of tobacco and alcohol should be examined for the presence of adenomatous polyps at earlier ages than is usually required. Special attention should be given to patients who previously resided in other geographic areas and patients with a family history of CRC diseases. In case an adenomatous polyp is diagnosed in patients with hypercholesterolemia, mutations diagnostic should be performed. Identifying a significant correlation between CRC and hypercholesterolemia might increase cancer survival rates and decrease potential risks of CRC incidences.

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РАК ПРЯМОЙ КИШКИ И ГИПЕРХОЛЕСТЕРИНЕМИЯ: ОБЗОР СОВРЕМЕННЫХ ДАННЫХ

Цель: **несмотря на результаты широких исследований, свидетельствующие о высоком уровне холестерина в крови больных раком прямой кишки (РПК), взаимосвязь между факторами, вызывающими гиперхолестеринемию, и факторами, вызывающими развитие РПК до сих пор не установлена. Целью работы был анализ данных литературы о факторах, приводящих к гиперхолестеринемии и РПК, и выявление взаимосвязи между этими факторами.** ***Методы:*** **проведен систематический поиск в базах данных MEDLINE и PUBMED за период 1990–2005 гг. для выявления исследований факторов риска, вызывающих РПК и гиперхолестеринемию. Из 255 найденных публикаций были отобраны 66 по следующим критериям: (1) сообщение об оригинальном исследовании; (2) обсуждается хотя бы один из 8 факторов; (3) обсуждается гиперхолестеринемия; и/или (4) обсуждается рак толстой или прямой кишки.** ***Результаты:*** **публикации были сгруппированы по 4 направлениям исследования: (1) работы, изучающие взаимосвязь различных факторов и заболеваемость РПК; (2) работы, изучающие взаимосвязь различных факторов и заболеваемость РПК и роль мутаций в развитии РПК; (3) изучение факторов, вызывающих гиперхолестеринемию; и (4) работы, изучающие взаимосвязь различных факторов, гиперхолестиринемии и развития РПК. Представлено обсуждение этих данных, основные результаты приведены в таблицах.** ***Выводы:*** **установлена взаимосвязь между факторами, которые могут привести к развитию РПК, и таковыми, вызывающими гиперхолестеринемию. Несмотря на то, что роль ряда индивидуальных факторов риска по-прежнему противоречива, анализ их общей значимости может иметь важное значение для диагностики и для моделирования прогноза заболевания.**

Ключевые слова: **рак прямой кишки, факторы, гиперхолестеринемия, аденоматозные полипы, мутации.**