# ALCOHOL CONSUMPTION AND COLORECTAL CANCER: A CASE-CONTROL STUDY IN ARMENIA

**Master of Public Health Thesis Project Utilizing Professional Publication Framework**

**Narek Sarkissian, MD**
**MPH Candidate**

**College of Health Sciences**
**American University of Armenia**

**Primary Advisor: Marie Diener-West, PhD**
**Secondary Advisor: B. Grace Sullivan, ARPN, PhD**

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# Table of Contents

## Abstract

***Objectives:*** Colorectal cancer is one of the leading causes of cancer mortality in the industrialized world. During the last decade, the incidence rate of colorectal cancer in Armenia has increased. The study aimed to explore an association between alcohol consumption and risk of colorectal cancer in Armenia.

***Subjects and Methods:*** The study utilized a case-control design with one control for each case. 144 patients diagnosed with colorectal cancer during the study period from May to August, 2005 were included in the study as cases. The control group included patients seen in the same departments during the same period with diagnoses other than colorectal cancer such as hemorrhoid, perianal fistula, paraproctitis, anal fissure and others that are free of bowel disorders. Information was collected using self-administered questionnaire on various health-related issues, including drinking and smoking habits. All data were analyzed using SPSS and STATA software.

***Results:*** The analysis showed that preference of vodka as the type of alcohol increases the risk of having colorectal cancer after controlling for other variables (OR=2.06; 95%CI 1.15-3.69 p-value 0.016) compared with non-drinkers. The risk of having colorectal cancer also increases with alcohol consumption of 3 or more drinks versus 1-2 drinks after controlling for other variables (OR=1.36; 95%CI 1.05-1.76; p-value 0.02). The analysis also showed no association between colorectal cancer and the frequency of alcohol use (OR=1.00; 95%CI 0.72-1.40; p-value 0.98). In addition, usage of alcohol in the participants' family during childhood significantly increases the risk of developing colorectal cancer (OR=6.45; 95%CI 1.74-13.54; p-value

0.000). There is no confounding effect of smoking and BMI (OR=0.97; 95% CI 0.83-1.14; p-value 0.71). There is a potential confounding effect of age (OR=1.06; 95% CI 1.04-1.09; p-value 0.000).

***Conclusion:*** The study has demonstrated evidence that there is a need for educational programs regarding the risks of alcohol consumption to make such information available for the public. Based on the results of the study, the public educational program should recommend avoiding use of vodka as the preferred alcohol type, shifting from amount of 3 or more drinks to a lesser amount of alcohol (1-2 drinks), and also should make people understand and get them acquainted with the result that the common use of alcohol in a child's upbringing significantly increases the risk of developing colorectal cancer. However, more research is needed to obtain data that might serve for decision-making regarding nation-wide preventive programs. Further, the observed protective effect of the frequent use of wine on developing colorectal cancer needs to be confirmed by additional research, since the results are not in agreement with those of previous studies.

# Introduction

***General Overview. Burden of Disease.***

Colorectal cancer is one of the leading causes of cancer mortality in the industrialized world (2). Colorectal cancer is the second most common cause of death among patients with neoplastic diseases in the United States, after lung and breast cancer in women, and lung and prostate cancer in men (2). In the United States, 1 in 20 persons has colorectal cancer and about 60,000 people die annually, 93% of whom are at the age of 50 years and above (1, 23). The American Cancer Society estimates that about 106,370 new cases of colon cancer (50,400 men and 55,970 women) and 40,570 new cases of rectal cancer (23,220 men and 17,350 women) will be diagnosed in 2004 (6). Colorectal cancer is expected to cause about 56,730 deaths (28,320 men and 28,410 women) during 2004, accounting for about 10% of cancer deaths (6).

In 38 European countries, five cancers – lung, colon and rectum, breast, stomach, and prostate – accounted for more cases and deaths than all other cancers combined (71). Depending on sex, just four cancers accounted for more than half of the disease burden (71). The four most common primary sites in males were the lung, colon and rectum, stomach, and prostate (71). In females the main cancer sites were the breast, colon and rectum, stomach, and lung (71). In European countries, deaths from cancers of the colon and rectum ranked second (71).

In Armenia colorectal cancer is an important topic of discussion and concern in almost all branches of medicine. During the last decade, the incidence rate of colorectal cancer in Armenia has increased (1,3,23). In 1996 colorectal cancer appeared to be the

sixth most common cause of death among patients with neoplastic diseases, whereas in 2002, according to the statistical data from the World Health Organization (WHO), it appears to be the third, after breast and lung cancer in women, and lung and stomach cancer in men, and the sixth cause of death in Armenia (1,3,23). It has become a great public health concern in Armenia, and according to the forecasts of specialists, soon colorectal cancer will rank as the most widespread oncological disease. The incidence of colorectal cancer varies across locations of the colon. The most common site for colorectal cancer (up to 70%) is in the distal parts of the colon (sigmoid colon and rectum), followed by tumors in the ascending colon and caecum (16-18%) (22). Transverse and descending colons are affected in 10-12% and 8-10% respectively (22).

The 5-year relative survival rate is 90% for people whose colorectal cancer is treated at an early stage, before it has spread. But, only 38% of colorectal cancers are found at that early stage. Once the cancer has spread to nearby organs or lymph nodes, the 5-year relative survival rate goes down to 66%. For people whose colorectal cancer has spread to distant parts of the body such as the liver or lungs, the 5-year relative survival rate is 9% (6).

Only 3-5% of colorectal cancers are discovered at an early stage ($1^{st}$ and $2^{nd}$ stages) (1, 23), and late-stage surgical or chemotherapeutic treatment offer poor prospects for survival. More than half of the colorectal cancer patients examined in Yerevan have disease that has spread to nearby organs or lymph nodes, already has a complicated inflammatory process and abscess present, or has spread to distant parts of the body such as the liver or lungs which negatively impact the life expectancy of the patients (1,23).

***Literature Review.***

Colorectal cancer is one of the most studied types of cancer. Colon cancer is essentially the only cancer that occurs with approximately equal frequency in men and women (4). Rates of colon cancer vary by race and ethnic status; the highest rates are seen among Caucasians of northern European origin and the lower rates among Caucasians of southern European background (4). Migrant studies have shown that the disease is particularly sensitive to changes in environment (4).

The risk factors for developing colorectal cancer include medical conditions, such as having inflammatory bowel diseases, a personal or family history of colorectal cancer or colorectal polyps, and certain hereditary syndromes. The risk of developing colorectal cancer increases with advancing **age**. There are also some modifiable factors, which enhance the risk of colorectal cancer, such as lack of physical activities, incorrect nutrition and absence of regular screening. Other factors, which might contribute to the risk of colorectal cancer, include obesity, alcohol consumption, and tobacco use.

One of the most important factors for the development of colorectal cancer is **polyps** (5, 31). Although there are many types of colonic polyps, only adenomatous polyps have the potential to develop into invasive cancer (5, 31, 42). Adenomas are benign neoplasms which are found throughout the large bowel. Although they are benign, they are considered true neoplasms and precursors of most colon cancer; there is evidence for an adenoma-carcinoma sequence (5, 31, 42, 48, 49). Some studies have found that 57% of early cancers were contiguous with benign adenomatous tissue (5). Others supported the suspected relationship between colorectal polyps and cancer incidence and extend the association to colorectal cancer mortality (42). The presence of

contiguous benign and malignant tissue suggests that cancer arose from the adenoma. More than 90% of cancers of the colon are adenocarcinomas (4). Finally, adenomatous polyps and carcinomas have similar risk factors (5).

There are some modifiable factors related to colon cancer. Some factors influence polyp development, while others influence neoplastic change. Physical activity, obesity, and consumption of a diet high in fat and low in fiber, bowel movement frequency, are associated with an increased risk of colorectal cancer (4, 7, 8, 10).

The majority of epidemiologic studies to date indicate that **obesity** is associated with an increased risk for colon cancer, especially among men (4, 7, 8). More than one billion adults worldwide are overweight and at least 300 million are clinically obese (72). In the analysis carried out for the World Health Report, 8-42% of certain cancers were attributable to high body mass index (BMI) (72). Several studies show a stronger relation between BMI and colon cancer death rates in men than in women (8, 72). The results of Ford's study agree with those of other prospective studies that have reported on the relation between obesity and colon cancer among men (7). However, in contrast to some other studies, Ford also found a strong association between body mass index and colon cancer among women (7). Increased stature, independent of weight, is associated with increased colon cancer risk, with odds ratios for men of 2.1 and for women of 1.6 (4).

Some studies have shown the importance of **inflammatory bowel diseases** in the colorectal cancer development (4, 11, 52). Crohn's disease and ulcerative colitis, the inflammatory bowel diseases of unknown etiology, have long been known to be associated with a higher risk of colon cancer (4, 11, 52, 53). The risk of colon cancer increases with the duration of inflammatory bowel disease and the cancer in ulcerative

colitis should not be disregarded or underestimated (2, 52). Professor J.M. Rhodes in his study (1996) made a hypothesis that environmental factors work with an inherited genetic factor to produce Crohn's disease, ulcerative colitis, or colon cancer (54).

Decreased **physical activity** has emerged as a factor that is consistently associated with an increased risk of colon cancer (4, 32, 33). Physical activity may reduce the risk of colon cancer by effects of prostaglandins, reduced intestinal transit time, and higher antioxidant levels (72).Most studies have concentrated on occupational activity, although studies examining leisure time and total activity and participation in college athletics also have shown a reduced risk for the more active (4, 32, 33). The association has been observed in both sexes. The population-based cohort study conducted in Norway by Thune and Lund (1996) supports a protective effect of total physical activity on colon cancer, but not rectal cancer, in both males and females (32). Overall physical inactivity was estimated to cause 1.9 million deaths and 19 million DALYs globally, and about 10-16% of cases of colon and rectal cancers (72).

Various **occupational risk factors** have been studied in relation to colorectal cancer. The association has been most consistent for occupational exposure of asbestos. Also, described an elevated risk for colorectal cancer and adenomas among workers exposed to polypropylene (31).

The finding of significant interaction by **educational level** in men is hard to explain. This may reflect change or inadequate control for factors associated with lower education such as increased physical activity (8). All these data stress the importance of incorporating physical activity into one's lifestyle, not becoming overweight, and eating a diet that is low in animal products and high in plant foods and low-fat daily products (9).

Several studies investigated prospectively the association between **infrequent bowel movements** (every third day or less) and the use of laxatives in relation to incidence of colorectal cancer in women (10). It has been suggested that low bowel movement frequency, by increasing concentrations of carcinogens in the stool and increasing their contact with the gut wall, elevates the risk of colorectal cancer (10). No significant association was seen between laxative use and colorectal cancer risk (10). For regular laxatives users a slight but non-significant association was found for colon cancer. This association was limited to distal colon cancer. It showed a slight indication of a decreased risk for rectal cancer for all categories of laxative users (10).

As with many cancers, men and women who have a **family history** of colon cancer are at increased risk of the disease; first-degree relatives of patients with common colorectal cancer have an increased risk for colorectal cancer (4, 31, 45, 48). This risk is greater if a diagnosis was at an early age and is greater when other first-degree relatives are affected (45). Some investigators estimate the risk to be approximately twofold (4). Most studies have examined only the risk associated with having a history of colon cancer in first-degree relatives, comparing cases with individuals without such a family history (4).

It has been suggested that, in women, a **family history of breast, ovarian, and endometrial cancer** may be related to an increased risk of colon cancer (4, 51). There is an approximate 30 percent increased risk of colorectal cancer if first-degree relative had breast cancer (4, 16). Results of several studies suggest that the observed breast and colorectal cancer relationship in women may be a result of shared reproductive hormonal factors (51).

Colorectal cancer has provided fascinating insights into the **genetic** events involved in adult tumorigenesis (49). Family studies have suggested that there may be an inherited predisposition to many apparently sporadic colorectal cancers (49). Several studies suggest that an inherited susceptibility to colonic adenomatous polyps and colorectal cancer is common and that it is responsible for the majority of colonic neoplasms observed clinically (47, 48). The challenge for the future will involve understanding the interaction between environmental and genetic factors (49). Colorectal cancer is a disease of industrialized Western countries. There is clear evidence for the role of environmental factors in the etiology from the geographical correlation between incidence rates and the average level of fat and (inversely) the level of fiber in the diet (49). The rapid change in incidence rates for migrants moving from low to high incidence areas supports this view (49). According to Giancarlo Marra and Richard Boland (1995), hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant disorder characterized by the occurrence within a family of multiple cases of colorectal cancer in the absence of gastrointestinal polyposis (50). The prevalence of this syndrome is not yet clear, but in may account for 1%-5% of all colorectal cancers (50).

Low intake of fruit and vegetables is estimated to cause about 19% of gastrointestinal cancer (72). The relation between **vegetable and fruit consumption** and colorectal cancer risk was comprehensively assessed in many studies. For colon cancer, no statistically significant association with total vegetable intake or total fruit intake was found (14, 62, 63, 70). However, among men and women, an inverse association was observed with vegetables and fruit combined (4, 14, 62, 63, 70). *Brassica* vegetables (the genus *Brassica* belongs to the vast family of plants, the *Brassicacea*; the most familiar is

the common cabbage - *Brassica oleracea* , with its varieties broccoli, cauliflower, kale, and Brussels sprouts - *Brassica* cruciferae) and cooked leafy vegetables showed inverse association for both men and women (14). Among women and, to a lesser extent, among men, inverse associations were stronger for distal colonic tumors than for proximal colonic tumors (14). For rectal cancer, no statistically significant associations were found for vegetable consumption or fruit consumption (14). As in other cohort studies, the observed inverse relationships between vegetable and fruit consumption and occurrence of colorectal cancer were less strong than relations reported in case-control studies (14).

There is considerable evidence that the high intake of red **meat** increases the risk of colorectal cancer among both men and women (2, 60, 65, 67, 70). Meat, protein, and fat are consistently, almost universally, positively related to risk (4, 60, 65, 67, 70). The analysis showed that the risk of having colorectal cancer increased with everyday meat use compared with not-daily meat use, with preference of heavily browned surface of fried meat compared with lightly browned (15, 60, 65, 67, 70). There is no statistically significant risk of having colorectal cancer across different types of meat as well as across preferred cooking methods for different meat types (15). Some studies have also shown a protective effect of frequent use (more that once/week) of boiled and fried sausage use on risk of colorectal cancer (15). Possible explanation of the association of meat intake with colorectal cancer risk include carcinogenic effects of fatty acids or protein metabolites as well as formation of some cancer-promoting substances during cooking (2, 4). Several studies postulated an association between frequency of food intake and risk of colon cancer (4, 60, 65, 67, 70). They reasoned that, as bile acids are secreted into the bowel with each intake of food, and as the concentration of secondary

bile acids in bile is determined, in part, by the frequency of recirculation, risk of colon cancer would rise with frequency of food consumption (4). Other authors (Martha L. Slattery, Kenneth M. Boucher et. all) support the hypothesis that overall dietary intake pattern is associated with colon cancer, and that the dietary pattern associated with the greatest increase in risk is the one which typifies a Western-style (higher body mass index and a greater intake of total energy and dietary cholesterol) diet (60, 65, 67, 70). Another study does not support a role of fresh meat and dietary fat in the etiology of colon cancer; as an exception, some processed meats may increase the risk, but the mechanisms is not yet clear (64). High consumption of seafood was associated with decreased risk of colorectal cancer in males, but increased risk in females; the reason for this discrepancy is unclear (68).

Several ecologic studies have demonstrated no significant association or inverse association between **calcium, vitamin D, and milk** intake and colorectal cancer mortality (4, 61, 66). Several studies suggests that a high intake of either cereal fiber, total fiber, calcium, and phosphorum in relation to energy intake was found to be associated with a reduced risk ratio of colorectal cancer (61, 66). Another study suggests that carotene and ascorbic acid can have a protective effect on risk of colorectal cancer, while there is no evidence of protection by other micronutrients considered, such as retinol, Vitamin D, and calcium (69).

Evidence that **female sex hormones** may play a role in the subsequent development of colorectal cancer has accumulated from time trends in colorectal cancer rates and from epidemiologic studies (36, 37). Results from several studies provide additional support for earlier suggestions that parity may have a protective effect against

the development of colorectal cancer, similar to the effect reported in the case of breast, endometrial and ovarian tumors (35, 38). These studies provide evidence in support of a protective effect of pregnancy on colon cancer risk, and more specifically a trend of increasing protection with increasing number of pregnancies (35, 38). Postmenopausal hormone use (HRT) was associated with a statistically significant reduction in colon, but not in rectum, cancer incidence (36, 37). Colon cancer is clearly on the list of conditions against which postmenopausal HRT provides useful protection (36, 37). The results of a population-based prospective study (63,000 women) in Norway suggest that reproductive factors, which are of importance in the etiology of cancer of the breast and genital organs in women, are not similarly related to risk of colorectal cancer (39).

Numerous studies have investigated the positive association between **cholecystectomy** and subsequent colorectal cancer (24, 25, 26). Two possible explanations for such an association have been advanced: (a) cholecystectomy alters bile acid metabolism, producing specific bile acid concentrations in the colon that may be carcinogenic: and (b) symptomatic chelelithiasis, leading to cholecystectomy, may share certain risk factors, such as obesity, with colon cancer.

Several investigations studied the risk of colorectal cancer in relation to **serum cholesterol** and beta-lipoprotein (43). These studies found a significant, direct relation between serum cholesterol levels and the incidence of rectal cancer (43). The findings from a prospective study, conducted by Abraham M.Y. Nomura, provide evidence that a low serum cholesterol level preceding the diagnosis of colon cancer in men could be a preclinical manifestation of the disease process, but it is unclear why the association may be stronger for cecum-ascending or right-sided colon cancer (44).

Most studies' results suggest that **smoking** is associated with colorectal cancer (13, 27, 29, 30, 31). The smoking and adenoma association has been demonstrated in several studies (13, 27, 29, 30, 31). Smoking in the prior 20 years has a strong relation to small colorectal adenomas, smoking at least 20 years in the past is related to larger adenomas, and the indication period for colorectal cancer is at least 35 years (27). The study of Polly M. Newcomb (1995) where smoking habits were ascertained by interview from Wisconsin women aged 30-74 years with newly reported diagnoses of colon (n=536) and rectal (n=243) cancer and 2315 randomly selected population controls showed that risk significantly increased with greater number of cigarettes smoked per day, longer duration of smoking, and earlier age at initiation for both the colon and the rectum; among former smokers, risk for both colon and rectal cancer remained elevated; these data suggest that women who smoke are at elevated risk of both colon and rectal cancer and that increased risk persists even among former smokers (29). Several studies showed that smoking cigarettes is not associated with colorectal cancer, while smoking cigars and pipes has been shown to be more common in cases than in controls (4). To clarify the relationship between tobacco use and risk of colorectal cancer, the study, conducted by Ellen F. Heineman (1994), evaluated a cohort of 248,046 American veterans followed prospectively for 26 years that showed a positive association between smoking and colorectal cancer (30). The possible explanation was irreversible damage due to carcinogens in cigarette smoke (13). The other data suggest that older women who smoke have a lower of colorectal cancer than non-smokers. The effect may be mediated by an antiestrogenic effect of smoking (28).

Each year over 55 000 young Europeans die from the effect of alcohol abuse: one in four deaths in European men aged 15-29 years is related to alcohol (71). The welfare, health service, insurance, enforcement and penal costs associated with drinking, and the costs resulting from loss of production, accrue to a total societal cost of 1-3% of GDP (71). The consumption of alcoholic beverages is estimated to be responsible for about 9% of the total disease burden within the European Region, increasing among others the risk of liver cirrhosis, raised blood pressure, heart disease, stroke, pancreatitis and cancers of the oropharynx, larynx, oesophagus, stomach, liver and rectum (71). Over 90% of the countries in the Region have an annual consumption per person exceeding two liters of absolute alcohol (the level suggested by the evidence as being associated with the lowest average death rate) (71). The European Region has the highest alcohol consumption in the world (71).

Various studies have tried to explore an association between **alcohol** and tobacco use and the risk of colorectal cancer. Global alcohol consumption has increased in recent decades, with most or all of this increase occurring in developing countries such as Armenia (72). Worldwide, alcohol accounts for 3.2% of deaths (1.8 million) and 4.0% of DALYs (58.3 million) (72). In developing countries with low mortality, alcohol accounts for 6.2% of disease burden measured in DALYs (72). High alcohol consumption is a probable independent risk factor for cancers of the colon and rectum (8, 55). The risk of polyps has been demonstrated to be three times higher for those who drink and smoke, and twelve times more for those drink and also smoke compared with those who did not use alcohol and did not smoke (12). It has been suggested that alcohol has an indirect

effect on colorectal cancer development (12, 31, 55). In patients with at least one carcinoma, the risk of having cancer increases with alcohol consumption (12).

The relationship between alcohol consumption and colorectal cancer in humans has been examined in 52 major studies during 35 years from 1957 to 1991 and was summed up by Gabriel A. Kune and Luis Vitetta in their report (55). An association was found in five of the seven correlational studies. An elevated risk was found in about half of the 31 case-control studies and, of these, in 9 of the 10 studies using community controls but in only 5 of the 17 studies using hospital controls ($p=0.008$), suggesting that the absence of association when hospital controls are used is due to a high prevalence of alcohol consumption/alcohol related illness in the hospital controls. Of the 14 cohort studies, an association with alcohol was found in 10. A positive dose-response effect was found in 2 of 3 cohort studies and in all 4 case-control studies with community controls in which this effect was examined. In both case-control and cohort studies, a positive association was found for females and males between alcohol and both colon and rectal cancer. When the type of alcohol consumed was examined separately, beer was the principal type of at-risk alcohol beverage, with much less risk for spirits and least risk for wine. Statistically significant elevations of risk were more often found in males than in females and slightly more frequently for rectal than for colon cancer and were related almost entirely to beer, rather than to wine and spirit, consumption. In addition, several studies showed an association between alcohol/beer consumption and adenomatous polyps, consistent with the hypothesis that alcohol stimulates the colorectal mucosa (55).

There is a contradiction between several studies: some showed that smoking is an independent risk factors (56), others showed that cigarette has a synergistic effect with

alcohol (57). Other authors concluded that risk for adenoma is not significantly associated with alcohol consumption after adjustment for cigarette smoking (58).

In 1957, Stocks first reported an elevated, though not statistically significant, risk of colorectal cancer among daily beer drinkers compared with abstainers (OR=1.4) (4). Subsequently, the association between alcohol and cancer of the large bowel has been explored in other studies. The frequency of consumption (i.e., none, infrequently, occasionally, or daily) also has been used to compare cases with non-cases (4). Many of ecologic studies of alcohol and colon cancer have shown a positive association (4, 5, 55). The association is similar for men and women in the studies that reported sex-specific associations, with the exception of a single study where colon cancer mortality was significantly correlated with both total alcohol and beer consumption in men, but only with beer in women (4). Geographic differences in cancer mortality have been positively correlated with beer consumption (4). Changes in per capita beer consumption from 1950-1952 to 1960-1962 have been positively correlated with changes in colon cancer mortality rates from 1960-1964 to 1970-1974 in the US, United Kingdom, Australia, and New Zealand (4). A significant, positive correlation between wine and cancer mortality rates across 41 US states has been reported (4). However, a non-significant negative correlation was found across 29 countries in the only other study that considered this association (4). Consumption of spirits across 41 US states correlated positively with colon cancer mortality rates (4).

A case-control study of both adenoma and colorectal cancer in Japan found that daily alcohol drinking was associated with an increased risk of adenoma in proximal colon (OR=1.95) (5). This study did not find an association between beer drinking and

risk of adenomas or cancer, but it did find a strong association with whiskey drinking. In a British case-control study conducted among colonoscopy patients, current drinkers in comparison with non-drinkers had three times the risk of adenoma (5). Naveau et al. (5) studied the effect of alcoholism and cirrhosis on the risk of adenoma. Alcoholics were over three times more likely to have adenomas than were nonalcoholics, controlling for cirrhosis (5). The prevalence of adenoma was over three times greater in patients with cirrhosis than in those without cirrhosis, even after controlling for alcoholism (5). Of the different types of alcoholic beverages, beer in particular has been found to be a risk factor for adenoma in a number of studies. Kikendall et al. compared subjects with adenomas (n=102) at colonoscopy with colonoscopy-negative controls (n+89) and found beer consumption to be associated with polyps (5). Drinking five or more beers per week resulted in an estimated relative risk of 2.81 (5). In a case-control study in North Carolina, Sundler et al. found alcohol to be a significant risk factor for adenomas in men (5). When patterns of alcohol consumption were analyzed, it was found that beer, rather than wine or liquor, was a risk factor for adenoma (5). In the Australian case-control study, men who drank beer were more than twice as likely to have adenomas as nondrinkers (5). In a cross-sectional survey of Japanese male "self-defense officials", total ethanol consumption was positively associated with risk of adenomatous polyps (OR=2.4) among men who consumed 60 ml of ethanol per day compared with nondrinkers (5).

Several studies have found no association between alcohol consumption and risk of adenoma. In the Health Professionals Follow-up Study, no association of alcohol intake with adenoma was found after adjustment for saturated fat and fiber intake (5). In

examining the alcohol data from the French case-control study, Riboli et al. found no association between risk of polyps with total ethanol intake or with consumption of wine or distillates (5). A Danish case-control study found no association between risk of adenoma and alcohol as a percentage of total caloric intake (5). Alcohol consumption in drink-years was not associated with adenoma in a recent study based on colonoscopy patients (5).

Many studies show a positive correlation between alcohol use and different cancers. There are several studies that investigated the joint effects of tobacco and alcohol consumption on the risk of squamous cell carcinomas of the upper aero-digestive tract using data from a hospital-based case-control study (17, 20). Another study showed the association between alcohol use and cancer death carried (18, 20). The risk of cancer death showed a similar trend, but increased more in heavy drinkers (18. 20). The authors conclude that moderate alcohol consumption was associated with the lowest risks of all-cause and cancer mortality, especially among nonsmokers (18). Also, there is a study that shows the association between alcohol consumption and increased risk of lung cancer in men; however, because of the possibility of residual confounding by smoking, this finding should be interpreted with caution (19). In the same study, intake of wine was associated with a reduced risk of lung cancer (19). This seemingly protective effect may be related to the antioxidant properties of wine and deserves further attention (19). There is also evidence of positive association between alcohol and breast cancer in women. Alcohol drinking appears unrelated to prostate cancer risk (21).

With alcohol consumption, the overall conclusion present evidence is that alcohol, particularly beer consumption, is an etiologic factor for colon and rectal cancer for both

females and males (55). Despite a very wide range of different epidemiological studies on the etiology of colorectal cancer, few have paid attention to the role of alcohol as the risk factor of the colorectal cancer and these studies have contradictory results.

***Objectives.***

The incidence of colorectal cancer in Armenia has remained high over the past decade and has demonstrated an increasing trend. At the same time, colorectal cancer etiology research has been absent in our country. The current study is designed to explore whether or not there is an association between alcohol consumption and colorectal cancer in Armenia. The *research hypothesis* is that risk of having colorectal cancer increases with increased alcohol consumption and the risk varies across different types of alcohol.

## Subjects and Methods

***Research Question and Study Design.***

*The research question* addressed by the study is to determine whether alcohol intake is an independent risk factor for the development of colorectal cancer, and whether any such effect depends on the type of alcoholic beverage consumed. The *research hypothesis* is that risk of having colorectal cancer increases with increased alcohol consumption and the risk varies across different types of alcohol (Ho: OR = 1 Ha: OR ? 1). *Study design and rationale for that design.* The study designed as a case-control study with one control for each case. A case-control study design was proposed in order to determine the association between alcohol consumption, its risk variation across different types of alcohol, and risk of developing colorectal cancer in both men and women in Armenia. This is an appropriate design considering the descriptive and analytical aims of

the study and also the short period of time and shortage of financing. The *target population* is the general population of Armenia. The *study population* will include one case and one control group. The patients, both men and women, from the all existing specialized proctology departments in Yerevan ("Michaelyan" Institute of Surgery, "Saint Nerses" Hospital, "Saint Grigor Lusavorich" Medical Center) served as ***cases*** who have undertaken the examinations to confirm the presence of cancer (rectoscopy/colonoscopy). Yerevan city is chosen by convenience, because MPH students can conduct the research in Yerevan, and because the specialized coloproctological departments exist only in Yerevan. The total list of potential cases included approximately 144 patients in period from May to August. Patients, being treated in the department at the time of the study, were interviewed by filling in the self-administered questionnaires. The ***control*** group included patients, both men and women, seen in the same department during the same period, with diagnoses other than colorectal cancer such as hemorrhoid, perianal fistula, paraproctitis, anal fissure and others that are free of bowel disorders. The patients were from the same department of coloproctology. The reason for choosing this group of patients from the same department as the controls is that all patients are required to undergo the rectoscopy/colonoscopy according to the protocol so that we could undoubtedly mark as controls patients who do not have colorectal cancers. The main advantage for choosing these controls is that they did undergo the same diagnostic procedures as cases (rectoscopy/colonoscopy). The numbers of subjects available as cases, as well as controls, are limited. In addition, controls of the study as designed are not more available than are cases. Thus, it is proposed to conduct the study with one control for each case. The self-administered questionnaires were

distributed to all potential cases and controls. In order to minimize bias, it was decided to ask the orientation question to all controls regarding a family history of colorectal cancer. Family members and friends of cases were excluded as possible controls if they had not undertaken procedures such as rectoscopy and/or colonoscopy. After identification of their eligibility, controls were matched with cases by age (5 year interval age groups.

***Study population.***

Definition of cases

All patients, regardless of gender and age, who are diagnosed with colorectal cancer (proved both histologically and by rectoscopy/colonoscopy) for the first time during the period from May to August, 2005 in specialized proctological departments of Michaelyan" Institute of Surgery, "Saint Nerses" Hospital, "Saint Grigor Lusavorich" Medical Center, and are residents of Armenia.

Definition of controls

Patients seen in the same departments of Michaelyan" Institute of Surgery, "Saint Nerses" Hospital, "Saint Grigor Lusavorich" Medical Center with diagnoses other than colorectal cancer such as hemorrhoid, perianal fistula, paraproctitis, anal fissure and others that are free of bowel disorders, who do not have family history of colorectal cancer, and are residents of Armenia, will be matched by age and gender to the cases.

Exclusion criteria

Patients unwilling to participate in the study, controls that self-report bowel problems or report family history of colorectal cancer.

***Main Variables.***

The presence of the colorectal cancer was considered an outcome (dependent) variable of the study. Independent variables included different alcohol consumption levels and preference of different types of alcohol. A summary of the study variables and their measurement scales are presented in the table 1 below.

***Table 1. proposed research variables by name and type***

| Variable type/name | Type | Measure |
|---|---|---|
| **Outcome (dependent)** Presence of colorectal cancer | Binary | Measures as 1 (cases) or 0 (control group) |
| **Hypothesized determinants (independent)** Drinking status | Ordinal | Measured by Likert-type as 1 – never, 2 – former, 3 - current |
| Alcohol type preference | Nominal | Measured as vodka – yes/no, brandy – yes/no, whiskey – yes/no, beer – yes/no, wine – yes/no, liquor – yes/no |
| Frequency of alcohol consumption | Ordinal | Measured by Likert-type scale as 1 – daily, 2-weekly, 3 – monthly, 4 – yearly, 5 - never |
| Amount of alcohol used | Ordinal | Measured by Likert-type scale as 1- 1 drink a day, 2 – 2 drinks a day, 3 – 3-5 drinks a day, 4 – 6-9 drinks a day, 5 – more than 10 drinks a day |
| Frequency of 5 or more drinks in the last month | Ordinal | Measured by Likert-type scale as 1 – none, 2 – once, 3 – twice, 4 – 3-5 times, 5 – 6-9 times, 6 – 10 and more times |
| Smoking status | Ordinal | Measured by Likert-type scale as 1 – never used tobacco, 2 – ex-cigarette smokers, 3 – current light smokers, 4 – current moderate smokers, 5 – current heavy smokers |
| Age | Continuous | Numerical |
| Body mass index ($kg/m^2$) | Continuous | Numerical |

***Ethical Consideration.***

The study was implemented after approval from the Institutional Review Board/Committee on Human Research (IRB) of the American University of Armenia. The permission of the hospital Department heads selected for participation in the study is obtained prior to the program implementation. The study involves minimal risk for the participants. Minimal risk, defined by Institutional Review Board, is a risk, where "the

probability and magnitude of harm or discomfort anticipated in proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests". The slight inconvenience for the participants is time-consuming for the procedure of filling in the questionnaire. Only heavy alcohol users might felt a bit embarrassed while answering the self-administered questionnaires.

An oral consent form (is attached as Appendix) has been developed to provide all possible participants with an opportunity to analyze the information presented, to ask questions about the study and decide whether or not they want to participate in the study. The consent form includes information about who is conducting the study, the topic of the study, its purpose, procedures, participant's role in the study, risks and benefits of the study, the duration and type of participation, confidentiality, and right to withdraw at anytime they want without any penalty. It was decided to mention in the consent form all procedures regarding the issues of confidentiality and anonymity. No identifying information is included in the questionnaires. The personal information of the participants, obtained from the Departments, will be not disclosed and be destroyed immediately after the completion of the data collection process.

***Sample size.***

Sample size was calculated based on the formula offered for case-control study (calculations by STATA for different values is presented in Appendix 3):

$$n = \frac{\left\{z_{1-a/2}\sqrt{2P_2(1-P_2)} + z_{1-b}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right\}^2}{(P_1-P_2)^2}$$

$$P_1 = \frac{(OR)P_2}{(OR)P_2 + (1-P_2)}$$

Where $P_1$ – proportion exposed in cases, $P_2$ – proportion exposed in controls

Taking into account the values of odds ratio from previous research (1.4-3.0), the proportion of people consuming alcohol (14-22%), and power equal to 0.8, the cases and controls were calculated to include at least 117 participant each (4, 5, 7, 8, 12, 31, 55, 56, 58). Taking into account the hypothesized refusal rate of 10%, the sample size is estimated to be no less than 140.

***Data Collection. Description of the Instrument.***

The study instrument is a self-administered questionnaire (Appendix 4). For both case and control groups, the subjects filled in self-administered questionnaires on various health-related issues, including drinking and smoking habits. All participants were asked multiple-choice and open-ended questions about the average number of glasses of wine, beers, and drinks of spirits consumed per day, week, month, and year. Healthy lifestyle factors were studied by assessing smoking status, type of tobacco used, number of years of smoking, and body weight. Data on smoking habits, age and body weight were analyzed to minimize the risk of residual confounding by smoking, age, and BMI, which are the key issues. In addition to the questions of the questionnaires, the controls were asked a question about family history of colorectal cancer. Questionnaires do not contain any identification information. It was pre-tested internally among patients at "Michaelyan" Institute of Surgery and some changes were made to avoid misunderstanding. Questionnaires were distributed to participants at the departments and the oral consent forms were presented beforehand. Answering the question lasted approximately 10-15 minutes.

***Data Analysis.***

All data were analyzed using SPSS and STATA software. Data collected through self-administrated questionnaires interviews was entered into the SPSS computer software. Appropriate computations and calculations were performed for making possible further analysis. Statistical analysis included descriptive statistics made using SPSS software (frequency tables, cross-tabulations) and logistic regression analysis using STATA software. The data from SPSS were also imported into a STATA file for performing conditional logistic regression. Some additional variables were generated in the STATA file in the final analysis. The results from SPSS and STATA were compared. The purpose of the analysis is to estimate the odds ratio of colorectal cancer by considering the amount and type of alcohol consumption, while taking potential confounding into account.

The strength of association was examined using ORs and 95% confidence interval derived from the logistic regression.. All ORs were adjusted for such potentially confounding factors as age (continuous variable), body mass index (continuous variable), and smoking status (ordinal variable). All $p$ values were based on 2-sided tests, and $p < 0.05$ was considered statistically significant.

## Results

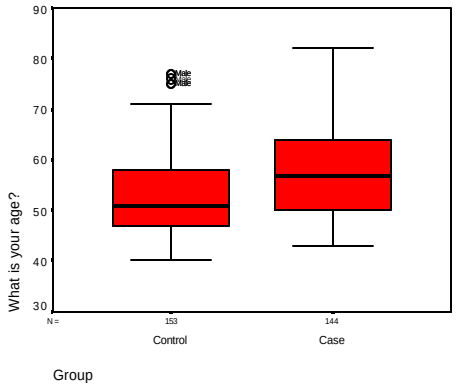
The data were collected from 144 cases and 153 controls. The refusal rate was 0.7% among cases (1 out of 145 patients refused to participate), and 1.3% among controls (2 out of 155 persons refused to participate). No questionnaire was considered as incomplete (maximum two unanswered questions in a questionnaire)

The results show that cases tended to be older than controls: the most frequent age interval in cases is 55-59 years old (32 cases), whereas in controls is 45-49 (51 cases). Moreover, there are few controls with age greater that 70 years old (6), whereas in cases there are 27 persons with age greater than 70 years. Thus, the results have shown the evidence that cases with colorectal cancer in this study are generally older than non-cancer patients (controls) (table2, graph1).

***Table 2. Age distribution of cases and controls***

| Age group | Group | | Total |
|---|---|---|---|
| | Control | Case | |
| 40-44 | 14 | 8 | 22 |
| 45-49 | 51 | 22 | 73 |
| 50-54 | 24 | 28 | 52 |
| 55-59 | 34 | 32 | 66 |
| 60-64 | 17 | 20 | 37 |
| 65-69 | 6 | 8 | 14 |
| 70-74 | 1 | 16 | 17 |
| 75-79 | 5 | 9 | 14 |
| 80-84 | - | 2 | 2 |
| Total | **153** | **144** | 297 |

***Graph 1. Age distribution of cases and controls***



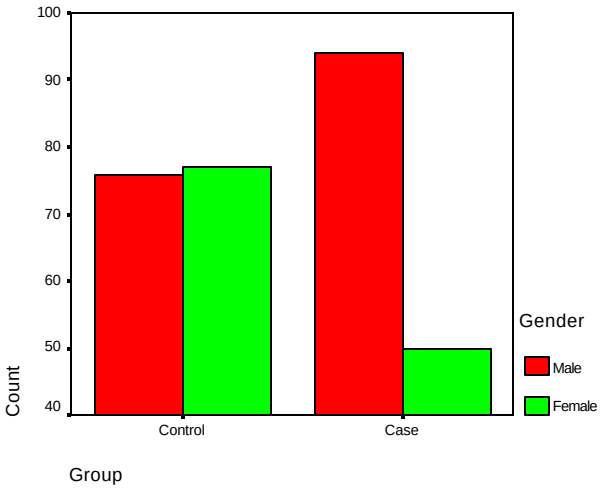

In cases, the majority of participants are male (65.3%); in this group the proportion of participants who are male is greater than proportion of participants who are

female by almost twice (94 vs. 50). In controls, the proportions of male and female participants are approximately the same (49.7% vs. 50.3%) (table 3, graph 1).

***Table 3. Gender distribution of cases and controls***

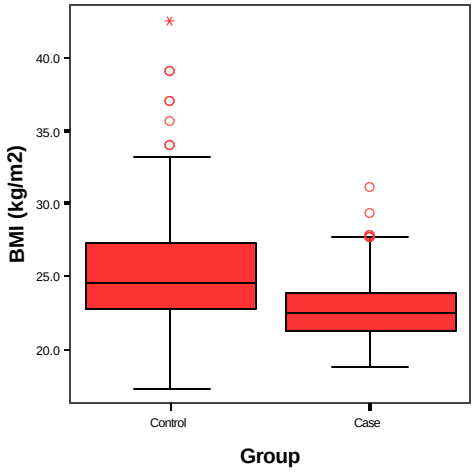
| | | | Gender | | |
|---|---|---|---|---|---|
| | | | Male | Female | Total |
| Group | Control | Count | 76 | 77 | 153 |
| | | % within Group | 49.7% | 50.3% | 100.0% |
| | Case | Count | 94 | 50 | 144 |
| | | % within Group | 65.3% | 34.7% | 100.0% |
| Total | | Count | 170 | 127 | 297 |
| | | % within Group | 57.2% | 42.8% | 100.0% |

***Graph 1. Gender distribution of cases and control***

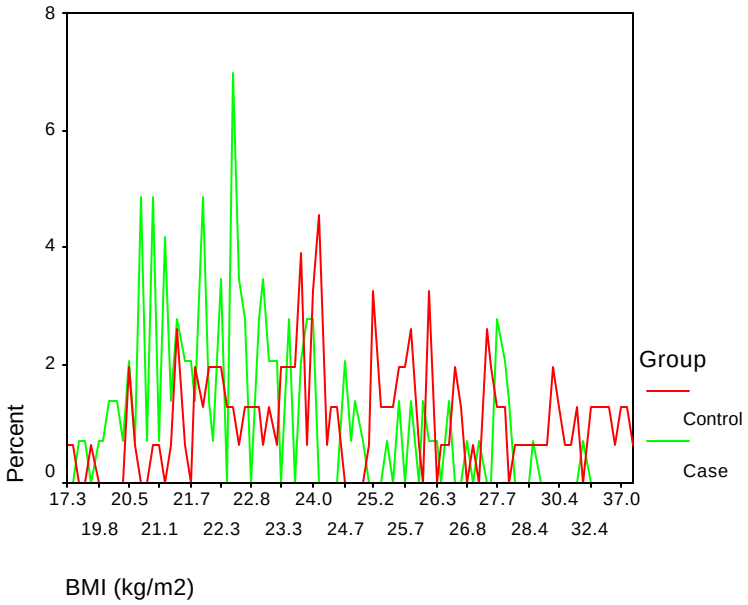



The body mass index (BMI) is lower in cases than in controls which explains the oncological nature of disease; patients with any kind of cancers are more likely to lose weight then others. In cases, the median body mass index is 22, in controls – 24.25 $kg/m^2$ (Graph 2, 3).

***Graph 2.Distribution of cases and controls by BMI***

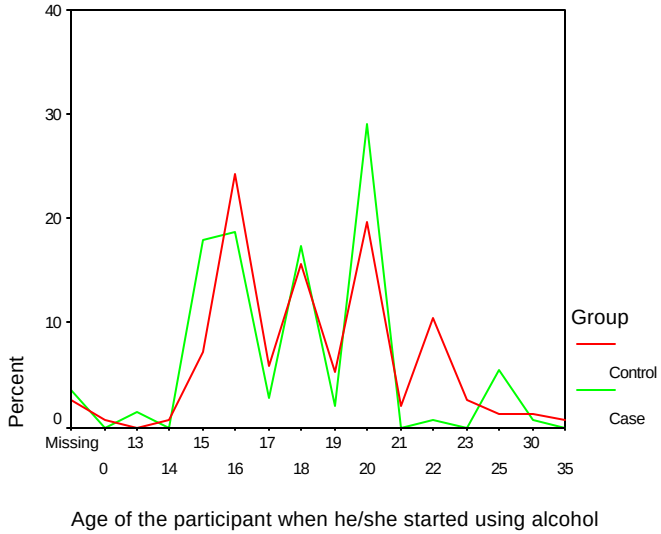



***Graph 3. Distribution of cases and controls by BMI***



According to the results, the majority of the participants started using alcohol at the age of 15-20 (Graph 4).

***Graph 4. Distribution of cases and controls by the age when they first used alcohol***




The results have shown that 13.1% of all controls and 2.1% of all cases have never used alcohol of any kind. From cases, 14.6%, 28.5 %, and 50.7% consume alcohol daily, weekly, and monthly respectively. For controls, 12.4% consume alcohol daily and 22.2 and 47.1 consume alcohol weekly and monthly respectively. The majority of cases, as well as controls, consume vodka (80.1% vs. 55.6%). Wine is consumed more frequently in controls than in cases (46.6% vs. 26.2%). Brandy is the second most common alcohol beverage consumed by both case and control groups and is almost the same proportion in both groups (50.4% vs. 54.1%). The amount of alcohol consumed varies among cases and controls; 6-9 and 10+ more drinks (in a day when participants consume alcohol) occurs more often in cases than in controls (12.8% and 13.5% vs. 4.5% and 1.5%).

Results for conditional logistic regression controlling for multiple different variables and corresponding 95% Confidence Interval (CI) as well as the total number of responses for each item are summarized in the table 4 below:

***Table 4. Unadjusted ORs and 95% CIs for colorectal cancer by frequency of alcohol consumption, alcohol type preferred, and amount of alcohol preferred***

| Alcohol item | Number (%) of | | OR (95%CI) |
|---|---|---|---|
| | Cases | Controls | |
| ***Alcohol frequency*** | | | |
| daily | 21 (14.6) | 19 (12.4) | **7.37 (1.89-28.79)[1]** |
| weekly | 41 (28.5) | 34 (22.2) | **8.04 (2.20-29.38)[1]** |
| monthly | 73 (50.7) | 72 (47.1) | **6.76 (1.92-23.74)[1]** |
| yearly | 6 (4.2) | 8 (5.2) | 5.00 (1.00-25.02) |
| never | 3 (2.1) | 20 (13.1) | 1.00[2] |
| | 144 (100) | 153 (100) | |
| ***Alcohol preferred*** | | | |
| Vodka | 113 (80.1) | 74 (55.6) | **3.22 (1.88-5.50)[1]** |
| Brandy | 71 (50.4) | 72 (54.1) | 0.37 (0.13-1.08) |
| Whiskey | 5 (3.5) | 12 (9.0) | 0.86 (0.53-1.38) |
| Beer | 27 (19.1) | 22 (16.5) | 1.19 (0.64-2.22) |
| Wine | 37 (26.2) | 62 (46.6) | **0.40 (0.25-0.68)[1]** |
| Liquor | 11 (7.8) | 19 (14.3) | 0.50 (0.23-1.11) |
| ***Amount of alcohol preferred (quantity)*** | | | |
| 1 drink | 20 (14.2) | 29 (21.8) | 1.00 |
| 2 drinks | 46 (32.6) | 47 (35.3) | 1.42 (0.70-2.86) |
| 3-5 drinks | 38 (27.0) | 49 (36.8) | 1.12 (0.55-2.29) |
| 6-9 drinks | 18 (12.8) | 6 (4.5) | **4.35 (1.47-12.88)[1]** |
| 10+ drinks | 19 (13.5) | 2 (1.5) | **13.78 (2.88-65.84)[1]** |
| | 141 (100) | 133 (100) | |
| ***Daily*** | | | |
| 1-2 drinks | 11 (52.3) | 13 (68.4) | 1.00 |
| 3+ drinks | 10 (47.7) | 6 (31.6) | 1.17 (0.74-1.84) |
| | 21 (100) | 19 (100) | |
| ***Weekly*** | | | |
| 1-2 drinks | 4 (9.8) | 11 (32.3) | 1.00 |
| 3+ drinks | 37 (90.2) | 23 (67.7) | 1.17 (0.74-1.84) |
| | 41 (100) | 34 (100) | |
| ***Monthly*** | | | |
| 1-2 drinks | 45 (61.6) | 46 (63.9) | 1.00 |
| 3+ drinks | 28 (38.4) | 26 (36.1) | 1.17 (0.74-1.84) |
| | 73 (100) | 72 (100) | |

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| | | | |
|---|---|---|---|
| ***Yearly*** | | | |
| 1-2 drinks | 6 (100.0) | 6 (75.0) | 1.00 |
| 3+ drinks | - | 2 (25.0) | 1.17 (0.74-1.84) |
| | 6 (100) | 8 (100) | |
| ***Daily*** | | | * |
| Vodka | 18 | 14 | |
| Brandy | 1 | - | |
| Whiskey | 6 | 12 | |
| Beer | 4 | 4 | |
| Wine | 2 | 1 | |
| Liquor | 0 | 2 | |
| ***Weekly*** | | | ***** |
| Vodka | 35 | 27 | |
| Brandy | 2 | 8 | |
| Whiskey | 28 | 19 | |
| Beer | 19 | 13 | |
| Wine | 8 | 9 | |
| Liquor | 2 | 3 | |
| ***Monthly*** | | | ***** |
| Vodka | 57 | 28 | |
| Brandy | 2 | 4 | |
| Whiskey | 34 | 38 | |
| Beer | 3 | 4 | |
| Wine | 25 | 48 | |
| Liquor | 9 | 13 | |
| ***Ever drink alone*** | 83 (57.6) | 35 (22.9) | **4.59 (2.78 -2.58)[1]** |
| ***Usage of alcohol in participants' family during the growing up(childhood)*** | 37 (25.7) | 5 (3.3) | **10.24 (3.89 -26.9)[1]** |

**[1] Statistically significant variables (p<0.05)**
**[2] Reference group**
*** For these variables the data were insufficient to obtain interpretable results for conditional logistic regression**

According to the results of simple conditional logistic regression, statistically significant increases of risk of colorectal cancer were estimated for some variables. The risk of having colorectal cancer increases with daily, weekly, and monthly alcohol consumption (OR=7.37 with 95% Confidence Interval 1.89-28.79 and p-value 0.004,

OR= 8.04 with 95%CI 2.20-29.38 and p-value 0.002, and OR=6.76 with 95%CI 1.92-23.74 and p-value 0.003 respectively). There was a statistically significant association between preference of vodka and the risk of developing colorectal cancer (OR=3.22; 95% CI 1.88-5.50; p-value 0.000). The association also was estimated between amount of alcohol preference and colorectal cancer. The risk of having colorectal cancer increases with amount of 6-9 and 10+ drinks of alcohol consumption (OR=4.35; 95% CI 1.47-12.88; p-value 0.008 and OR=13.78; 95% CI 2.88-65.84; p-value 0.001 respectively). In addition, a statistically significant effect was observed between preference of alcohol consumption alone, without company, and the risk of developing colorectal cancer (OR=4.59; 95% CI 2.78-2.58; p-value 0.000) and usage of alcohol in participants' family during upbringing (childhood) and the risk of having colorectal cancer (OR=10.24; 95% CI 3.89-26.9; p-value 0.000).

The results of simple conditional logistic regression also demonstrated a protective effect of wine consumption and the risk of developing colorectal cancer (OR=0.40; 95% CI 0.25-0.68; p-value 0.001).

There was no statistically significant effect of yearly alcohol consumption on the development of colorectal cancer (OR=5.00; 95% CI 1.00-25.02; p-value 0.05). There were also no statistically significant associations between the alcohol type preferred, other than vodka and wine (brandy: OR=0.37; 95% CI 0.13-1.08; p-value 0.07; whiskey: OR=0.86; 95% CI 0.53-1.38; p-value 0.531; beer: OR=1.19; 95% CI 0.64-2.22; p-value 0.574; liquor: OR=0.50; 95% CI 0.23-1.11; p-value 0.09) and colorectal cancer. Similar non-significant results were obtained for amount of alcohol preferred as 2 drinks and 3-5 drinks (OR=1.42; 95% CI 0.70-2.86; p-value 0.327; and OR=1.12; 95% CI 0.55-2.29; p-

value 0.746 respectively). The OR's of the four alcohol items (daily 1-2, 3+ drinks, weekly 1-2, 3+ drinks, monthly1-2, 3+ drinks, and yearly 1-2, 3+ drinks) are the same (OR=1.17; 95% CI 0.74-1.84; p-value 0.51) and it is not surprisingly because they represent the same variable but on different measurement scales. The interpretation is not that daily usage of 3+ alcohol is the same as monthly usage of 3+ alcohol, but rather, that the comparison of 3+ versus 1-2 drinks is the same, whether participants express it as daily, weekly, monthly or yearly consumption. The data were insufficient to obtain interpretable results from conditional logistic regression for preference of alcohol type (vodka, brandy, whiskey, beer, wine, and liquor) for the frequency of alcohol used (daily, weekly, monthly, and yearly).

Possible interactions between different statistically significant risk factors were examined. No association between them was revealed. All variables with statistically significant associations ($p < 0.05$) were included in different multiple logistic regression models. Models were tested by Log Likelihood Ratio test to determine the best fitting model. Characteristics of different tested models are summarized in the table below.

***Table 7. Results of Log Likelihood Ratio test for different multiple logistic regression models:***

| | Variable name | OR | SE | z | P(z) | 95%CI | Llog likelihood test |
|---|---|---|---|---|---|---|---|
| M1 | Vodka as alcohol type preferred | 3.22 | 0.88 | 4.27 | 0.000 | 1.88-5.50 | $Chi^2$ 19.25 p 0.0000 |
| M2 | Vodka as alcohol type preferred | 3.27 | 0.92 | 4.22 | 0.000 | 1.89-5.67 | $Chi^2$ 19.33 p 0.0001 |
| | Frequency of alcohol use | 1.04 | 0.17 | 0.27 | 0.79 | 0.76-1.43 | (compared Model 1) |
| M3 | Vodka as alcohol type preferred | 2.39 | 0.68 | 3.08 | 0.002 | 1.37-4.16 | $Chi^2$ 39.66 p 0.0000 |
| | Usage of alcohol in participants' family during the growing up (childhood) | 6.86 | 3.45 | 3.83 | 0.000 | 2.56-18.40 | (com pared with Model 1) |
| M4 | Vodka as alcohol type preferred | 2.08 | 0.62 | 2.45 | 0.014 | 1.16-3.72 | $Chi^2$ 36.31 p 0.0000 |
| | Ever drink alone | 3.12 | 0.87 | 4.07 | 0.000 | 1.80-5.38 | (compared |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | with Model 1) |
| M5 | Vodka as alcohol type preferred | 2.69 | 0.76 | 3.51 | 0.000 | 1.55-4.68 | $Chi^2$ 27.00 p 0.0000 |
| | Amount of alcohol preferred | 1.39 | 0.17 | 2.72 | 0.007 | 1.10-1.77 | (compared with Model 1) |
| M6 | Vodka as alcohol type preferred | 1.72 | 0.52 | 1.79 | 0.074 | 0.95-3.11 | $Chi^2$ 50.81 p 0.0000 |
| | Usage of alcohol in participants' family during the growing up(childhood) | 5.51 | 2.83 | 3.34 | 0.001 | 2.02-15.06 | (compared with Model 3, 4) |
| | Ever drink alone | 2.60 | 0.75 | 3.32 | 0.001 | 1.48-4.58 | |
| M7 | Vodka as alcohol type preferred | 2.05 | 0.60 | 2.47 | 0.014 | 1.16-3.64 | $Chi^2$ 45.39 p 0.0000 |
| | Usage of alcohol in participants' family during the growing up(childhood) | 6.45 | 3.27 | 3.68 | 0.000 | 2.39-17.44 | (compared with Model 3, 5) |
| | Amount of alcohol preferred | 1.36 | 0.18 | 2.35 | 0.019 | 1.05-1.76 | |
| M8 | Vodka as alcohol type preferred | 2.33 | 0.68 | 2.90 | 0.004 | 1.32-4.13 | $Chi^2$ 39.79 p 0.0000 |
| | Frequency of alcohol use | 0.94 | 0.15 | -0.36 | 0.715 | 0.68-1.30 | (compared |
| | Usage of alcohol in participants' family during the growing up(childhood) | 7.00 | 3.54 | 3.85 | 0.000 | 2.60-18.88 | with Model 2,3) |
| M9 | Vodka as alcohol type preferred | 1.93 | 0.58 | 2.18 | 0.029 | 1.07-3.47 | $Chi^2$ 39.52 p 0.0000 |
| | Ever drink alone | 2.74 | 0.79 | 3.51 | 0.000 | 1.56-4.83 | (compared with Model 4, 5) |
| | Amount of alcohol preferred | 1.25 | 0.16 | 1.78 | 0.076 | 0.98-1.61 | |
| M10 | Vodka as alcohol type preferred | 2.77 | 0.80 | 3.54 | 0.000 | 1.58-4.87 | $Chi^2$ 27.27 p 0.0000 |
| | Amount of alcohol preferred | 1.40 | 0.17 | 2.75 | 0.006 | 1.10-1.78 | (compared with |
| | Frequency of alcohol use | 1.09 | 0.18 | 0.52 | 0.604 | 0.79-1.50 | Model 2,5) |
| **M11** | **Vodka as alcohol type preferred** | **2.06** | **0.61** | **2.42** | **0.016** | **1.15-3.69** | **$Chi^2$ 45.39 p 0.0000** |
| | **Amount of alcohol preferred** | **1.36** | **0.18** | **2.32** | **0.020** | **1.05-1.76** | **(compared with** |
| | **Frequency of alcohol use** | **1.00** | **0.17** | **0.02** | **0.984** | **0.72-1.40** | **Model 7,8,10)** |
| | **Usage of alcohol in participants' family during the growing up(childhood)** | **6.45** | **3.28** | **3.66** | **0.000** | **2.38-17.48** | |
| M12 | Vodka as alcohol type preferred | 1.66 | 0.51 | 1.65 | 0.100 | 0.91-3.04 | $Chi^2$ 56.41 p 0.0000 |
| | Frequency of alcohol use | 1.41 | 0.28 | 1.70 | 0.088 | 0.95-2.09 | (compared |
| | Amount of alcohol preferred | 1.26 | 0.17 | 1.67 | 0.095 | 0.96-1.65 | with Model |
| | Ever drink alone | 3.18 | 1.13 | 3.26 | 0.001 | 1.59-6.39 | 6,7,8,9,10) |
| | Usage of alcohol in participants' family during the growing up(childhood) | 4.86 | 2.54 | 3.02 | 0.003 | 1.74-13.54 | |

Based on the results of likelihood ratio test, the best fitting (parsimonious) model includes variables of vodka as alcohol type preferred, amount of alcohol preferred, frequency of alcohol use, and usage of alcohol in participants' family during the growing up(childhood). The model was tested with goodness-of-fit test to compare with saturated model. There was no significant difference between the selected model and the saturated model (Hosmel-Lemeshow $chi^2$ = 0.00; Prob>$chi^2$=0.9837), which supports the choice of the selected model is the best fitting model. According to the model, preference of vodka as the type of alcohol increases the risk of having colorectal cancer after controlling for other variables (OR=2.06; 95%CI 1.15-3.69 p-value 0.016) compared with non-drinkers. The risk of having colorectal cancer also increases with amount of 3+ drinks of alcohol consumption versus 1-2 drinks after controlling for other variables (OR=1.36; 95%CI 1.05-1.76; p-value 0.02). According to the model, there is no statistically significant association between colorectal cancer and the frequency of alcohol use (OR=1.00; 95%CI 0.72-1.40; p-value 0.98). In addition, usage of alcohol in participants' family during the growing up (childhood) significantly increases the risk of developing colorectal cancer (OR=6.45; 95%CI 1.74-13.54; p-value 0.000). There is no confounding effect of smoking and BMI (OR=0.97; 95% CI 0.83-1.14; p-value 0.71). There is a potential confounding effect of age (OR=1.06; 95% CI 1.04-1.09; p-value 0.000).

## Discussion and recommendations

The main findings demonstrated by the study were statistically significant associations between consumption of vodka as alcohol preferred, amount of 3+ drinks of alcohol used, and usage of alcohol in participants' family during childhood, and the risk

of developing colorectal cancer. Based on conditional logistic regression analyses, wine has a protective effect against developing colorectal cancer. This finding of the current study regarding the negative association of positive and cancer was consistent with previous reports from other studies that examined the relationship between different type of alcohol beverages and colorectal cancer (55). A significant, positive correlation between wine and cancer mortality rates across 41 US states has been reported (4). However, a non-significant negative correlation of wine and colorectal cancer was found across 29 countries in the only other study that considered this assoc iation (4). This contradictory finding might be explained by geographic differences in cancer mortality.

The results of the previous study indicated higher risk of total ethanol consumption associated with risk of adenomatous polyps (OR=2.4) (5). The result of the current study also indicated higher colorectal cancer risk with preference of vodka as alcohol beverage used (OR=2.06).

Previous researches reported the association between amount of 60 ml of alcohol per day and the risk of colorectal cancer (5) compared with non-drinkers, whereas this cases-control study shows no association between frequency of alcohol and colorectal cancer but is consistent with amount of alcohol (3+ drinks is more then 60 ml of ethanol).

The findings of the current study regarding an elevated, but not statistically significant (OR=1.19, 95%CI 0.64-2.22), risk of colorectal cancer among beer drinkers compared with non-drinkers are consistent with Stock's results (OR=1.4) in 1957 who first reported that association (4). Subseque ntly, other studies showed that beer is a significant risk factor for developing colorectal cancer (5).

Some studies showed that smoking is independent risk factors (56); others showed that cigarette smoking has a synergistic effect with alcohol (57). Other authors, as the current study, showed that risk for developing colorectal cancer is not significantly associated with alcohol consumption after adjustment for cigarette smoking (58).

The majority of the study limitations were the result of lack of time and resources. The most serious limitation was that proportion of women and men in controls were almost the same (50%-50%) whereas in cases women were 35% and men in majority. Women tend to drink less alcohol compared with men which might have exaggerated the true relationship between alcohol consumption and developing of colorectal cancer.

The next limitation dealt with questions in the study instrument referring to 5-year period. The latency period of any cancer is longer then 5 year which means that etiology of the colorectal cancer requires long period for the development of the disease. With respect to this issue, it would be better to recall the habits of the participants regarding alcohol consumption for the past 10-15 year period. On the other hand, it could result in heightened recall bias. Another limitation is that the reliability and validity of the instrument were not determined.

One of the potential limitations of the study was avoided by excluding people with a family history of colorectal cancer from controls (in the current study 3 persons reported the family history of colorectal cancer). During the analysis controls who were younger then the youngest case were excluded as well as controls who were older then oldest cases. In departments of coloproctology many patients with diseases other then colorectal cancer were too young or too old, and it was decided to exclude them from controls.

The main strength of the study is that controls did undergo the same diagnostic procedures as cases (rectoscopy/colonoscopy). Thus, there was complete absence of misclassification in current study.

The results of conditional logistic regression were not interpretable for some variables, which could be explained by the absence, or very small number of observations for a particular item and certain group (cases and controls). This could be explained as the result of small sample size. It is recommended to increase the sample size in future studies. One acceptable way of increasing the sample size is to recruit patients with colorectal cancer from other health care facilities.

This study demonstrated evidence of a need for educational programs regarding the alcohol consumption to make the information available for the public. Based on the results of this study, the public educational program should recommend avoiding use of vodka as alcohol type preferred, shifting from amount of 3+ drinks to less amount of alcohol (1-2 drinks), and also should make people understand and get them acquainted with the result that alcohol use in the childhood atmosphere significantly increases the risk of developing colorectal cancer. It could be possible to organize separate educational program for health care professionals, especially family physicians, as well as for residents at the departments of Oncology and Coloproctology at National Institute of Health and also at departments of clinical Oncology, Surgeon, and Internal Medicine of Yerevan State Medical University.

However, the results of this study's analysis demonstrated the need for further and comprehensive investigations taking into account the listed limitations. Further, the protective effect of frequent use of wine on subsequent development of colorectal cancer

need to be confirmed by additional research, since the results conflicted with that of a previous study. Additional information is needed to make conclusions regarding the variables that did not demonstrate interpretable results during the analysis. The results of a comprehensive research may serve as a basis for decision-making and implementation of nation-wide prevention programs in the future.

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**List of Potential Journals for Publication**

1. Cancer Epidemiology
2. British Journal of Cancer
3. Cancer Causes and Controls
4. International Journal of Cancer

# APPENDIXES

**APPENDIX 1. English version of Study Consent Form**

American University of Armenia
College of Health Sciences
Master of Public Health Program
CONSENT FORM

**Title of Research Project:**

Alcohol Consumption and Colorectal Cancer: A Case-Control Study in Armenia

**Explanation of Research Project:**

Hello, my name is Narek Sargsyan and I am a second year student of MPH program at the American University of Armenia and, also I am a research fellow in Department of Coloproctology at the National Institute of Health of the Ministry of Health. As a part of my course requirement at the American University of Armenia, Public Health department is conducting a study. The purpose of the study is to determine the association between alcohol consumption and colorectal cancer among both men and women in general population in Armenia. The study design for the research includes the interviews using the questionnaire on alcohol use. You will not undergo any examinations and procedures in future. The interview will take place only once and will last about 5-10 minutes. The time and the location of the interviews will be selected to be convenient for you. The information collected from you on alcohol use is needed in order to conduct the valuable research. Inclusion criteria are the following: The patients of the department of coloproctology regardless of age old that passed the rectoscopy or colonoscopy examinations. Exclusion criteria are the following: 1. Patients unwilling to participate in the study 2. Patients who report family history of colorectal cancer 3. Patients that are not residents of Armenia

**Risk/Benefit:**

The study does not involve any kind of risks. Only slight discomfort you may feel by sharing with us about your alcohol consumption experience.

You will not receive any incentives, financial or other benefit directly for the participation in the study. The information obtained from you will help us (investigators) to find out whether or not there is an association between alcohol consumption and colorectal cancer so that the results of the research will result in some suggested and recommended actions to increase awareness about association between alcohol consumption and colorectal cancer, and thus decrease the incidence of colorectal cancer in Armenia.

**Confidentiality:**

Interviews will be conducted anonymously without recoding your name, address, or telephone number and also, the questionnaires do not include these items. All such kind of identifying information of you will be kept confidential.

**Right to refuse participation:**

You have the right to stop the interview at any time you want. Your participation in this study is completely voluntary. Your refusal to participate in the study or your decision to withdraw from the study at any time is on your on decision. Whether or not you are in the study will not affect your job.

**Identification of researchers:**

The access to the data will have only a student investigator (*Narek Sarkissian*, 2nd year student of MPH program at the AUA, phone: +3741-266014 and +3749 413754, e-male: nareks1@hotmail.com) and, if necessary, principal and co-investigators (professor *Marie Diener-West*, phone: 410-502-6894, e-male: mdiener@jhsph.edu and *B.Grace Sullivan*, ARPN, PhD, Assistant Professor, AUA, room 47, phone: +3741 512570, e-male: sullivan@aua.am). All data obtained from you will be destroyed when research will be done in the end of summer.

If you have any questions regarding the study, please do not hesitate to contact the investigators in charge of the study: ***Narek Sarkissian, Professor Marie Diener-West, Professor Grace Sullivan.***

If you want to talk to anyone about the research study because you feel you have not been treated fairly or think you have been hurt by joining the study you should contact the American University of Armenia at (3741) 51 25 92 and ask ***Dr. Michael Thompson*** or at (3741) 51 25 68 and ask ***Dr. Yelena Amirkhanyan.***

***Thank you very much for participation.***

**APPENDIX 2. Russian Version of Study Consent Form.**

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**APPENDIX 3. Estimated sample size for two-sample comparison of proportions (equal samples). STATA results.**

| Test Ho | Assumption | Estimated required sample sizes |
|---|---|---|
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.4<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.18<br>$P_2$=**0.14** | $N_1$=1367<br>$N_2$=1367 |
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.8<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.23<br>$P_2$=**0.14** | $N_1$=313<br>$N_2$=313 |
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.2<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.26<br>$P_2$=**0.14** | $N_1$=190<br>$N_2$=190 |
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.6<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.30<br>$P_2$=**0.14** | $N_1$=117<br>$N_2$=117 |
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=3.0<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.33<br>$P_2$=**0.14** | $N_1$=88<br>$N_2$=88 |

*Estimated sample size for two-sample comparison of proportions (equal samples). STATA results.*

| Test Ho | Assumption | Estimated required sample sizes |
|---|---|---|
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.4<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.24<br>$P_2$=**0.18** | $N_1$=756<br>$N_2$=756 |
| $P_1=P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.8<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.28 | $N_1$=297<br>$N_2$=297 |

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|---|---|---|
| | $P_2$=**0.18** | |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.2<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.33<br>$P_2$=**0.18** | $N_1$=145<br>$N_2$=145 |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.6<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.36<br>$P_2$=**0.18** | $N_1$=106<br>$N_2$=106 |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=3.0<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.39<br>$P_2$=**0.18** | $N_1$=81<br>$N_2$=81 |

*Estimated sample size for two-sample comparison of proportions (equal samples). STATA results.*

| **Test Ho** | **Assumption** | **Estimated required sample sizes** |
|---|---|---|
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.4<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.28<br>$P_2$=**0.22** | $N_1$=850<br>$N_2$=850 |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=1.8<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.34<br>$P_2$=**0.22** | $N_1$=235<br>$N_2$=235 |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.2<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.38<br>$P_2$=**0.22** | $N_1$=140<br>$N_2$=140 |
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=2.6<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.42<br>$P_2$=**0.22** | $N_1$=94<br>$N_2$=94 |

| | | |
|---|---|---|
| $P_1$=$P_2$, where $P_1$ is the proportion exposed in cases and $P_2$ is the proportion exposed in controls | OR=3.0<br>alpha=0.05 (two-sided)<br>power=0.80<br>$P_1$=0.46<br>$P_2$=**0.22** | $N_1$=69<br>$N_2$=69 |

*Estimated sample size for two-sample comparison of proportions (equal samples). STATA results.*

| | **OR = 1.4** | **OR = 1.8** | **OR = 2.2** | **OR = 2.6** | **OR = 3.0** |
|---|---|---|---|---|---|
| **$P_2$ = 0.14** | 1367 | 313 | 190 | **117** | 88 |
| **$P_2$ = 0.18** | 756 | 297 | 145 | 106 | 81 |
| **$P_2$ = 0.22** | 850 | 235 | 140 | 94 | 69 |

*Different sample sizes at different OR and $P_2$ (proportion exposed in controls)*

**APPENDIX 4. English version of the Questionnaire.** ***ID ?*** **_____/_ _/___**

**1. Date of interview_____**

**2. Age _____**

**3. Gender:** Male Female

**4. Weight: _____ Height:_____ BMI (kg/m$^2$) = _____**

**5. Smoking status:**

1. Never smoker
2. Ex-smoker
3. Non-inhaling current smoker

Inhaling current smoker of

4. 1-10 cigarettes per day
5. 10-20 cigarettes per day
6. 20+ cigarettes per day

**6. How long have you smoked? (if you are non-smoker go to the question ? 8)**

1. Less than one year
2. More than one year and less than 5 years
3. More than 5 years and less than 10 years
4. More than 10 years and less than 20 years
5. More than 20 years

**7. What type of tobacco do you use?**

1. Cigarettes with filters
2. Cigarettes without filters
3. Cigar
4. Pipe
5. Mixed types

**8. At what age did you start using alcohol and what was the circumstance?**
**_____**

**9. Did you continue to use it regularly after that?** [ ] YES [ ] NO

**10. Do you presently consume alcohol beverages?** [ ] YES [ ] NO
If "NO", date of last drink _____

**11. How often did you use alcohol of any kind during last 5 years?**

1. Daily
2. Weekly
3. Monthly

4. Yearly
5. Never

**12. Which type of alcohol beverage did you use most of the time during last 5 years?** *(Check all that apply):*

1. VODKA
2. BRANDY
3. WHISK?Y
4. BEER
5. WINE
6. LIQUOR

**13. On the days that you drink, about how many drinks do you usually have each day?**

1. One
2. Two
3. 3-5
4. 6-9
5. 10 and more

**14. When did you last have an alcoholic drink?**

1. Today
2. Yesterday
3. In past week
4. In past 30 days
5. More than a month ago, but less that a year ago
6. More than a year ago

**15. Think back over the *last month*, how many times have you had five or more drinks in a row?**

1. None
2. Once
3. Twice
4. 3-5 times
5. 6-9 times
6. 10 or more times

**16. Do you ever drink alone?** [ ] YES [ ] NO

**17. Was alcohol used in your family as you were growing up?** [ ] YES [ ] NO

**18. Have you or your family members ever had a colorectal cancer?** [ ] YES [ ] NO

(The question ? 18 only for controls!)

**APPENDIX 5. Russian version of the Questionnaire.** ***ID ?*** **_____/_ _/___**

**6. ???? ?????????? _____**

**7. ??????? _____**

**8. ???**: ? ?????? ? ??????

**9. ???: _____ ????:_____ BMI (??/? $^2$) = _____**

**10. ?????? ???????:**

1. ? ? ???? ? ?? ?????
2. ?????? ??????
3. ????, ?? ?? ?????? ???
   ???? ? ?????? ???
4. 1-10 ??????? ? ????
5. 10-20 ??????? ? ????
6. 20+ ??????? ? ????

**6. ??? ????? ?? ??????? (???? ?? ?? ??????, ?????????? 8-?? ??????)**

1. ?????? ????
2. ?????? ????, ?? ?????? 5 ???
3. ?????? 5 ???, ?? ?????? 10 ???
4. ?????? 10 ???, ?? ?????? 20 ???
5. ?????? 20 ???

**7. ????? ?? ????? ?????? ?? ?????????????**

1. ???????? ? ????????
2. ???????? ??? ???????
3. ??????
4. ??????
5. ????? ?

**8. ? ????? ???????? ?????? ???? ? ??? ????? ???????????????**
**_____**

**9. ??????????? ?? ?? ??????????? ???????? ????????? ????? ??????**

[ ] ? ? [ ] ???

**10. ???????????? ?? ?? ???????? ? ??????? ?? ?????** [ ] ? ? [ ] ? ??
???? «???», ?? ??????? ???? ????????? ??????? _____

**11. ??? ????? ?? ??????????? ???????? (?????) ?? ????????? 5 ????**

1. ?????????
2. ???????????
3. ??????????

4. ??????????
5. ???????

**12. ????? ??? ?? ???????? ?? ??????????? ?????? ?? ????????? 5 ????:**
**(??????? ?? ??? ??????? ????????)**

1. ?????
2. ?????
3. ?????
4. ? ???
5. ????
6. ?????

**13. ? ???? ????? ?? ???????????? ????????, ??????? ???????? ????? ?? ?????? ??????**

1. ????
2. ???
3. 3-5
4. 6-9
5. 10 ? ??????

**14. ????? ?? ????????? ??? ??????????? ?????????**

1. ???????
2. ?????
3. ? ???? ??? ??????
4. ? ????????? 30 ????
5. ???? ?? ??? 30 ???? ?????, ?? ?????? ??? ??? ?????
6. ?????? ??? ??? ????? o

**15. ?????????, ??????? ??? ?? ????????? ????? ?? ???? 5 ??? ????? ??????**

1. ??????
2. ???? ???
3. ??? ????
4. 3-5 ???
5. 6-9 ???
6. 10 ? ????? ???

**16. ?? ????? ???? ???? ? ?????????** [ ] ? ? [ ] ???

**17. ? ????? ????? ???????????? ???????? ????? ?? ??????** [ ] ? ? [ ] ???

**18. ?????? ?? ???? ???????????? ????? ???? ?????????????? ?????? (?????? ? 18 ?????? ??? ??????????? ??????1)**