Chapter

Colorectal Cancer in Vietnam

Ngoan Tran Le and Hang Viet Dao

"Policy frameworks for cancer control in general and colorectal cancer in Vietnam are in place, but there is still a lack of proper financing and governing models necessary to support a sustainable program"

Abstract

In this chapter, we focus on the up-to-date status of colorectal cancer occurrence in an Asian country with nearly 100 million in population. Protective and risk factors, time trend of colorectal cancer from 2005 to 2018 will be presented. Perspective of colorectal cancer prevention and research will be highlighted. Data will be derived and based out of current running research projects of prospective cohort study, case-control study, and population-based mortality registration in Vietnam from 2005 to 2020. The association colorectal cancer with lifestyle, diet, cooking methods, demographic factors is taken into analysis. Time trend, colorectal cancer survival, mortality will be presented.

Keywords: colorectal cancer, risk factor, time trend, mortality, incidence

1. Introduction

1.1 Colorectal cancer is an ancient disease

Homo sapiens and other species have suffered from cancer since ancient times. However, while cancer incidences in other animals are very low, human's internal organs tend to be exposed to a lot of risk factors which can develop into cancer [1, 2]. Therefore, the management of risk factors, at community and household levels, becomes the focus in environmental health and oncology.

Both the incidence and mortality rate of all types of cancer in humans have been increasing over time. Determining etiology and causality is difficult and research findings are inconsistent among populations, which lead us to the question of whether scientists' observation was incorrect or risk factors of cancer are different in different populations. Although an estimated 80% of cancer cases, in general, and 98% of colorectal cancer cases, in particular, were associated with environmental factors [3], it is uncertain to determine what the situation will be in a defined population.

1.2 Vietnam country and facilities of cancer research

1.2.1 Improving life expectancy

The culture of Vietnam is a combination between Chinese and French because the country was occupied by China for nearly 1000 years and by France for around

100 years in the past. As colorectal cancer is reported to have connection with Western dietary habits, it is a favorable condition to observe its distribution and etiologies in Vietnam.

Located in Southeast Asia, Vietnam is bordered by China to the north, Laos to the northwest, Cambodia to the southwest, and the East Sea to the east. With a population of approximately 96,491,142 people in 2018 [4], Vietnam is the 13th most populous country in the world. The Socialist Republic of Vietnam has placed a significant emphasis on economic development since the introduction of the "Doi moi" (the economic reform) in 1986. As a result, Vietnam has achieved significantly in a short amount of time. For example, the percentage of the population living on less than a dollar a day has decreased from 58–29% over 10 years, and the life expectancy of Vietnamese people has reached 71 years for men and 75 years for women [5–7]. These progressing economics and urbanizations have changed lifestyles, dietary habits, increasing pollutions in living and working environments, which might be associated with the occurrence of colorectal cancer.

1.2.2 Developing descriptive cancer epidemiology

Regarding the source of data of colorectal cancer, for many countries, civil registration and vital statistics systems are considered the main sources for mortality data [8]. Civil registration was initiated in Vietnam in 1956, and despite the 50 years of collecting data about cancer mortality, limited information was published [9]. However, a recent study assessed the civil registration and vital statistics system in Vietnam and reported that the system had significant restrictions including a lack of data particularly about early neonatal deaths, deaths of temporary residents, and/or migrants [9].

Beyond Vietnam's civil registration and vital statistics system, a national mortality reporting system was introduced in 1992 and periodic updating guidelines to improve the quality of data collecting [10]. Under the auspices of the Ministry of Health (MOH), the A6 mortality reporting system relies on commune-level health officials providing basic demographic data and information on the cause of death, which is recorded in an official book referred to as the A6. The data from the A6 is collated by the district-level health service and the information is then sent to the provincial and central level governments. The community plays a significant role in maintaining the current mortality reporting system, and in turn, can actively use the information to plan commune-level health services. Using the A6 system, mortality data regarding cancer were collected and analyzed [11–14]. Verbal autopsy designed by WHO was applied in the community to determine all causes of death, including cancer [15]. Using the verbal autopsy as a reference, the sensitivity and completeness of the system were observed to be about 80% and 94%, respectively [16]. These findings have suggested that the accuracy and completeness of cancer mortality are feasible, and therefore, it was a source of data for colorectal cancer presented in the present study. The A6 system, with the detailed recordings of deaths in all communes, can easily be conveniently used by health workers. In Vietnam, during the last decade, 7081 (65.1%) medical doctors were working at commune health stations (CHS) [6, 17, 18]. Health workers are trained and work at CHS and they will contribute to the improvement of the mortality data quality and registration completeness gradually soon. Cancer epidemiology and population-based cancer registration were introduced by IARC during the 1980s, focused in the two biggest cities, Hanoi and Ho Chi Minh, representing the north and south of Vietnam, respectively. Cancer incidence during 1988–1997 in the Hanoi city and 1995–1998 in the Ho Chi Minh city was published by IACR [19–21]. Data on

colorectal cancer incidence produced by these two population-based cancer registries include a database of cancer mortality extracted from MOH's national mortality reporting system that was also used to present in the study.

1.2.3 Developing analytical cancer epidemiology

Cancer was observed to be the second most common cause of death nationwide during 2005–2006 (about 16%) [11, 12, 14], after vascular heart diseases (about 25%). Colorectal cancer (ICD-10: C18–20) has occurred at a national level in Vietnam. This study aims to generate a comprehensive picture of the fatal disease in the eight regions of Vietnam, with the hope to facilitate epidemiological studies in our country. For data of risk factors of colorectal cancer, we conducted a molecular epidemiological case–control study on the incident cases of the disease from 2002 to 2011. The study was designed by the leading experts of cancer epidemiologists from Japan and Vietnam. The protocol was approved by the scientific and ethics committees of the MONBUKAGAKUSHO (Japan) and the Ministry of Science and Technology (Vietnam). Initial results and findings were published elsewhere [22–24].

2. Characteristics of colorectal cancer cases in Vietnam

2.1 The occurrence of colorectal cancer at nationwide

From 2005 to 2006, we reported 4646 cases of fatal colorectal cancer among all 93,719 cancer death cases. It was responsible for about 5% of all cancer cases. Colorectal cancer was distributed in all 671 districts within 63 provinces/cities of Vietnam. Among 4646 colorectal cases, there were 2450 men (52.7%). The average age at death was 62 in men and 66 in women [14]. In 2002, the estimated number of death from colorectal cancer was 1730 cases in men and 2401 cases in women, provided that the total number of cases was 4131 [25]. The average reported number per year was 2323 cases in 2005–2006, which was only 56% of the estimated number of 4131 cases. According to GLOBOCAN 2018, colon ranked the fifth in the incidence and mortality among malignant diseases, with 5457 new cases and 3183 deaths per year [4].

2.2 Colorectal cancer caused a premature death

These characteristics suggest that an epidemiological study must be performed:

Colorectal cancer caused thousands of deaths in Vietnam, and it was considered as one of the most important public health problems in our country.

Causality and risk factors of colorectal cancer were presented at nationwide because the cancer was observed in all 671 districts within all 63 provinces/cities. Therefore, we should observe and examine etiology and causality at the household and community levels in identifying and controlling risk factors.

Registration of colorectal cancer mortality nationwide might be underreported for about 40% of total cases. Data on cancer mortality registration will promptly be improved and it will be used for cancer control and prevention in our country.

Using referred data of cancer from China to estimate the cancer incidence and mortality of all sites as well as of colorectal cancer, it might be an overestimated colorectal cancer in 2002 for Vietnam [25].

- Colorectal cancer caused premature death for an average of 7.3 years [18].

3. Colorectal cancer incidence and mortality

3.1 Childhood colorectal cancer

In terms of colorectal cancer in under-18 year-old people, 52 cases (1.13% of 4646 cases) were found [14]. Children and adolescents are not employed and therefore they are not exposed to occupational carcinogens. They are also rarely exposed to tobacco smoking and alcoholic beverages, according to a recent report on student health surveillance by WHO [26], as well as to dioxins in herbicides during the Vietnam War. What were the risk factors that induced colorectal cancer during the 1990s in Vietnam among children and adolescents?

3.2 Incidence of colorectal cancer

Two population-based cancer registrations have been running in the two prominent cities of Hanoi and Ho Chi Minh. The covered population was about 13 million (15% of the country population) in 2008 [6, 19, 21].

Age-standardized incidence rates per 100,000 (ASR) of colorectal cancer was 10.5 in men and 6.5 in women, during 1993–1997, in Hanoi and 12.4 in men and 9.0 in women, during 1995–1998, in Ho Chi Minh City [19, 21]. The incidence rate of colorectal cancer in Vietnam was one fifth of that in the United States (ASR 52.6 in men and 37.0 in women, respectively) [27].

Data on the cancer incidence rate in Vietnam might be deviated by 15–25% since the death certificate was not available at that time. During the 1990s, only 12% of Vietnamese had health insurance (HI). Thus, many cancer patients were not admitted to hospitals, which impacted directly on number of mortality in oncology patients [17]. According to GLOBOCAN 2018, 114,871 cancer patients in Vietnam are deceased in 2018, which takes up more than one third of the prevalent cases [4].

3.3 Mortality from colorectal cancer

In eight regions, ASR colorectal cancer mortality rates were from 4.0 to 11.3 per 100,000 in men and from 3.0 to 7.8 per 100,000 in women (**Table 1**). The highest mortality rates were seen in both men (11.3 per 100,000) and women (7.8 per 100,000) in the region of the Mekong Delta River in the South of Vietnam.

In a specific province population, the colorectal cancer mortality rate per 100,000 person-years during 2005-2018 was 5.8, men 6.9, and women 5.0. Men to

Region	Men			Women		
	Cases	Crude	ASR	Cases	Crude	ASR
Red Delta River	68	5.5	6.9	75	5.8	5.2
Northeast	20	3.1	4.4	34	5.0	5.0
Northwest	7	2.8	4.7	9	3.4	5.0
North central coast	29	3.3	4.0	34	3.7	3.0
South central coast	18	5.4	7.7	13	3.7	4.1
Central highlands	9	3.1	6.0	7	2.3	3.7
Northeast South	34	4.0	6.3	24	2.7	3.4
Mekong Delta River	83	7.5	11.3	78	6.8	7.8

Table 1.
Colorectal cancer mortality rate per 100,000 (ASR) by sex and regions, 2005–2006.

women ratio was 1.4 in the Lang Son province located in North Vietnam, remote areas of the country (**Table 2**).

The age-specific rate per 100,000 sharply increased in the age group of 50–59 with a peak of age group of 80+ at as high as 346.6 and 275.3 per 100,000 in men and women at the region of the Mekong Delta River in the South Vietnam, respectively (**Figure 1**). It supported the mentioned statement of the average age at death of 62 in men and 66 in women.

ASR colorectal cancer mortality rates per 100,000 in men ranged from 4.0 to 11.3 and it was lower than the rate in the developed countries, which was as high as 17.7 (**Figure 2**). Nationwide, it was estimated to be 5.6 per 100,000 (ASR) or it was one third when compared to that of the developed countries [25].

ASR colorectal cancer mortality rates per 100,000 in women ranged from 3.0 to 7.8 and it was lower than the rate in the developed countries, which was as high as 12.3 (**Figure 3**). Nationwide, it was estimated to be 5.2 per 100,000 (ASR) or it was nearly half when compared to that of the developed countries [25].

3.4 Survival of colorectal cancer

Regarding colorectal cancer survival, there was a lack of surveillance data for cases incidence and mortality to estimate the relative survival in Vietnam. Two population-based cancer registries have been running in Vietnam, one in Hanoi

Sex	Year	Total	Crude rate[&]	ASR-Segi[@]	% < 70[#]	ASR-WHO[$]
Men	2005–2018	201	4.4	6.2	66.7	6.9
Women	2005–2018	203	4.5	4.3	55.2	5.0
Both genders	2005–2018	404	4.5	5.1	60.9	5.8

[&]Crude rate per 100,000 person-years.
[@]Age-standardized rate per 100,000 person-years using the SEGI World standard population (in the 1960s).
[#]Proportion of death cases aged under 70 year-olds.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025. Men to women ratio (ASR-WHO) = 1.4 (6.9/5.0).

Table 2.
Mortality due to colorectal cancer by sex during 2005–2018 in Lang Son province.

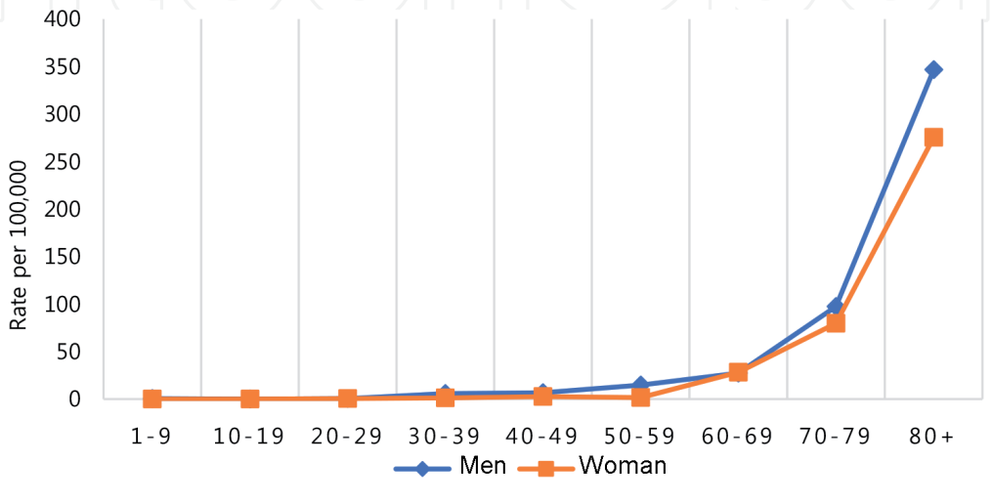

Figure 1.
Age-specific mortality rate per 100,000 in men and women, 2005–2006.

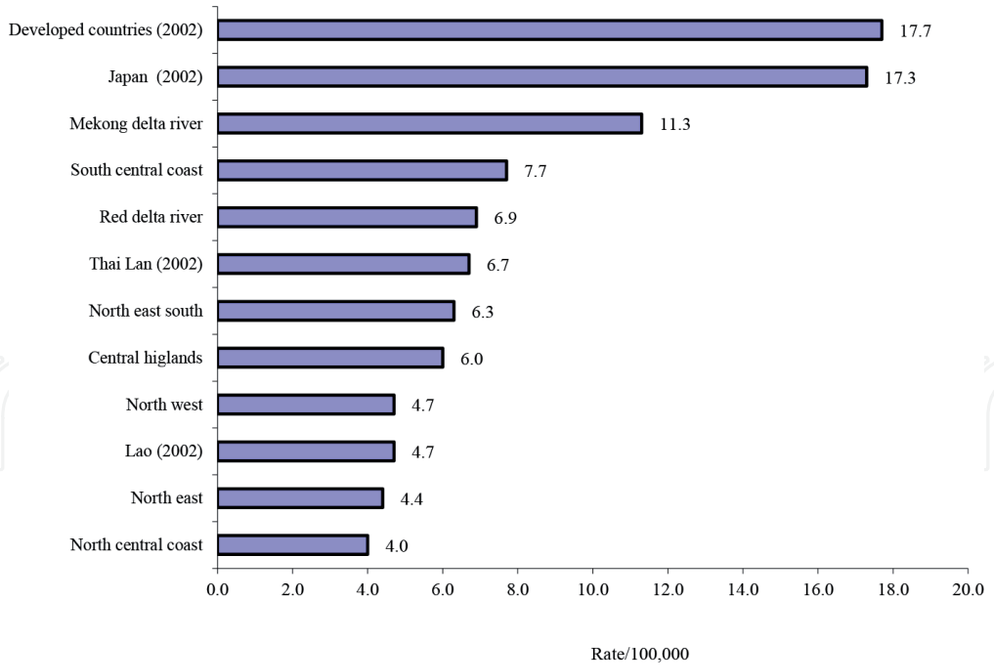

Figure 2.
ASR mortality rates per 100,000 by regions and in Vietnamese men, 2005–2006.

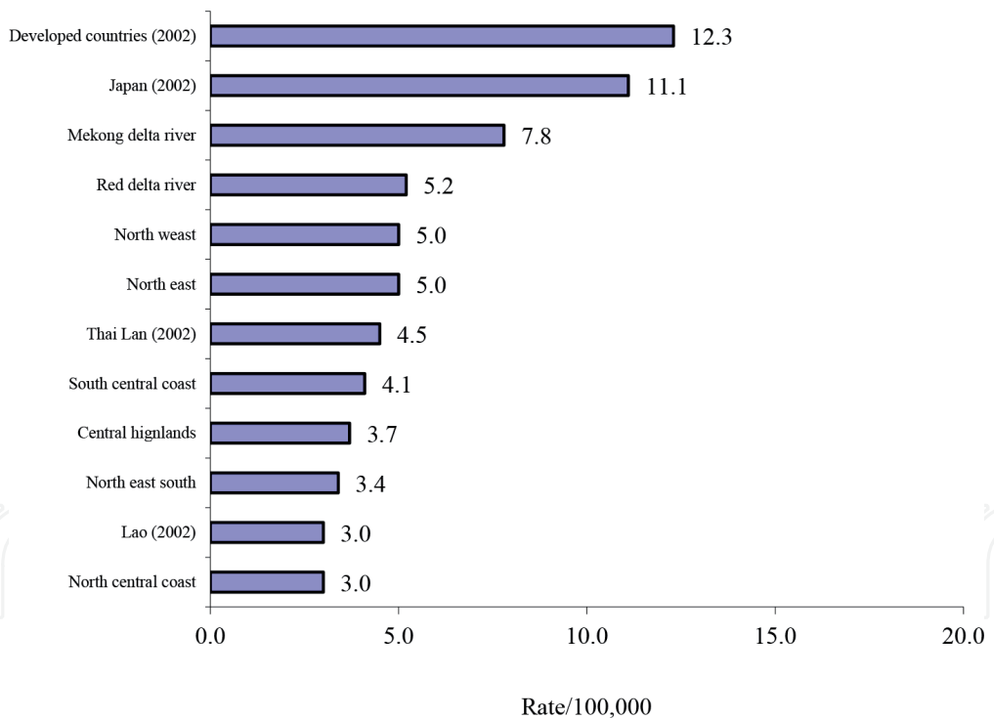

Figure 3.
ASR mortality rates per 100,000 by regions and in Vietnamese women, 2005–2006.

established in 1988, and the other in Ho Chi Minh city established in 1990 [19, 21]. These institutions collected data from medical records only and there was a lack of follow-up data, so the data of incidence rates might be underestimated. We analyzed the survival rate for fatal colorectal cancer cases: 1-year survival was 33.5% and 5-year survival was 4.3%, men and women combined [13].

These data of incidence, mortality, and survival (among fatal cases only) of colorectal cancer cases in Vietnam have suggested that:

- Risk factors-induced colorectal cancer might slightly be related to sex's life-styles, we should examine the risk factors that affect both men and women.

- Prevention of colorectal cancer should be prioritized because the diseases were estimated to be caused by 98% of environmental risk factors [3].

3.5 Time trend of colorectal cancer mortality

Between 2005 and 2018, the age-standardized mortality rate per 100,000 person-years (ASR-WHO) was increased from 3.4 to 9.8 in men and 2.2 to 3.9 in women (**Figure 4**). The significant increase trend was seen in both genders by 3.4% per year (**Table 3**). However, this significant increasing trend was observed in men only (5.2% per year, **Table 4**) but not in women (1.8% per year, **Table 5**).

Figure 4.
The trend of colorectal cancer mortality from 2005 to 2018 by gender in the Lang Son province located in North Vietnam. Missing data in 2009-2010; ASR-WHO: Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025.

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[$$]	p
2005	16	2.2	75.0	2.8	1 (Reference)	
2006	23	3.1	69.6	3.9	1.413 (0.747, 2.675)	0.288
2007	26	3.5	73.1	4.6	1.590 (0.853, 2.964)	0.144
2008	31	4.2	45.2	5.4	1.869 (1.023, 3.418)	0.042
2011	35	4.8	60.0	6.3	2.147 (1.188, 3.879)	0.011
2012	47	6.3	59.6	8.3	2.831 (1.605, 4.992)	<0.001
2013	34	4.6	61.8	5.9	2.073 (1.144, 3.775)	0.016
2014	47	6.0	55.3	8.1	2.706 (1.534, 4.772)	0.001
2015	41	5.2	61.0	6.9	2.343 (1.315, 4.174)	0.004
2016	41	5.2	68.3	6.8	2.349 (1.318, 4.186)	0.004
2017	27	3.4	44.4	4.5	1.527 (0.823, 2.834)	0.180

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[$$]	p
2018	36	4.6	66.7	6.3	2.065 (1.146, 3.721)	0.016

The estimated proportion of deaths due to colorectal cancer was 0.82% (404 cases of colorectal cancer vs. 49,253 total cases), both genders.[$$]Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+) and sex. Per year increment MRR (95% CI): 1.034 (1.010, 1.059), p = 0.005.
[&]Crude rate per 100,000 person-years.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.
[#]Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018, for both genders, WHO-ASR: 5.8 per 100,000 person-years.

Table 3.
Mortality due to colorectal cancer in both genders by year from 2005 to 2018 in Lang Son province.

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[##]	p
2005	9	2.5	88.9	3.4	1 (reference)	
2006	12	3.3	75.0	4.7	1.311 (0.552, 3.112)	0.539
2007	11	3.0	63.6	4.7	1.196 (0.496, 2.886)	0.691
2008	14	3.8	57.1	5.4	1.501 (0.650, 3.468)	0.342
2011	15	4.1	53.3	6.6	1.636 (0.716, 3.739)	0.243
2012	18	4.8	55.6	7.8	1.928 (0.866, 4.290)	0.108
2013	17	4.6	76.5	6.8	1.843 (0.821, 4.134)	0.138
2014	23	5.9	65.2	9.6	2.354 (1.089, 5.089)	0.029
2015	19	4.9	68.4	7.9	1.930 (0.873, 4.267)	0.104
2016	26	6.7	69.2	10.1	2.649 (1.241, 5.654)	0.012
2017	14	3.5	64.3	5.7	1.408 (0.609, 3.252)	0.424
2018	23	5.9	69.6	9.8	2.346 (1.085, 5.070)	0.030

The estimated proportion of deaths due to colorectal cancer was 0.64% (201 cases of colorectal cancer vs. 31,262 total cases) in men.[##]Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). Per year increment MRR (95% CI): 1.052 (1.017, 1.089), p = 0.003.
[&]Crude rate per 100,000 person-years.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.
[#]Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018 in men, WHO-ASR: 6.9 per 100,000 person-years.

Table 4.
Mortality due to colorectal cancer in men by year from 2005 to 2018 in Lang Son province.

3.6 Screening for colorectal cancer and treatment

Risk factors of colorectal cancer include certain unhealthy dietary regimens, precancerous lesions detected on colonoscopy, and genetic factors. According to the guideline for colorectal cancer diagnosis and treatment released by Vietnam's Ministry of Health in 2018, screening should be conducted on high-risk patients with a history of inflammatory bowel disease (Crohn's disease or ulcerative colitis) or colorectal polyps, or a family history of polyposis syndrome, colorectal polyps, or colorectal cancer. Fecal occult blood test (FOBT) and colonoscopy are pivotal in screening. During 2008–2010, the National Cancer Control Program organized a screening program for five malignant diseases in which 9634 people were screened for oral and colorectal cancer. However, stage I-II colorectal cancers accounted only for 32.2% [28].

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO[$]	MRR (95% CI)[##]	p
2005	7	1.9	57.1	2.2	1 (reference)	
2006	11	3.0	63.6	3.2	1.545 (0.599, 3.986)	0.368
2007	15	4.1	80.0	4.7	2.097 (0.855, 5.144)	0.106
2008	17	4.5	35.3	4.9	2.344 (0.972, 5.652)	0.058
2011	20	5.4	65.0	6.3	2.805 (1.186, 6.633)	0.019
2012	29	7.7	62.1	8.8	3.994 (1.749, 9.117)	0.001
2013	17	4.6	47.1	5.0	2.369 (0.982, 5.714)	0.055
2014	24	6.1	45.8	7.0	3.159 (1.361, 7.332)	0.007
2015	22	5.6	54.5	6.2	2.874 (1.228, 6.727)	0.015
2016	15	3.8	66.7	4.3	1.965 (0.800, 4.818)	0.140
2017	13	3.3	23.1	3.5	1.681 (0.670, 4.212)	0.268
2018	13	3.3	61.5	3.9	1.704 (0.680, 4.272)	0.255

The estimated proportion of deaths due to colorectal cancer was 1.13% (203 cases of colorectal cancer vs. 17,990 total cases) in women.[##]Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). Per year increment MRR (95% CI): 1.018 (0.985, 1.052), p = 0.294.
[&]Crude rate per 100,000 person-years.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.
[#]Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018 in women, WHO-ASR: 5.0 per 100,000 person-years.

Table 5.
Mortality due to colorectal cancer in women by year from 2005 to 2018 in Lang Son province.

Treatment is decided based on multiple factors including staging, tumor location, and histopathology. Available treatment modalities in Vietnam are surgery, radiotherapy, and chemotherapy (systemic and targeted) [29].

In terms of surgery strategy, it depends on the curative/non-curative approaches as well as the operation indication relates to the complications or not. Pham et al. (2020) conducted a study on patients who performed single-port laparoscopic right hemicolectomy. The mean survival time was 67.9 ± 3.3 months and the recurrence rate was 16.7%. The survival rates at 2, 3, and 5 years were 87.5, 79.9, and 66.7%, respectively. Survival was shown to be associated with age, tumor size, and TNM stage at 61.7 ± 3.9 months after treatment [30]. For advanced stages, three main agents were 5-fluoropyrimidines, oxaliplatin, and irinotecan, combined in common regimens including FOLFOX/XELOX, FOLFIRI/XELIRI, or FOLFOXIRI. Trinh et al. followed up with metastatic colon cancer patients treated with FOLFOXIRI. The mean disease-free survival time was 13.37 ± 9 months, with the response after 3 and 6 cycles being 82 and 79.4%, respectively [31]. Radiation therapy is indicated in patients who have metastatic lesions in the liver, bone, or lungs [29].

The surgery method for rectal cancer depends on the extent and location of the tumor [29]. Truong et al. conducted a cohort study during 2009–2016 on patients with low rectal cancer undergoing laparoscopic sphincter-saving resection. The local and distant recurrence rates were 10.4 and 20.8%, respectively. The overall survival was 52.7 ± 3.9 months and the disease-free survival was 38.3 ± 2.9 months [32]. In another study on rectal cancer patients who were treated with surgery, survival was reported to be associated with staging, lymph nodes metastasis, and tumor size. The mean overall survival time was 48.9 ± 52.7 months and the 3-year survival rate was 91.7%. Patients at stage I-II or having lymph nodes <10 mm in diameter had better prognosis [33]. Vi et al. conducted a study on metastatic rectal

cancer patients who were treated with FOLFOX4 and bevacizumab. The median overall survival time was 19 months and the survival rates after 1 and 2 years were 56.9 and 27.6%, respectively. In this population, survival was associated with the CEA level, the number of organs having metastasis, histopathology, and response to bevacizumab [34]. The overall survival time in this study was similar to some studies using similar regimens in the world [35, 36].

3.7 Social health insurance and colorectal cancer control

3.7.1 Health insurance in Vietnam

Health insurance (HI) provides access to health examination and treatment for all patients, including those who cannot cover their medical expenses using out-of-pocket money, ensuring equity and social security. All public health establishments in Vietnam participate in the national health insurance scheme. Private hospitals, especially centers managing chronic diseases, are also encouraged to participate.

After enrolling in the national health insurance program, most of the general populations pay an annual amount of 1,117,000 VND (approximately 48.5 USD). Insurance fees can be waived for some special populations (e.g., poor households and veteran's relatives). In 2018, 86.8% of Vietnamese people are covered with national HI, allowing them to access most health-care services in Vietnam [37].

The mean direct costs for an outpatient and inpatient with colorectal cancer were 13.594 million VND (588 USD) and 63.371 million VND (2741 USD), respectively. This renders a financial burden for people who are not covered by HI and creates a barrier to access to health care [38]. As 80–100% of treatment costs for colorectal cancer are covered by HI in public hospitals and private clinics, patients enrolling in the insurance program can access expensive diagnostics and treatments. However, some targeted drugs and bevacizumab are only covered 30–50% by HI [39]. In Vietnam, the primary care levels are communal health stations and district health centers/hospitals. People who are treated at these facilities are fully covered if they participate in the HI program. If they must be transferred to higher-level (provincial/central) hospitals, patients have to present valid official letters of referral to the insurance agency to maintain maximum insurance coverage. The maximum coverage for a general person who is admitted to a central hospital is 80%; this will be reduced to 40% if they fail to present valid letters of referral [40].

3.7.2 Colorectal cancer control

In Vietnam, a majority of colorectal cancer patients are detected at late stages. In a study in 2015, 67.8% of the patients were diagnosed at stage III/IV [28]. Early detection of colorectal cancer through screening may significantly increase the 5-year survival to 89.9%, compared with 13.8–71.1% in patients with regional and distant colorectal cancer metastasis [41].

Having acknowledged the situation, the Vietnamese Government issued the National Strategy for the Prevention and Control of Non-Communicable Disease (NCD) (2015–2025). One of the objectives of this strategy is to reduce late diagnosis and increase survival for colorectal cancer [42]. Colorectal cancer screening is conducted annually, supported by the National Cancer Control Program, and is accessible in many health-care facilities [28, 43]. For community screening, FOBT is applied in many health-care centers, with the advantage of being a noninvasive, quick, and reliable method. When the patients have positive FOBT, the next step to be performed would be colonoscopy. This strategy helps to screen mass population, especially the people with

risk factors (family history, colon polyp history, or age), as well as save up the human and economic resources. Some preliminary data have shown the effectiveness of this approach in early colorectal cancer; however, the long-term benefits in national screening and management program requires bigger data from multicenters [44, 45].

Efforts have been made to raise the awareness of lifestyle and diet modification, including limiting alcohol consumption and smoking, promoting a healthy diet, and encouraging physical exercises [46–48].

4. Risk factors and benefit factors of colorectal cancer in Vietnam

4.1 Performing case-control study on colorectal cancers

A case-control study was performed for colorectal cancers admitted to Hanoi Cancer Hospital, Viet Duc Surgery Hospital, and Bach Mai General Hospital located in Hanoi. The ratio of case-control is 1:1 with the standards for matching are gender and age (±5). Cases and controls were interviewed to collect data in using demographic and lifestyle questionnaire and semiquantitative food frequency questionnaire. Blood samples were collected in the early morning on the day of operation [23, 24]. Most patients came from the provinces near Hanoi within the Red Delta River. They will be represented as Vietnamese in the north.

4.2 Host factors related to colorectal cancer

4.2.1 Blood ABO group and risk of colorectal cancer

Distribution of blood ABO group in Vietnamese is 45.00, 21.20, 28.30, and 5.50% for types O, A, B, and AB, respectively [49]. In our study, the distribution is different, with 42.97, 23.67, 27.95, and 5.42% for types O, A, B, and AB, respectively [50]. The proportion of type A plus AB is 26.70% while type O plus B is 73.30% in Vietnamese. However, in our study, it is 29.10% and 70.90%, respectively. Distribution of blood ABO group in our study population is similar to that in Vietnamese. Blood ABO group was observed to be associated with cancer risk, whereas blood A was seen to increase the risk of stomach cancer in many studies [51]. Blood A, AB, and B have also increased the risk of pancreatic cancer [52].

In our study, blood type A plus AB was seen to increase the risk of colorectal cancer, with OR = 1.58, 95% CI = 1.05–2.38 [50] (**Table 6**). The mechanism of developing colorectal cancer in patients with blood types A and AB is unknown.

When we separated colon and rectal cancer, the estimated risk was significantly increased for colon cancer, with OR = 3.36, 95% CI = 1.91–5.92, but not significantly increased for rectal cancer, with OR = 0.84, 95% CI = 0.54–1.32.

4.2.2 CYP1A1 genotypes risk of colorectal cancer

The function of CYP1A1 is recognized to be a major chemical carcinogen-induced cancer, in general, and colorectal cancer, in particular, in humans. We found that CYP1A1 (A/G and G/G genotypes) increased the risk of colorectal cancer, with OR = 1.86, 95% CI = 1.16–2.98 (**Table 7**) [50].

4.2.3 Family and personal history of health and risk of colorectal cancer

When parents and close relatives suffered from cancer, the patients are at a higher risk of colorectal cancer, with OR = 3.00, 95% CI = 1.29–6.99, and OR = 3.63,

Blood type	Control	Case	OR	95% CI		P
O and B	187	150	1.00	*Reference*		
A and AB	58	73	1.58	1.05	2.38	0.027

Table 6.
Blood ABO group and risk of colorectal cancer.

CYP1A1 genotypes	Control	Case	OR	95% CI		P
AA	57	32	1.00	*Reference*		
AG and GG	226	237	1.86	1.16	2.98	0.010

Table 7.
CYP1A1 genotypes and the risk of colorectal cancer.

95% CI = 1.31–10.01, respectively. Patients with a past history of colorectal pain and inflammation are also at a higher risk of cancer, with OR = 3.68, 95% CI = 2.01–6.75. Regarding body mass index (BMI), three levels were categorized, including <18.5; 18.5- < 25, and 25- < 30. Patients with body mass index of 25- < 30 are also at a higher risk of cancer, with OR = 2.09, 95% CI = 0.79–5.51, and p for trend <0.05 (**Table 8**) [50]. The Vietnamese households traditionally follow the multigenerational pattern and, therefore, members share living environments as well as similar dietary habits. As a result, all family members might be exposed to the risk of cancer, in general, and the risk of colorectal cancer, in particular. Regarding the body mass index, the mechanism of developing colorectal cancer among the group of obesity was unknown.

4.3 Environmental factors related to colorectal cancer

4.3.1 Drinking habits of alcohol and/or beer and risk of colorectal cancer

Alcoholic beverages have been proven to be a major part of human's diet [53]. Excluding the poisonous effect of heavy intake of alcohol, we considered alcoholic beverages as a promoter of cancer in human. Most carcinogenic chemicals have a higher solubility in alcohol than in water. For example, aflatoxin B is soluble in ethanol but has a limited water solubility [54].

There is sufficient evidence for the carcinogenicity of alcohol beverages in human but inadequate evidence for the carcinogenicity of ethanol and alcoholic beverages in experimental animals [55]. Based on these facts and figures, we hypothesized that alcoholic beverages are promoters for cancer in humans. In this study, three levels of alcoholic drinking were categorized, including not drinking, some drinking per week, and daily drinking. Those who daily consume alcoholic beverages were at a significantly higher risk of colorectal cancer, with OR = 1.91, 95% CI = 0.98–3.72, and p for trend <0.05 (**Table 9**) [50].

4.3.2 The dietary habit of heated foods and risk of colorectal cancer

Referred to earlier statements regarding cancer occurrence in species, only human's internal organs of lung, liver, stomach, and others are seriously exposed to risk factors and can develop cancer. In contrast, animals suffer from cancer with a very rare occurrence in the internal organs [1, 2]. Animals consume natural foods

Factors	Control	Case	OR	95% CI		P
Parent suffered from cancer						
No	303	290	1.00	*Reference*		
Yes	8	21	3.00	1.29	6.99	0.011
Close relative suffered from cancer						
No	305	294	1.00	*Reference*		
Yes	5	17	3.63	1.31	10.01	0.013
History of colorectal pain and inflammation						
No	286	255	1.00	*Reference*		
Yes	15	48	3.68	2.01	6.75	0.000
Body mass index (BMI) (rectal cancer only)						
<18.5	32	17	1.00	*Reference*		
18.5- < 25	108	119	2.03	.12	3.33	0.005
25- < 30	7	8	2.09	.79	5.51	0.135
P for trend = 0.013						

Table 8.
Family and personal history of health and risk of colorectal cancer.

Alcohol and/or beer	Control	Case	OR	95% CI		P
Not drinking	175	145	1.00	*Reference*		
Some drinking per week	29	33	1.61	.90	2.87	0.110
Daily drinking	21	27	1.91	.98	3.72	0.058
P for trend = 0.030						

Table 9.
Drinking habits and risk of colorectal cancer.

without any preparation, while humans consume both natural foods and prepared foods [56, 57]. Also, humans used at least 10,000 chemical additives, which serve as contaminants [58]. Besides, heat-generated carcinogens due to the cooking temperature were reported in many previous studies. One of such carcinogens is acrylamide, which was detected in heated foods. It was evaluated by IARC to be a potential carcinogen to humans (Group 2A) [59].

The concentration of acrylamide was 50 μg/kg in hamburgers prepared at the temperature of 240°C, while it was zero in the control [60]. With this evidence, we hypothesized that the intake of heated foods might be a contributor to the development of colorectal cancer in our study population. Three food items were categorized to be heated food items because they were heated in cooking temperature at 165°C or higher during preparation processing [56, 57]. The concentration of heat-generated carcinogens (acrylamide) was generated and significantly increased when the temperature increased from 100–240°C [60]. Daily and weekly intake of barbecued meats (Usual outside appearance: medium-, well-, and blackened/charred of cooked meats vs. lightly browned of cooked meats), bread, and biscuits significantly increased the risk of colorectal cancer, with OR = 1.70, 95% CI = 1.09–2.63; OR = 2.15, 95% CI = 1.36–3.40; and OR = 2.05, 95% CI = 1.03–4.07, respectively (**Table 10**) [50].

Heated food items and heated levels	Control	Case	OR	95% CI		P
Barbecued meats						
Usual outside appearance: lightly browned of cooked meats	220	194	1.00	Reference		
Usual outside appearance: medium-, well-, and blackened/ charred of cooked meats	43	62	1.70	1.09	2.63	0.019
Bread						
No intake or rare	207	179	1.00	Reference		
Some intake per month	66	67	1.17	0.79	1.74	0.432
Daily or weekly intake	35	65	2.15	1.36	3.40	0.001
P for trend = 0.002						
Biscuits						
No intake or rare	231	206	1.00	Reference		
Some intake per month	68	81	1.34	0.92	1.95	0.125
Daily or weekly intake	14	25	2.05	1.03	4.07	0.040
P for trend = 0.016						

Table 10.
Dietary habits and risk of colorectal cancer.

4.3.3 Cigarette smoking and risk of colorectal cancer

The heating and burning of tobacco products lead to the formation of mainstream smoke and sidestream smoke. Mainstream smoke from cigarettes and cigars is generated during puff-drawing in the burning cone and hot zones; it travels through the tobacco column and exits from the mouthpiece. Sidestream smoke is formed during puff-drawing and is emitted freely from the smoldering tobacco product into the ambient air. A variety of chemical and physical processes occur in the oxygen-deficient, hydrogen-rich environment of the burning cone at temperatures up to 950°C. Tobacco smoke contains more than 3800 constituents and many of them are chemical carcinogens to humans [61]. Tobacco smoking was reported to be responsible for about 25–35% of all cancer in humans [3]. In our study, daily smoking of 11 cigarettes or more increased the risk of colorectal cancer, with OR = 2.08, 95% CI = 0.62–6.91, but it is not significant (**Table 11**) [50].

Both the burning of tobacco and heating of foods leads to the formation of chemical carcinogens, known as "heat-generated carcinogens" or "dietary carcinogens." Thousands of chemicals were reported in the smoke of burning tobacco and heating foods. These chemicals were detected in the user's blood and urine after the intake of these products [60–67]. With this evidence, we should seriously consider the study of heat-generated carcinogens and dietary carcinogens to prevent the development of cancer in humans.

5. Benefit factors preventing colorectal cancer in Vietnam

Humans cannot synthesize micronutrients to meet the body's requirement, so supplement from outside is necessary. Good foods provide good materials for the body's energy metabolism and for activities preventing cancer [68].

Number of cigarettes per day	Controls	Cases	OR	95% CI		P
Nonsmoker	151	140	1.00	*Reference*		
1–10	22	15	0.82	0.37	1.82	0.618
11+	5	9	2.08	0.62	6.91	0.233

Table 11.
Number of cigarettes per day and colorectal cancer.

Refrigerator available at home	Controls	Cases	OR	95% CI		P
No	123	145	1.00	*Reference*		
Yes	121	99	0.69	0.48	0.99	0.045

Table 12.
Refrigerator available at home and risk of colorectal cancer.

The refrigerator is the equipment providing good conditions to keep fresh micronutrients for humans' daily life. An indirect beneficial factor that reduces the risk of colorectal cancer was observed for the refrigerator available at home, with OR = 0.69, 95% CI = 0.48–0.99 (**Table 12**) [50].

5.1 The potential ways to improve the health-care system

With the focus on clinical epidemiology studies on colorectal cancer, the specific risk factors for Vietnamese patients have been identified and they require further investigations to have an instruction on the diet and lifestyle modification. Based on multiple factors in pathological mechanism, the strategy to control this malignancy should have an impact on comprehensive sides: environmental factors, screening strategy, and personalized management. The integration of different diagnostic methods in community, hospital, and individual levels enhanced the improvement in detection of early colorectal cancer and should be invested more. Besides issuing guideline for colorectal cancer from the perspectives of specialists, it is important to have a strategy of prevention and screening in community and to foster educational activities.

5.2 New areas of interest for future research

In the near future, to identify the relationship between risk factors and colorectal cancer in Vietnam as well as to optimize the environmental factors, the microbiome studies in our population should be performed. It is necessary to have a database for healthy people to compare with the colorectal cancer patients, with the collecting of data on diet and lifestyle habits. Furthermore, the studies on health-care cost-effectiveness in this specific field should be performed to support for building up an effective approach in the prevention, screening, and treating of colorectal cancer patients.

6. Perspectives

Based on the observations in Vietnam for colorectal cancer, the distribution of this disease and its causality as well as risk factors were identified. With these findings, some points can be induced:

Colorectal cancer is related to unrecognized heat-generated carcinogens in our foods: we found that tobacco smoking, barbecued meats, bread, and biscuits intake increase the risk of the disease. Tobacco heated at 950oC and smoking carcinogens can generate as much as 3800 types of chemicals [56, 57, 61]. These findings were partly published [24]. Chemical is an independent factor inducing cancer, which was successfully performed and reported for the first time in 1967 by Dr. Sugimura [60, 69]. Our epidemiological observations in humans consisted of these numbers from previous studies.

Control of cooking temperature in both family's kitchen as well as public restaurants in humans' daily life should be a significant consideration to prevent colorectal cancer in particular and all cancer sites in general.

In our study, although alcoholic beverages play an integral role in humans' diets worldwide, alcoholic consumption would be categorized as a promoting factor of colorectal cancer development. Because of the organic solution of chemical carcinogens, similar to tobacco smoking, barbecued meats, bread, and biscuits are promoting colorectal cancer in our body.

- Host factors committed to developing colorectal cancer included blood types A and AB, CYP1A1 genotypes A/G and G/G, family history of cancer, body mass index, history of colorectal pain, and inflammation.

7. Conclusions

Three groups of risk factors were determined to develop colorectal cancer, including tobacco smoking, barbecued meats, bread, and biscuits intake as the first group; alcohol consumption as the second group; and the identified host factors as the third group. Possible management of identified risk factors in preventing colorectal cancer can be refrainment of smoking and reduction of intake of heated foods at unsafe cooking temperatures. A screening for colorectal polyp and cancer for people aged 40+ is highly recommended. Policy frameworks for cancer control in general and colorectal cancer in Vietnam are in place, but there is still a lack of proper financing and governing models necessary to support a sustainable program.

Acknowledgements

The authors deeply appreciate former Prof. Hiroshi Nozawa, Doctor of Laws and Honorary Member of the Institute for Science of Labor, Emeritus Professor of Kanazawa University for the support at the Institute for Science of Labor, Kawasaki, Japan in 1994.

DOI: http://dx.doi.org/10.5772/intechopen.93730

Author details

Ngoan Tran Le[1,2*] and Hang Viet Dao[3,4]

1 Institute of Research and Development, Duy Tan University, Da Nang, Vietnam

2 Department of Public Health, International University of Health and Welfare, Narita city, Japan

3 Department of Internal Medicine, Hanoi Medical University, Hanoi City, Vietnam

4 Institute of Gastroenterology and Hepatology, Hanoi City, Vietnam

*Address all correspondence to: letranngoan@yahoo.com; letngoan@hmu.edu.vn

References

[1] National Cancer Institute. The Occurrence of Tumors in Domestic Animals. Bethesda, Maryland: National Institutes of Health; 1980

[2] Wells HG, Slye M, Homes HF. Comparative pathology of cancer of the alimentary canal, with a report of cases in mice. American Journal of Cancer Research. 1938;**33**:223-238

[3] Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. Journal of the National Cancer Institute. 1981;**66**:1191-1308

[4] Vietnam - Global Cancer Observatory, 2018 704 Viet-Nam-fact-sheets. International Agency for Research on Cancer. 2019. Available from: https://gco.iarc.fr/today/data/factsheets/populations/704-viet-nam-fact-sheets.pdf

[5] GSO. Socio-Economic Statistical Data of 671 Districts, Towns, and Cities under the Authority of Provinces in Vietnam. Hanoi: Statistical Publishing House; 2006

[6] Ministry of Health. Health statistics yearbook. Injury Mortality by Regions/Causes/Provinces. Ha Noi City: Ministry of Health; 2008. p. 2009

[7] United Nations. World population prospects: the 2008 revision – highlights (Working paper no. ESA/P/WP.210). New York: NY: United Nations; 2009. 2009. Report No.: Working paper no. ESA/P/WP.210

[8] United Nations. Principles and Recommendations for a Vital Statistics System, Revision 2. New York: NY: United Nations Statistical Commission; 1999

[9] Rao C, Osterberger B, Anh TD, MacDonald M, Chuc NT, Hill PS. Compiling mortality statistics from civil registration systems in Viet Nam: The long road ahead. Bulletin of the World Health Organization. 2010;**88**:58-65

[10] Ministry of Health - Vietnam. Circular no 27/2014/TT-BYT on Data collection and Reporting Form for Provincial, District and Commune level; 2014

[11] Ngoan LT. Cancer mortality in a Hanoi population, Viet Nam, 1996-2005. Asian Pacific Journal of Cancer Prevention. 2006;**7**:127-130

[12] Ngoan LT. Development of population-based cancer mortality registration in the north of Vietnam. Asian Pacific Journal of Cancer Prevention. 2006;**7**:381-384

[13] Ngoan LT, Long TT, Lua NT, Hang LT. Population-based cancer survival in sites in Vietnam. Asian Pacific Journal of Cancer Prevention. 2007;**8**:539-542

[14] Ngoan LT, Lua NT, Hang LT. Cancer mortality pattern in Vietnam. Asian Pacific Journal of Cancer Prevention. 2007;**8**:535-538

[15] Huong DL, Minh HV, Byass P. Applying verbal autopsy to determine the cause of death in rural Vietnam. Scandinavian Journal of Public Health. Supplement. 2003;**62**:19-25

[16] Tra LN, Dung TV. Study on the Cause of Death at Soc Son District, Hanoi City. MOH Research Project. Hanoi City: Hanoi Medical University; 2003

[17] Ministry of Health, Health Statistics Yearbook 1997. Hanoi City: Medical Publishing House; 1998

[18] Ministry of Health. Health Statistics Yearbook 2006. Hanoi City: Medical Publishing House; 2007

[19] Anh PTH, Duc NB, Khang HX, Truong TH, Nga NH. Viet Nam, Hanoi 1991-1993. In: Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. Cancer Incidence in Five Continents Vol VII. IARC Scientific Publications No. 143. Lyon: IARC, WHO, IACR; 1997. pp. 442-445

[20] Anh PTH, Parkin DM, Hanh NT, Duc NB. Cancer in the population of Hanoi, Vietnam, 1988-1990. British Journal of Cancer. 1993;**68**:1236-1242

[21] Quoc NM, Hung NC, Parkin DM. Cancer incidence in Ho Chi Minh City, Viet Nam, 1995-1996. International Journal of Cancer. 1998;**76**:472-479

[22] Ngoan LT, Anh NTD, Huong NT, et al. Gastric and colorectal cancer mortality in Viet Nam in the years 2005-2006. Asian Pacific Journal of Cancer Prevention. 2008;**9**:299-302

[23] Ngoan LT, Khan NC, Mai LB, et al. Development of a semi-quantitative food frequency questionnaire for dietary studies-focus on vitamin C intake. Asian Pacific Journal of Cancer Prevention. 2008;**9**:427-432

[24] Ngoan LT, Thu NT, Lua NT, et al. Cooking temperature, heat-generated carcinogens, and the risk of stomach and colorectal cancers. Asian Pacific Journal of Cancer Prevention. 2009;**10**:83-86

[25] IARC. GLOBOCAN 2002. IARC: Lyon France; 2002

[26] WHO. Global School-based Student Health Survey: Vietnam 2013 Fact Sheet. WHO, WHO Website; 2013

[27] Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review. Bethesda, Maryland: National Cancer Institute; 2000. pp. 1973-1997

[28] Cancer control in Vietnam: Where are we? 2017. Available from: http://www.cancercontrol.info/cc2016/cancer-control-in-vietnam-where-we-are/

[29] Ministy of Health - Vietnam. Decision no. 2549/QĐ-BYT of Ministry of Health on promulgating the guideline on colorectal cancer diagnosis and treatment, issued on April 19th 2018; 2018

[30] VY PT. Apply Single-Port Laparoscopy on the Treatment of Right- Sided Colon Cancer. Hue University of Medicine and Pharmacy; Doctoral Thesis. Hue City, Vietnam: Hue University of Medicine and Pharmacy; 2020

[31] Le Huy T. The Outcome of Colon Metastasis Treatment by FOLFOXIRI Regimen. Hanoi Medical University; Doctoral Thesis. Hanoi City, Vietnam: Hanoi Medical University; 2017

[32] Quy TV. Evaluate the Radical Approach of Rectal Cancer Treatment by Laparoscopic Surgery with Sphincter Conservation. Hue University of Medicine and Pharmacy; Doctoral Thesis. Hue City, Vietnam: Hue University of Medicine and Pharmacy; 2018

[33] Cuong TA. Characteristic of Lymph Node Metastasis and the Result of Rectal Cancer Treatment by Surgery in Vietnam National Cancer Hospital. Hanoi Medical University; Doctoral Thesis. Hanoi City, Vietnam: Hanoi Medical University; 2017

[34] Vi Tran Doanh. Evaluate Rectal Metastasis Treatment by Chemotherapy with Monoclonal Antibody; Doctoral Thesis. Hanoi City, Vietnam: Hanoi Medical University; 2019

[35] Passardi A, Nanni O, Tassinari D, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: Final results for first-line treatment from the ITACa

randomized clinical trial. Annals of Oncology. 2015;**26**:1201-1207

[36] Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. British Journal of Cancer. 2011;**105**:58-64

[37] Ministry of Health - Vietnam. Health Statistics Yearbook 2018. Hanoi City, Vietnam: Ministry of Health; 2019

[38] Le N, Quang Vo T. Analyzing the variation in treatment costs for colorectal cancer (CRC): A retrospective study to assess an underlying threat among the Vietnamese. Journal of the Pakistan Medical Association. 2019;**69**:S34-S40

[39] Ministry of Health - Vietnam. Circular No. 30/2018/TT-BYT Dated October 30, 2018 of the Ministry of Health on Promulgation of List of Modern Medicines, Biologicals, Radiopharmaceuticals and Tracers Covered by Health Insurance, Insurance Coverage Ratio and Payment Conditions Thereof; 2018. Hanoi City, Vietnam: Vietnam Government; 2018

[40] Vietnam Social Security. Health Insurance policy. Hanoi City, Vietnam: Vietnam Government; 2008

[41] Colorectal Cancer Survival Rate by Stage. 2018. Available from: https://www.healthline.com/health/colorectal-cancer-survival-rate

[42] Ministry of Health - Vietnam. National Strategy for the Prevention and Control of Non-Communicable Disease (NCD) (2015-2025). Hanoi City, Vietnam: Ministry of Health; 2015

[43] Around 15,000 people receive free cancer screening and treatment. 2017. Available from: https://www.moh.gov.vn/web/ministry-of-health/top-news/-/asset_publisher/EPLuO8YEhk19/content/around-15-000-people-receive-free-cancer-screening-and-treatment?inheritRedirect=false

[44] Screening tests for early detection of cancer. Available from: https://www.benhvien108.vn/ca%CC%81c-xe%CC%81t-nghie%CC%A3m-sa%CC%80ng-lo%CC%A3c-pha%CC%81t-hie%CC%A3n-so%CC%81m-ung-thu.htm [Accessed: August 23, 2020]

[45] Update review of screening for colorectal cancer. 2020 [Accessed: August 23, 2020]

[46] Ministry of Health - Vietnam. National Strategy for the Prevention and Control of Non-Communicable Disease, Period 2015-2025. Hanoi City, Vietnam: Ministry of Health; 2015

[47] Vietnamese Government. Law no. 44/2019/QH14 on Alcohol Harm Prevention and Control. Hanoi City, Vietnam: Vietnamese Government; 2019

[48] Vietnamese Government. Law no. 09/2012/QH13 on Tobacco Harm Prevention and Control; 2012

[49] Duc PT. Physiology. Hanoi City: Medical Publishing House and Ministry of Health; 2007

[50] Ngoan LT, Thu NT, Lua NT, Hang LT, Bich NN, Hieu NV, et al. Cooking temperature, heat-generated carcinogens, and the risk of stomach and colorectal cancers. Asian Pacific Journal of Cancer Prevention. 2009;**10**:83-86

[51] Nomura A. Stomach cancer. In: David S, Joseph F, editors. Cancer Epidemiology and Prevention. Second ed. New York-Oxford: Oxford University Press; 1996. pp. 707-724

[52] Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and

the risk of pancreatic cancer. Journal of the National Cancer Institute. 2009;**101**:424-431

[53] Kass L. The Hungry Soul: Eating and the Perfecting of our Nature. New York, Toronto, Oxford, Singapore, Sydney: Maxwell Macmillan International; 1994

[54] Bioaustralis, Product Catalogue: Aflatoxin B. Australia: BioAustralis Fine Chemicals; 2019. p. 26. Available from: https://www.bioaustralis.com/pdfs/catalogue.pdf

[55] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Alcohol Drinking. WHO, IARC: Lyon, France; 1988

[56] Masako Y. The First Book of Japanese Cooking. First ed. Kodansha International: Tokyo-New York-London; 1984

[57] Stephanie A, Maggie B, Tetsuya W, Damien P, Christine M. The Food of Australia. First ed. Boston and Singapore: Periplus Editions (HK) Ltd.; 2001

[58] Adams RC. Natural foods. The New England Journal of Medicine. 1970;**283**:1058

[59] IARC. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Schistosomomes, Liver Flukes and Helicobacter Pylori. Lyon France: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 1994

[60] Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. Journal of Agricultural and Food Chemistry. 2002;**50**:4998-5006

[61] IARC. Tobacco Smoking. Lyon: IARC; 1985

[62] Chiu CP, Yang DY, Chen BH. Formation of heterocyclic amines in cooked chicken legs. Journal of Food Protection. 1998;**61**:712-719

[63] Friesen MD, Rothman N, Strickland PT. Concentration of 2-amino-1-methyl-6-phenylimidazo(4,5-b) pyridine (PhIP) in urine and alkali-hydrolyzed urine after consumption of charbroiled beef. Cancer Letters. 2001;**173**:43-51

[64] Hayatsu H, Hayatsu T, Ohara Y. Mutagenicity of human urine caused by the ingestion of fried ground beef. Japanese Journal of Cancer Research. 1985;**76**:445-448

[65] Li S, Pan D, Wang G. Analysis of polycyclic aromatic hydrocarbons in cooking oil fumes. Archives of Environmental Health. 1994;**49**:119-122

[66] Sinha R, Rothman N, Brown ED, et al. Pan-fried meat containing high levels of heterocyclic aromatic amines but low levels of polycyclic aromatic hydrocarbons induces cytochrome P4501A2 activity in humans. Cancer Research. 1994;**54**:6154-6159

[67] Skog K, Steineck G, Augustsson K, Jagerstad M. Effect of cooking temperature on the formation of heterocyclic amines in fried meat products and pan residues. Carcinogenesis. 1995;**16**:861-867

[68] Chatterjee IB, Maạumder AK, Nandi BK, Subramanian N. Synthesis and some major functions of vitamin C in animals. Annals. New York Academy of Sciences. 1975;**258**:24-47

[69] Sugimura T, Fujimura S. Tumour production in glandular stomach of rat by N-methyl-N-nitro-N-Nitrosoguanidine. Nature. 1967;**216**:943-944