Determining the Burden and Awareness of Hepatocellular Carcinoma and its correlates in Addis Ababa, Ethiopia

By

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EXCUTIVE SUMMARY

Background: Globally, the burden of hepatocellular carcinoma (HCC) is increasing; however, due to a lack of reliable epidemiological data, the incidence of HCC and its correlates remains masked in many sub-Saharan African countries, including Ethiopia. There is also a paucity of data in Ethiopia on public awareness of HCC and the infrastructure, education, and financial needs to control HCC. Addressing the aforementioned research gaps in Ethiopia could aid in careful HCC control planning. This is because careful HCC control planning entails, among other things, assessing the current incidence and trend of the disease and its risk factors, assessing public awareness as well as clinicians' perceptions toward measures required to control the disease. Thus, this thesis was carried out to 1) determine the incidence and trend of HCC over eight years (2012–2019) in Addis Ababa; 2) assess the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in HCC patients in Addis Ababa; 3) assess public awareness of cancer and HCC signs, symptoms, and risk factors in Addis Ababa; 4) report the best available evidence on the burden of HCC and its risk factors in Ethiopia; 5) identify the best available evidence on the combined roles of HCV and HBV in the development of HCC; and 6) explore liver cancer clinicians' perceptions of infrastructural, educational, and financial needs to control HCC in Ethiopia.

Methods: This thesis included six studies: one systematic review and meta-analysis, one systematic review, two retrospective studies, one cross-sectional survey, and a qualitative study comprising in-depth interviews.

Results: The systematic review found a paucity of data on HCC incidence, HCC risk factors, and public awareness of HCC in Ethiopia. The retrospective study on HCC incidence in Addis Ababa found that between 2012 and 2019, the incidence of HCC was higher in men and those aged 54 and older. The retrospective study on HCV and/or HBV infection among HCC patients found that HBV (32.8%), HCV (17.7%), and HBV and HCV coinfection (10.6%) were present in the majority of HCC patients in Addis Ababa. In Addis Ababa, the majority of HCC patients (54%) were in stages III and IV, with only a few cases (20.2%) in stage I at diagnosis. In the cross-sectional survey study of HCC and general cancer awareness, those aged 60 and older were found to be less aware of

cancer signs and symptoms than those aged 18 to 29, highlighting generational differences in HCC signs and symptoms which need to be considered in public health campaigns. The cross-sectional survey study also found that those with primary, secondary, and tertiary education were more aware of cancer symptoms and signs than those with no formal education. The qualitative study also identified the following needs for HCC control in Ethiopia, among others: increasing public awareness of HCC; improving health professionals' knowledge of HCC through continual training; and improving the budget for HCC diagnosis, treatment, and screening.

Conclusion: This study found a socio-demographic disparity in HCC incidence and awareness of cancer in Addis Ababa, Ethiopia, and demonstrated the need to increase funding for HCC and improve health professionals' knowledge of HCC in Ethiopia. A careful HCC or national cancer control plan or strategy that addresses sociodemographic disparities in HCC incidence and public awareness of HCC in the country is needed. The control strategy or plan should also emphasise the importance of increasing health professional knowledge of HCC as well as increasing funding for HCC diagnosis, treatment, and screening in the country.

DECLARATION

I certify that this thesis:

1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university

2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Signed:

Date: February 23, 2023

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GLOSSARY

Terms	Definitions
Inflammatory cytokine/ pro-inflammatory cytokine	An inflammatory signalling molecule that is produced by immune cells like macrophages and helper T cells as well as a few other cell types.
Kebele	Ethiopia's smallest administrative unit

ABBREVIATIONS

AFB1	Aflatoxin B1
AFP	Alpha-fetoprotein
ASIR	Age-Standardized Incidence Rate
ASMR	Age-Standardized Mortality Rate
ASR	Age-Standardized Rate
BCG	Bacille Calmette-Guerin
BMI	Body Mass Index
CAM	Cancer Awareness Measure
CT	Computed Tomography
EAPC	Estimated Average Percentage Change
GBD	Global Burden of Disease
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSDP	Health Sector Development Program
MRI	Magnetic Resonance Imaging
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic Fatty Liver Disease
PPP	Public Private Partnership
SPSS	Statistical Package for the Social Sciences
SSA	Sub-Saharan Africa
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 The global burden of hepatocellular carcinoma (HCC)

Primary liver cancer is the world's sixth most common cancer, and the third leading cause of cancer death in 2020 (1, 2). According to the most recent Global Burden of Disease Study, an estimated 534,364 new cases of primary liver cancer were diagnosed worldwide in 2019, with an estimated 373,390 deaths that year (3). The global incidence and mortality rate of primary liver cancer decreased in 2005 but have increased slightly since then (Fig 1-1) (3). This could be due to changes in global hepatitis prevention efforts over this time period, such as the hepatitis B virus (HBV) vaccination program, which have resulted in a decrease in 2005 but a slight increase since then in the global incidence of primary liver cancer due to HBV and HCV (Fig 1-2) (3). Moreover, alcohol consumption, one of the major liver cancer risk factors, increased globally from 2005 to 2010 (4). This may also explain the slight global increase in liver cancer incidence since 2005. Hepatocellular carcinoma (HCC) and cholangiocarcinoma (cancer of the bile ducts) are the two most common types of primary liver cancer (5). Angiosarcoma is a less common type of primary liver cancer (6). HCC accounts for more than 75% of all primary liver cancers and is a major public health concern worldwide, with a 5-year survival rate of less than 20% (7, 8).

HCC is recognised as a significant public health problem (9-11). The true impact on mortality and morbidity in various parts of the world, however, is masked by a paucity of reliable epidemiological data (12, 13). This is particularly the case for African nations. Sub-Saharan Africa (SSA), for instance, was reported to be one of the regions with the highest HCC burden in the world in 2020 (14). The disease's burden, on the other hand, has been reported to be underestimated in many SSA countries due to a variety of factors, including poor data recording in cancer care institutes and a lack of population-based cancer registries (15). Clarifying the burden of HCC, which is the primary focus of this thesis, is important to inform development of careful cancer control plans and strategies for management (16).

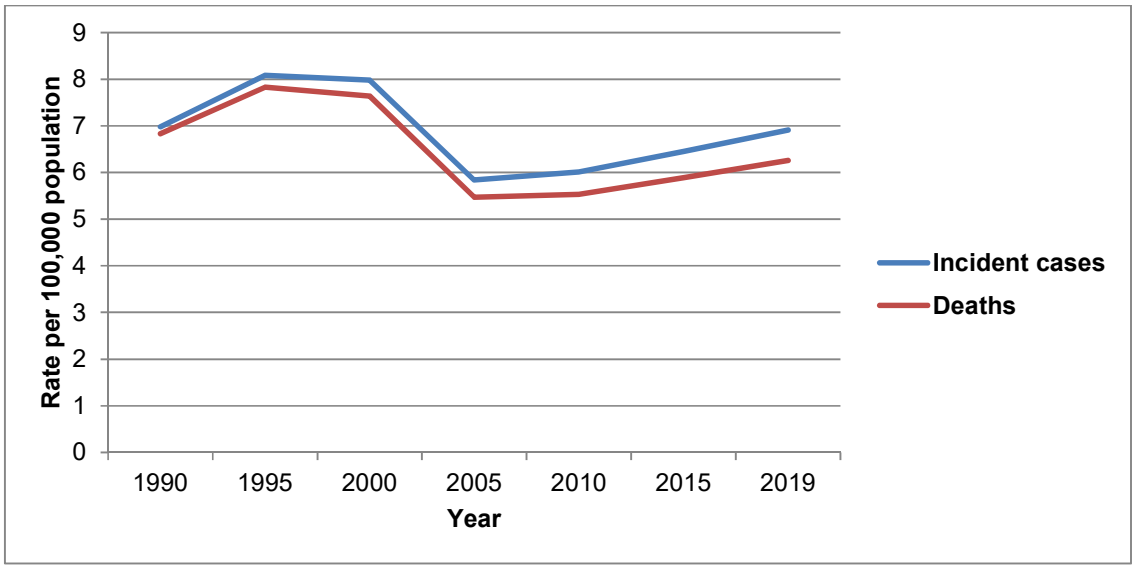

Figure 1-1: Primary liver cancer incidence and death rates worldwide, both sexes, all ages. Note: This graph is adapted from data reported by the Global Burden of Disease Study (GBD) (17).

Age-standardised HCC incidence rates vary by region (18, 19). Eastern Asia has the highest age-standardised incidence rate (ASIR) in the world (17.7 per 100,000). South-East Asia (13.3 per 100,000) and Africa (8.4 per 100,000) have the world's second and third-highest incidence rates, respectively. South-Central Asia has the lowest ASIR in the world (2.5 per 100,000) (Fig 1-3) (19).

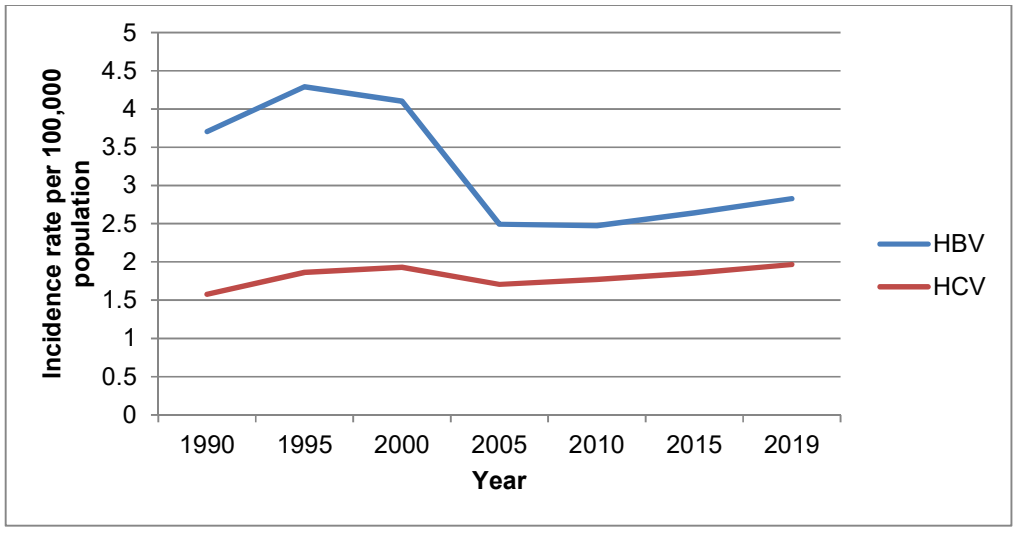

Figure 1-2: Primary liver cancer incidence rate due to hepatitis B virus (HBV) and hepatitis C virus (HCV) incidence rates worldwide, both sexes, all ages. This graph is adapted from data reported by the Global Burden of Disease Study (GBD) (17).

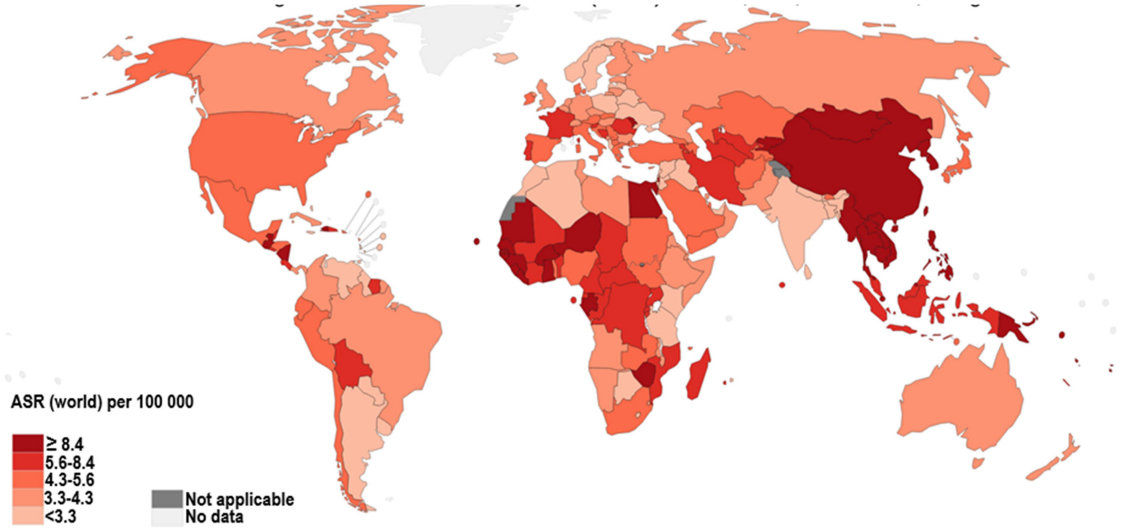

Figure 1-3: Age-standardised HCC incidence rates worldwide in 2020 (http://gco.iarc.fr/today) (20). This graph was produced by the International Agency for Research on Cancer (IARC) using data from the Global Burden of Cancer Study (GLOBOCAN). Information on the IARC website can be reviewed, reproduced, or translated for research purposes with acknowledgment to IARC and citation of the uniform resource locator (21).

In many countries, increasing age is associated with an increase in HCC incidence (22). The median age of diagnosis is under 75 years in many countries (22). For instance, the median age of diagnosis in the United States is 65-69 for women and 60-64 for men (23). The median age of HCC diagnosis in Africa is slightly younger, with 58 in Egypt and 48 in other African countries (24). This could be attributed to age differences in HCC risk factor exposure in Western and other countries (25). In Western countries, for instance, viral hepatitis B virus (HBV) infection, which is one of the known HCC risk factors, is less frequent than in adults in developing countries. In Asia and Africa, it is more common, and can be acquired during childhood or prenatally (26). In these regions, the virus can also be transmitted vertically during birth and infancy (27-29). Although males are more affected by HCC in almost every country around the world, the male-to-female ratio also varies by region (24). The ratio ranges between 2:1 and 4:1, with the greatest variation in Europe (4:1) and the smallest in Central and South America (1.2:1 in Colombia and 1.6:1 in Costa Rica) (22). Gender variations in HCC risk factor exposure have been hypothesised as a possible explanation for the disparity in HCC incidence between men and women (30-32). For instance,

men are more likely than women in many countries to use alcohol and be exposed to aflatoxin B1, two major HCC risk factors (33, 34). In addition, it has been reported that men have a higher prevalence of HBV than women (30, 31).

With 830,180 deaths in 2020, liver cancer caused the third highest number of cancer deaths worldwide, after lung (1,796,144 deaths) and colorectal (935,173) cancers, with mortality rates varying by geographic region (Fig 1-4) (7, 35). The highest age-standardised mortality rates (ASMRs) in 2018 from HCC were in Eastern Asia (16.0 per 100,000) and Northern Africa (13.9 per 100,000) (19). South-Eastern Asia has the second-highest ASMR (13.2 per 100,000), while South-Central Asia has the lowest (2.3 per 100,000) (19). The main contributor to the disparity in HCC incidence and mortality by geographic region is the difference in the distribution of HCC risk factors by geographic region, as discussed in the following section.

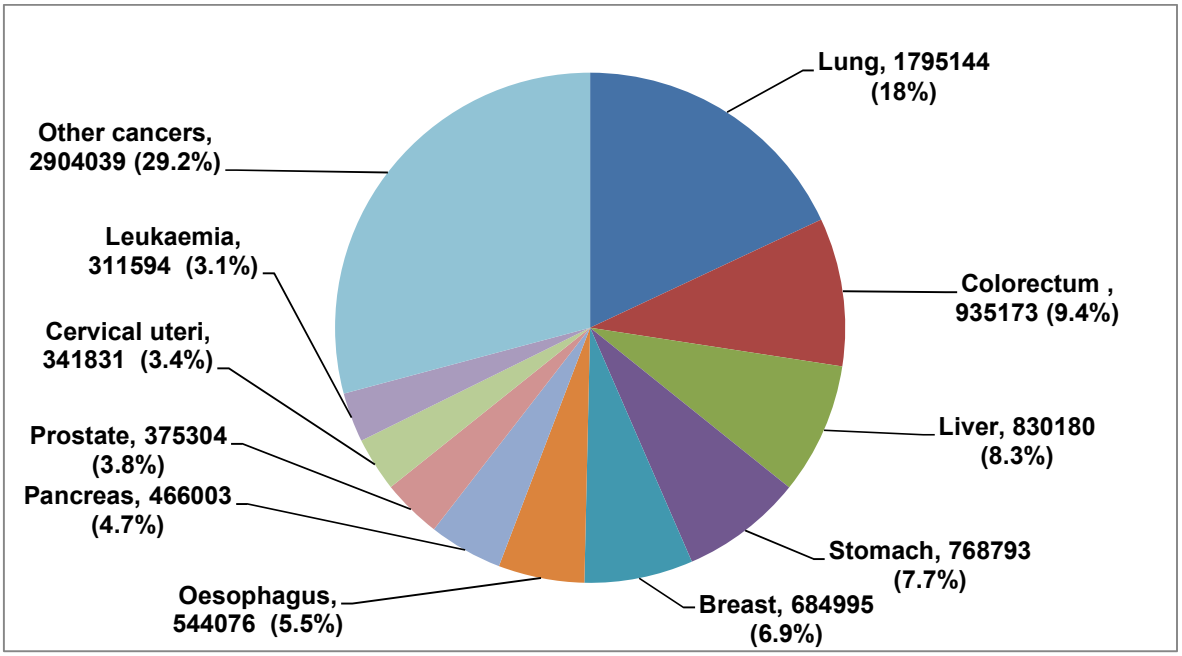

Figure 1-4: Estimated number of cancer deaths worldwide in 2020, according to GLOBOCAN (https://gco.iarc.fr/today) (36).

1.2 The global burden of hepatocellular carcinoma risk factors

In the twentieth century, advances in molecular biology have revealed new information about the role of some risk factors for the development of liver disease, including HCC (37). Since then, risk factors for HCC have been better characterized. Conditions or behaviours that impair liver function can increase the risk of developing HCC (38). Hepatitis B virus (HBV) infection (39), hepatitis C virus (HCV) infection (39), chronic alcohol consumption (i.e., consuming 80 grams of alcohol per day for more than ten years) (40), non-alcoholic fatty liver disease (NAFLD) (41, 42), and aflatoxin B1 (AFB1) exposure (43) are reported to be the major risk factors of HCC (41, 42). Less common risk factors include obesity (44), type II diabetes mellitus (44), tobacco smoking (45), and hemochromatosis (iron overload) (41, 42).

HBV is a partially double-stranded DNA virus that causes hepatitis B (46). Hepatitis B is usually short-term, or acute, and lasts less than six months in most people (47). However, for some, the infection becomes chronic, lasting longer than six months (48). Unsafe injections, contact with blood or other bodily fluids while having sex with an infected partner, or exposure to blood from unsafe sharp instruments can all result in HBV transmission (49). HBV can also be transmitted vertically from mother to child (50). Vertical transmission of HBV can occur via three routes: transplacental, perinatal, and postnatal (29). Transplacental transmission can occur through a variety of mechanisms, such as when the virus infects placental cells by crossing placental barriers or through germinal cell infection (29). HBV can also be transmitted prenatally via mechanisms such as infant exposure to maternal vaginal secretions (51). Postnatal transmission mechanisms include infant exposure to HBV-infected maternal secretions through breastfeeding (52, 53). Chronic hepatitis B increases the risk of cirrhosis and liver cancer-related death (49). HBV is the most common cause of HCC worldwide, accounting for roughly half of all HCC cases (54). People who are chronically infected with HBV are 15-20 times more likely to develop HCC than those who are not infected (55, 56). Vaccination can protect against hepatitis B infection (49), and by extension, reduce the likelihood of developing HCC related to hepatitis B infection.

WHO recommends that SSA countries include a birth-dose HBV vaccine in their Expanded Immunization Program to prevent HBV transmission from mother to child in the early perinatal

period (57). Several challenges, however, are impeding the availability and coverage of HBV vaccinations in the region (58). For instance, despite the availability of the HBV birth-dose vaccine in SSA since 1982, only 13 of 48 SSA countries (27%) administered it (59, 60). This is mainly due to factors such as the financial cost of vaccine transportation and administration and a lack of suitable vaccine storage (58, 60). Therefore, early perinatal HBV transmission continues to be a major cause of HBV-related disease in SSA (57). Moreover, there is no compulsory adult HBV vaccination program in some SSA countries like Ethiopia, where adult HBV immunization is only given to high-risk populations such as healthcare workers in public health facilities (61, 62). Long-term antiviral therapy can also halt or reverse liver fibrosis due to HBV and prevent HCC development (63, 64). Chronic hepatitis B patients in SSA, however, often go untreated due to limited resources, leaving clinicians in the region to follow the disease's natural course and provide palliative care (65).

Hepatitis C is a liver infection caused by HCV, an RNA virus (66). It is an acute infection, but in many cases, acute infection leads to chronic infection, and this progression is highly dependent on the age at the time of infection (49, 67). Poorly sterilized medical equipment, blood transfusion, needle stick injuries, and injected drug use are all associated with the transmission of HCV (68). It can also be passed from mother to baby during birth (69, 70). HCV is another common cause of HCC and can cause serious liver damage by inflaming the liver (69, 70). HCV infection is present in 10% to 25% of all HCC cases worldwide (54, 71-73). Chronic HCV-infected individuals have a more than 20-fold increased risk of HCC compared to those who are not infected (42). There is no vaccination available to protect against hepatitis C (74). Avoiding behaviours that can spread the disease is one of the most effective strategies to prevent it (75). This includes avoiding intravenous drug use and screening blood products and medical equipment (75). There are also antiviral drugs available for patients who have contracted HCV; nevertheless, the cost of HCV treatments are challenges in some parts of the world, including SSA (76, 77). Despite the fact that there is a low risk of sexual transmission of HCV (78), using condoms to prevent unprotected sexual exposure has also been found to reduce its transmission (79).

The third most common risk factor for HCC is chronic alcohol consumption (73, 80). A daily intake of more than 80 grams of alcohol has been associated with a fivefold increase in the risk of hepatocellular carcinoma (81, 82). Non-alcoholic fatty liver disease (NAFLD) and aflatoxin B1 are the other most common causes of HCC in the world. NAFLD refers to a group of illnesses caused by a build-up of fat in the liver (83). High cholesterol, type 2 diabetes, and obesity have all been linked to the development of NAFLD (84-86). Although alcohol does not cause NAFLD, it has been reported that alcohol consumption can worsen NAFLD by causing more damage and fat accumulation in the liver (87).

Another common cause of HCC in the world is exposure to aflatoxin B1 (73, 80). Some moulds, particularly Aspergillus species, produce a variety of carcinogens and mutagens called aflatoxins (88, 89). Aflatoxin B1 is the most potent carcinogenic of the four types of aflatoxins (aflatoxin B1, B2, G1, and G2) that have been identified as being cancerous to both humans and animals (90). Aflatoxin B1 has been linked to toxicity, mutagenicity (induction of mutation), and carcinogenicity (induction of cancer) (91). It has been estimated that Aflatoxin B1 exposure could be responsible for 5–28 % of all HCC cases worldwide (73, 80).

The distribution of major HCC risk factors introduced above varies by region (Table 1-1). In Europe, HCV is the most prevalent risk factor of HCC (19). Except in Andean Latin America, where HCV infection is the major risk factor, alcohol consumption is the most prevalent risk factor of HCC in America (19). The majority of HCC cases in SSA are associated with HBV and HCV infections (19). HBV was responsible for the greatest number of HCC cases (4,613) in Western SSA, followed by Eastern (1,645), Southern (1,559), and Central SSA (375; see Table 1-1). However, the existing literature on HCC and its risk factors in Ethiopia, a Sub-Saharan country, is extremely limited (92-97). Further complicating our understanding of risk factors for HCC in Ethiopia are several methodological limitations in existing studies from this region, including sampling and sample size (92-97), as discussed briefly in the following section. Addressing the existing limitations in the literature relating to HCC in Ethiopia is a key focus of this thesis, and is considered in-depth in Chapters Two and Four of this thesis.

The majority of primary liver cancer cases (77%) in SSA are HCCs (98). HCC is the second and fourth leading cause of cancer-related deaths in men and women respectively in the SSA region in 2020 (15). In SSA, age-standardized incidence rates (ASIRs) for HCC vary by region (15, 98-100). Between 2018 and 2020, ASIRs decreased in both sexes in Western and Central Africa, but only in the most recent year did they increase in Western Africa and among women in Eastern Africa (15, 98-100). Among SSA men and women, the average ASIR of HCC is 18.9 and 8.0 per 100,000 people/year, respectively (15). The studies described above that reported ASIR in SSA were reviews based on data from reliable sources such as GLOBOCAN, which collects cancer incidence and mortality data from cancer registries, implying that the incidence rates they reported reflect the actual burden of the disease in the region. The most common risk factor of HCC in the region are chronic alcohol use, HBV, HCV, and NAFLD (101).

Table 1-1: Burden of primary liver cancer including HCC by risk factor and region in 2019, according to the Global Burden of Disease Study (GBD)(102).

	Alcohol		HBV		HCV		NAFLD		Others	
Region	**Incident cases**	**ASR per 100 000**	**Incident cases**	**ASR per 100,000**	**Incident cases**	**ASR per 100 000**	**Incident cases**	**ASR per 100,000**	**Incident cases**	**ASR per 100,000**
Europe										
Western	16556	3.8	5341	1.2	2508	1.2	768	0.4	2006	0.5
Central	2985	2.6	2161	1.0	18946	4.3	3007	0.7	216	0.2
Eastern	3554	1.7	1371	1.2	1777	1.6	554	.05	413	0.2
America										
North America	10671	2.9	3657	1.0	133	0.2	3184	0.9	2506	0.7
Andean Latin America	549	0.9	740	1.2	10988	3.0	177	0.3	135	0.2
South Latin America	10671	2.9	326	0.5	680	1.0	186	0.3	116	0.2
Asia										
East Asia	19766	1.3	138505	9.4	35911	2.4	10459	0.7	12527	0.9
Asia-Pacific	8717	4.7	16844	8.9	37117	19.8	3357	1.8	1909	1.0
South-East Asia	11131	1.7	17138	2.5	9145	1.4	3972	0.6	1411	0.2
Africa										
North Africa, Middle East	2617	0.4	7258	0.4	12951	2.1	2872	0.5	1845	0.3
Southern (sub-Saharan)	781	0.9	1559	0.9	1036	1.3	420	0.5	217	0.3
Western (sub-Saharan)	1769	0.4	4613	0.4	1774	0.4	799	0.2	752	0.2
Eastern (sub-Saharan)	1317	0.3	1645	0.3	1166	0.3	601	0.2	708	0.2
Central (sub-Saharan)	180	0.1	375	0.1	541	0.4	90	0.1	177	0.1
Oceania	29	0.2	125	0.9	45	0.3	19	0.2	18	0.1

ASR, age standardised rate; HBV; hepatitis B virus, HCV; hepatitis C virus, NAFLD; non-alcoholic fatty liver disease.

1.3 The burden of hepatocellular carcinoma and associated risk factors in Ethiopia

Little attention has been paid to determining HCC burden in Ethiopia, a SSA country, owing to a lack of reliable data sources, such as population-based cancer registries (103). Until recently, research estimating the country's cancer burden relied on data from neighboring countries (103, 104). For instance, the Global Burden of Disease Cancer Collaboration (GBDCC) estimated cancer incidence for countries worldwide (103, 104), and drew on evidence from other African countries to predict the incidence in Ethiopia due to insufficient available evidence specific to this country. Thus, the accurate burden of various types of cancer in the country, including HCC, remains unknown (105).

Efforts have been made to address the paucity of cancer data in Ethiopia. Ethiopia's first population-based cancer registry, the Addis Ababa City Cancer Registry (AACCR), was established in Addis Ababa, Ethiopia's capital, in 2011 (105, 106). The AACCR is mandated by the Ethiopian Federal Ministry of Health to collect cancer data only from Addis Ababa residents (103, 104). All healthcare facilities in the city that provide cancer diagnosis and treatment are obligated to report cancer cases to the registry (107). Using such available data for 2019, the GBD identified breast, cervical, and colorectal cancers as the most common cancers in the country (Fig 1-5) (105, 108). The incidence of different cancer types, such as lung, stomach, breast, and cervix cancer types, in Addis Ababa has also been studied using data from the AACCR (103, 104). However, the existing publications are only the beginning of understanding the burden and risk factors for cancer in the city. To date, little attention has been paid to determining the burden of various cancer types, including HCC, in Addis Ababa using data from the AACCR and in Ethiopia in general using reliable country-specific data (103).

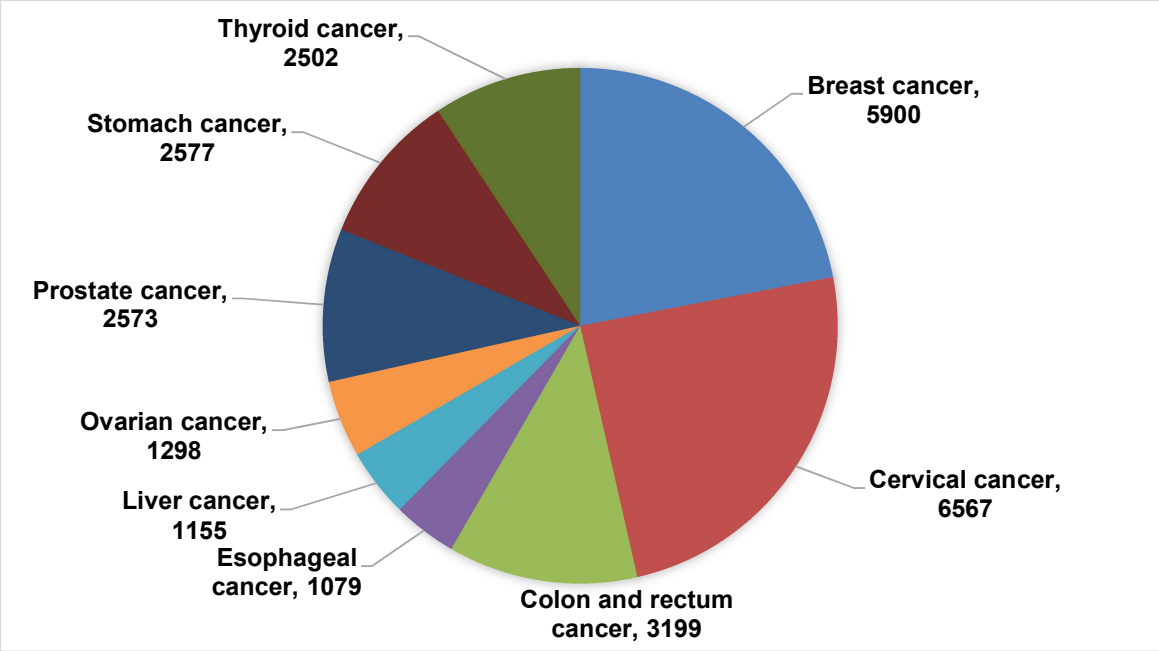

Figure 1- 5: Ethiopia's estimated cancer incidence in 2019, according to the Global Burden of Disease Study (GBD) (108).

Until recently, knowledge of the incidence of HCC in Ethiopia was largely based on the work of a few researchers who described the incidence of the disease by age, sex, and histology in patients visiting nine hospitals in the country (92, 93, 109-113). The majority of these studies focused on describing the number of HCC cases identified in certain cancer care hospitals in the country (94-97, 114). Moreover, the majority of these studies were not recent (92-97), and none used a representative sample (e.g., they did not use data from population cancer registries, nor did they draw on a representative sample from the population) (92, 93, 109-113), reliable data source (e.g., a cancer registry) (92, 93, 109-113), or considered any trends in HCC incidence (92, 93, 109-113). As a consequence, the findings of these studies have limitations in accurately reflecting the burden of HCC in the country (92-97, 115).

In the context of these challenges, studies conducted in Ethiopia found that the prevalence of HCC ranged from 16.1% to 33.5% among individuals admitted to certain hospitals in the country with liver disease (92, 96, 97). The studies also reported that HBV, HCV, and aflatoxin B1 were the common risk factors identified among HCC patients in the country (92, 96, 97). Current and

accurate data on the burden of HCC and its underlying causes in the Ethiopian population, as well as how the burden affects populations over time, is needed to understand the disease's actual burden in the country and to design effective cancer control plans, or update the old cancer control plan. To provide further context for the existing plan, the current cancer control strategy in Ethiopia is outlined below.

Reliable cancer incidence and death data sources, such as GLOBOCAN, report data on liver cancer rather than HCC (36). Given that HCC accounts for most liver cancer cases, data on liver cancer from such reliable sources is often discussed as HCC in the literature (36, 116). Some of the data on liver cancer in Chapter One and Chapter Two of the thesis are based on reports from reliable data sources such as GLOBOCAN. As a result, liver cancer cases are used interchangeably with HCC in some sections of Chapter One and Chapter Two of this thesis (116).

The cancer control plan of Ethiopia

Although the cancer burden in the country is increasing, until recently, the country's health system was focused on communicable diseases (117). Moreover, factors such as urbanization, economic growth, and market globalization have increased the prevalence of modifiable cancer risk factors such as alcohol and tobacco use in Ethiopia (117-123). These modifiable cancer risk factors are suggested to contribute to Ethiopia's rising cancer burden (105, 124). In Ethiopia, 5.8% of all deaths are attributed to cancer (105). Around 60,960 new cases of cancer are diagnosed each year, and over 44,000 people die from the disease (105, 117). Adults under 75 years of age have an estimated 11.35% chance of developing cancer, and a 9.4% chance of dying from it (105, 117).

However, because cancer has been treated as a low priority in Ethiopia for several decades, the country's healthcare system has been insufficient to address the aforementioned challenges (105). In addition, Ethiopia is one of the least developed countries in the world (125), with few resources to address the challenges that cancers, including HCC, pose (117). Further complicating the ability to inform cancer prevention strategies is a scarcity of data to use as a baseline (103), and no cancer screening program in the country (117). Despite these and other challenges, the country developed a national cancer control plan in 2015, which was finalized in 2020, to make the best

use of the limited resources available to address the problem (117, 126). The Ethiopian cancer control plan was adopted by the Federal Ministry of Health and Regional Health Bureaus in 2015 (105). This plan is based on the World Health Organization's global cancer control plan and is the first cancer control strategy document developed in the country (105). The plan has set goals to expand cancer preventive interventions and screening programs for early detection, which has seen increased efforts to achieve this over the past five years (105). Some of the goals of the Ethiopian cancer control plan are listed in Table 1-2 below:

Table 1-2: Summary of the goals of the Ethiopian national cancer control plan (117).

Strategy	Goals/Objectives
Raising public awareness of cancer	▪ Educating 50% of the population on cancer prevention by 2020. ▪ Integrating cancer prevention activities into routine healthcare by 2020.
Tobacco control	▪ Reducing tobacco use by 30% by 2020
Physical activity and a healthy diet	▪ Increasing public fruit and vegetable consumption by 15% by 2020. ▪ Reducing insufficient physical activity by 10% by 2020. ▪ Reducing obesity and overweight by 5% by 2020.
Controlling harmful alcohol use	▪ Reducing the prevalence of harmful alcohol use by 5% by 2020.
Controlling biological cancer-causing agents	▪ Pathological agent control, such as HPV and HIV
Minimizing exposure to environmental risks	▪ Reduction in exposure to environmental hazards linked to cancer.
Breast cancer self-awareness promotion	▪ Improving breast cancer early detection. ▪ Incorporate breast self-awareness health education into all healthcare facilities.
Screening for cervical cancer	▪ To achieve 80% coverage of precancerous cervical lesions using visual inspection with acetic acid in non-symptomatic women aged 30-49.
Early detection	▪ Increasing public and health professional awareness of breast cancer and cervical cancer signs and symptoms by 50%.
Improve access to diagnosis	▪ Providing 20% of patients who are detected by the early-detection method with adequate diagnosis and treatment.
Enhancing palliative care services	▪ Ensure that 20% of health institutions in the country provide palliative care by 2020. ▪ Increasing institutional capacity in palliative care.

To achieve the aforementioned and other goals, activities have been carried out at the three levels of the health care delivery system in Ethiopia, namely primary, secondary, and tertiary (117, 127). The section that follows discusses the three levels of healthcare, as well as the cancer control activities that have been implemented at each healthcare level in Ethiopia.

1.4 The health care delivery system in Ethiopia

Ethiopia is currently confronted with a burden of both communicable and non-communicable diseases (128). To address these health issues, Ethiopia's healthcare delivery system is structured into three tiers: primary, secondary, and tertiary level healthcare delivery systems (Fig 1-6) (105). The primary level of care includes primary hospitals, health centres, and health posts, and serves between 60,000 and 100,000 people country-wide. The first tier is set up to offer essential curative, preventive, and promotional healthcare services (128). Secondary-level health care consists of general hospitals that serve 1-1.5 million people per annum, whereas tertiary-level health care consists of tertiary hospitals that serve 3-5 million people (105).

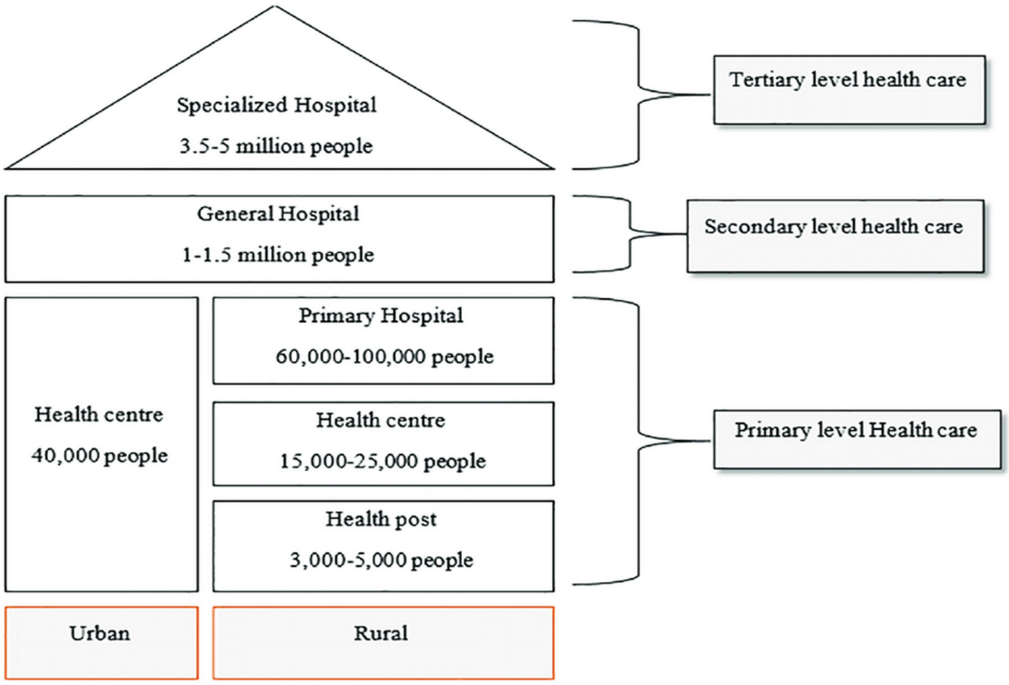

Figure 1-6: Ethiopian health tier system (105). Note: This graph is adapted from data reported by the Federal Democratic Republic of Ethiopia, Ministry of Health (128, 129).

The rapid expansion of the private, for-profit, and non-governmental sectors has improved the delivery of healthcare in Ethiopia (128). This is due to the significant contributions these organizations have made to increasing access to and use of health services (128). Private health institutes have been reported to be directly involved in cancer prevention, care, and control (117). However, many private health care institutions in the country lack qualified cancer care personnel and are ill-equipped to treat cancer cases (117). The Federal Ministry of Health also introduced the Public Private Partnership (PPP) strategy to increase private-sector involvement in the provision of health services, and foster collaboration between the public and private sectors (130, 131). The PPP strategy aimed to support and strengthen the domestic production of critical cancer-related supplies and medications (117). Such domestic production of medicines and supplies guarantees the ongoing availability of those products and significantly shortens the time between production and use (117). Through community involvement and social marketing, the private sector and non-governmental organizations also play a critical role in ensuring access to health services and products (117).

In Ethiopia, cancer care is available at all three healthcare levels (105, 132, 133). Some of the cancer intervention activities undertaken at the primary care level (health centres and training posts) include: training health professionals in cancer awareness skills, targeted screening of human papillomavirus (HPV) and human immunodeficiency virus (HIV) (105, 134, 135), raising public awareness of the link between alcohol, tobacco, environmental hazard agents (e.g., aflatoxin B1), obesity, and cancer (105, 136), and building the capacity of care providers and caregivers in palliative care (105). Secondary care level activities include improvements to cancer diagnosis and treatment facilities (137), increased access to surgical care, incorporating public cancer awareness into hospital health education, and providing diagnostic facilities for health providers to detect carcinogens (e.g., general hospitals) (105). Finally, the major activities carried out at the tertiary care level (e.g., tertiary hospitals) are improving access to advanced cancer diagnostic and treatment services (105, 132, 137), as well as increasing the availability of cancer medicines and medical equipment (105). Moreover, the majority of activities carried out at the primary and secondary healthcare levels are also carried out at the tertiary care level (105, 138).

Previous efforts at all levels of healthcare, however, have been hampered by a variety of factors. The majority of cities in Ethiopia lack hospitals with full-time physicians (139). Ethiopia's capital city, Addis Ababa, and a few other cities in the country, such as Gondar, are the only cities with such facilities (139, 140). Public health facilities in Ethiopia have also had trouble providing cancer care because of budgetary restrictions (141-143). Numerous patients are eligible for fee waivers or exemptions, and the government continues to spend much less on healthcare than the rest of Africa (142, 143). For instance, Ethiopia's healthcare spending in 2016 was only 1.4% of gross domestic product (GDP), making it one of the lowest in Africa (144). In Ethiopia, public healthcare institutions are where the majority of cancer prevention and control efforts are carried out (117). For these efforts to be successful, healthcare professionals, such as doctors at the institutes, must actively participate (117). Ethiopian doctors, however, frequently leave the public sector because of unmet salary expectations and higher earning potential in the domestic private sector or abroad (145, 146). Healthcare equipment and drug shortages are also ongoing issues in the country, impeding cancer care or prevention activities at various levels of healthcare (132, 147). Moreover, little attention has also been paid to training health professionals in the country, which could have aided cancer care activities provided at various levels of health care (132). Although several universities in the country continue to graduate health professionals and a few specialists, the rising demand for cancer care or health services is not being met (132, 148, 149). The summary of cancer interventions available in Ethiopia at various levels of healthcare is presented in Table 1-3. The burden of HCC and associated risk factors in the world and Ethiopia, the mechanisms used by HCC risk factors to increase the risk of HCC development, and HCC prevention strategies are explored in detail in Chapter Two.

Table 1-3: Summary of cancer intervention strategies in Ethiopia by the level of service delivery (105).

Strategy	Intervention strategies by the level of service delivery		
	Primary (e.g., health centre and health posts)	**Secondary (e.g., general hospital)**	**Tertiary (e.g., tertiary hospital)**
Public awareness of cancer	Providing basic cancer awareness creation training to health care workers.	Providing cancer prevention and control education to patients.	Providing patients with health information on cancer prevention and control.
Tobacco control	Raising awareness of the link between smoking and cancer.	Incorporating cancer education into routine hospital health education.	Integrating public cancer education into routine hospital health education.
Physical activity and a healthy diet	Raising public awareness of the role that an unhealthy diet, obesity, and inactivity play in the development of cancer.	Promoting public awareness of the dangers of obesity, an unhealthy diet, and physical inactivity in cancer development.	Raising awareness of the link between cancer development and unhealthy eating, inactivity, and obesity.
Control of harmful alcohol use	Increasing public awareness of alcohol-related health risks, including cancer, especially among young people.	Including information on alcohol's harmful effects in regular health education.	Providing care for those who abuse drugs, including alcoholism.
Control of the biological cancer-causing agents	Improving health promotion for cancers caused by infectious diseases.	Treating infectious diseases that are a direct cause of cancer (HPV, Hepatitis B, and HIV).	Establishing targeted methods for detecting and preventing pathological agents like HPV, HIV, and hepatitis B.

Minimizing exposure to environmental risks	Raising public awareness of the potential connection between environmental dangers and cancer.	Educating the public about the possible connection between environmental risks and cancer.	Public awareness campaigns about the potential connection between environmental risks and cancer.
Breast cancer self-awareness promotion	Integrating breast self-awareness health education into healthcare facilities.	Individual breast self-awareness training.	Integrating breast self-awareness health education into healthcare facilities.
Screening for cervical cancer	Conduct cervical cancer screening.	Training in cervical cancer screening and treatment for nurses, health officials, and doctors.	Training medical personnel about cervical cancer's early symptoms and signs.
Enhancing palliative care services	Building the knowledge and skills of caregivers and medical professionals in palliative care.	Encourage medical professionals to integrate palliative care techniques into their regular and daily services.	Encourage medical professionals to integrate palliative care practices into their standard daily procedures.

1.5 Statement of the problem

As the global cancer burden increases and the cost of cancer care continues to climb, countries are struggling to understand how to effectively mitigate or control the severe health and economic repercussions of cancer on their population (150, 151). Careful cancer control planning is essential in all resource settings (16). It responds to the needs of people by preventing cancer, diagnosing it early, or curing it (16). Effective cancer planning, even with limited resources, can significantly reduce the cancer burden (16, 152). If not planned carefully, available cancer control resources will be used inefficiently, failing to realize the benefits that should flow from the resource to the population (16). Population-level cancer control is challenging, and demands a considerable investment of resources from the health system because cancer is a heterogeneous disease that requires intervention at various stages (153, 154). In addition, a lot of interventions call for substantial involvement from non-health sectors (155, 156). They might include participants from the business community, the legislature, the media, and law enforcement. Such large-scale efforts require effective planning (152). For this reason, the World Health Organisation (WHO) has repeatedly urged nations to develop careful national cancer control plans (16, 152).

According to the WHO, cancer control planning consists of three basic steps (Fig 1-7) (16). The first step is to assess the current state of the cancer problem, as well as gaps in the existing cancer control plan and ongoing activities. Identifying age and gender differences in cancer prevalence, incidence, mortality, survival, and stage at diagnosis is part of assessing the current state of the cancer problem. Step one also includes assessing public awareness of cancer and cancer risk factors. Identifying gaps in physical (e.g., infrastructure), human resources (e.g., health-care personnel), and financial resources in cancer control is part of evaluating the existing cancer control plan and ongoing activities. The second step is policy formulation and adoption, and the final step is determining the steps required to put the policy into action (16).

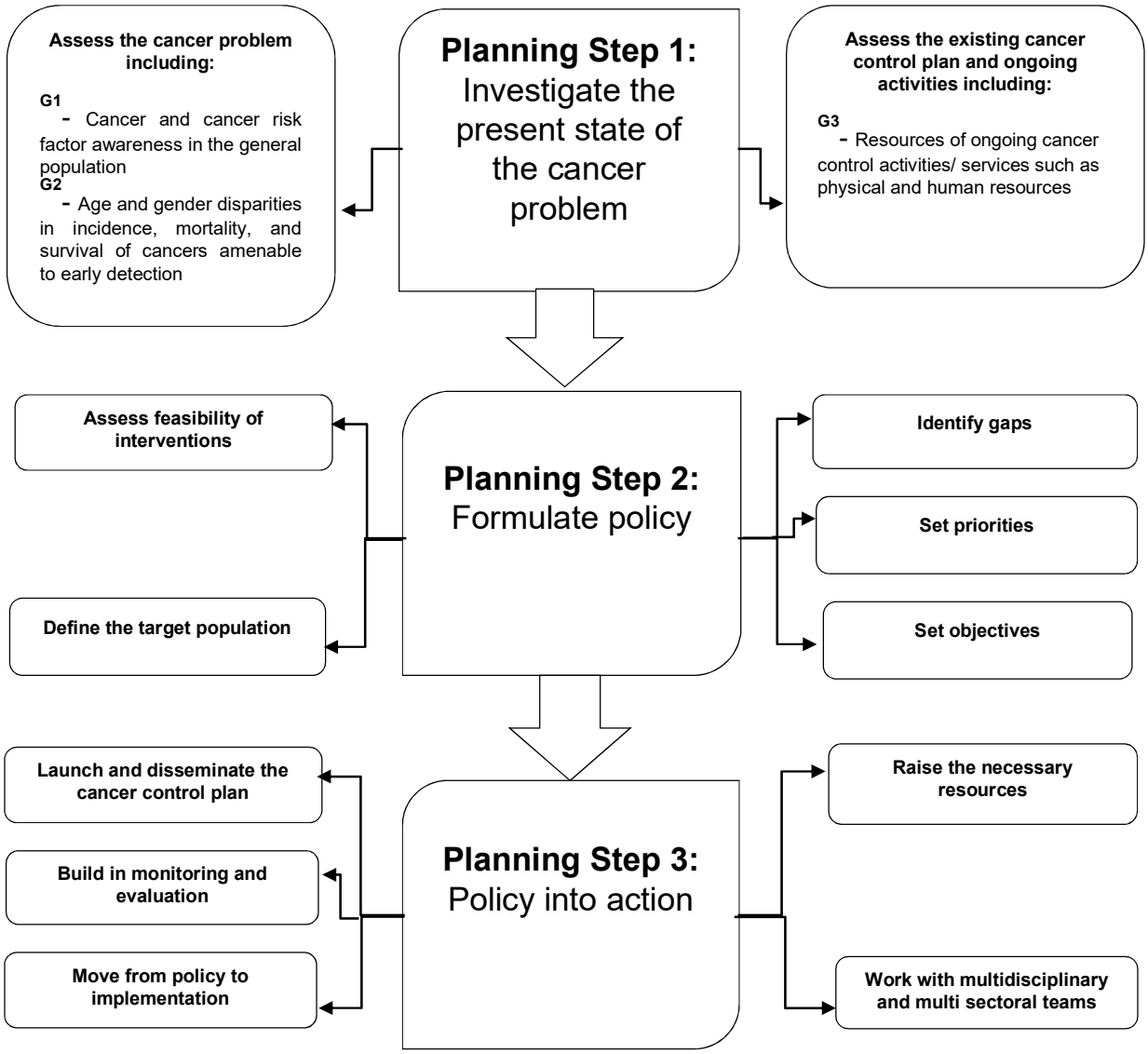

Figure 1-7: The World Health Organization's step-by-step framework for cancer control planning (16). Note: This flowchart was created using data from the WHO. This flowchart is a summary of the step-by-step framework and does not contain the full framework. G1 (research gap one), G2 (research gap two), and G3 (research gap three) are some of the research gaps that this thesis aims to fill.

However, for a variety of reasons, effective cancer control planning has received little attention in Ethiopia over the last few decades (117, 126, 136). First, there has been a paucity of reliable data and data sources for assessing the burden of cancer, including HCC, in the country (105, 117). As discussed in section 1.3, until recently, there was no population-based cancer registry in the

country, and research estimating the incidence of cancer in Ethiopia depended on data from neighbouring countries (103, 104, 157). Further complicating this, reporting bias exists in hospital-based cancer reports in Ethiopia, as does the accuracy and completeness of record-keeping affects reports on cancer patients/burden in the country's hospital-based series (105). Due to the aforementioned and other challenges, there is a paucity of reliable data on the burden of several types of cancer in the country (105). The scarcity of such data is impeding effective cancer and HCC control planning in the country, as such data is required for the first step in cancer control planning, according to the WHO (16).

The second reason for paying little attention to cancer control planning, including for HCC, is that cancer control, and research have not been priorities in Ethiopia in recent years (117). For instance, Ethiopia finalized a 20-year National Health Sector Development Program (HSDP) in 2015 (158, 159). The program was launched in 1997, and among its priorities are disease prevention, decentralization of healthcare delivery, and increased national health spending (126). In the HSDP era, communicable diseases were competing priorities, and non-communicable diseases, including cancer, were under-prioritized (158, 159). As a result, adequate government funds for cancer, including HCC, infrastructure, education, and financial have not been made available as needed (105).

The Ethiopian government's cancer control plan aimed to reduce the cancer burden by 15% by 2020 (117). Although the Ethiopian cancer control plan utilized several strategies to attain these goals, the incidence of cancer and cancer risk factors has been reported to increase in the country, emphasizing the need to either develop a new plan, or update the old one (103). Moreover, over the last few decades, there has been an effort in Ethiopia to determine the burden of some of the HCC risk factors on the general public. For instance, Ethiopia is classified as a hepatitis-endemic country by the WHO, and over 10 million Ethiopians have been reported to be infected with HBV (160-162), which is one of the major risk factors for HCC. Chronic hepatitis B and C viral infections are also responsible for more than 60% of chronic liver diseases in the country (163). Moreover, HBV vaccines were added to Ethiopia's standard expanded program on immunization in 2007 (164), and adult HBV vaccination is only administered to high-risk groups, such as healthcare

workers in public health institutions, with no compulsory HBV vaccination program for adults (61, 62). There have also been initiatives in Ethiopia to treat and screen for HBV and HCV; however, these efforts have been hampered by factors such as patients' low health-care-seeking behaviour due to a lack of awareness of the diseases, limited access to antiviral medications, limited health-care facilities, and patients' financial difficulties (105, 165). However, there has been minimal focus on determining the independent and combined role of HBV and HCV in HCC in Ethiopia (103).

Ethiopia, like many other countries globally, is experiencing rapid economic growth, urbanization, and increased globalization of unhealthy food and consumer goods markets (105, 124). These changes have increased exposure to modifiable cancer risk factors, such as alcohol and tobacco use, which may increase the burden of various cancers, including HCC, in the country (105). More recent research into the incidence and risk factors of HCC in Ethiopia, using reliable data, is thus required to aid in the country's HCC control planning. Further limiting public health action for HCC is limited data on general public awareness of cancer/HCC signs, symptoms, and risk factors that impede effective cancer control planning in Ethiopia (110, 117, 166, 167). According to the Federal Ministry of Health of Ethiopia, 80% of cancer cases in the country are identified at an advanced stage when treatment options are limited, which is suggested to be due to the general public's lack of awareness of cancer symptoms and risk factors (105). However, only a few studies on public awareness of cancer in Ethiopia have been conducted in recent decades, and these studies have focused on a few types of cancer such as colorectal, breast, and cervical cancer (166, 168-170). It is difficult to generalize the findings of these studies to HCC because they were conducted on cancer types other than HCC in different contexts, situations, times, and populations. No previous study has explored the public awareness of HCC symptoms and risk factors in Ethiopia.

Generally, Ethiopia's national cancer control plan, which was established in 2015 and was in use until 2020, gave little emphasis on HCC control in the country (117). The disease, on the other hand, is recognised as a significant public health problem and among the leading cause of cancer-related death worldwide (12, 171). Its risk factors are also increasing in Ethiopia and other SSA countries (117). There has also been little attention on determining the burden of HCC and the gaps in disease control activities in the country (137, 172). Thus, either developing an HCC control

strategy for the country, developing a new national cancer control plan emphasizing HCC, or revising Ethiopia's old plan to emphasize HCC is needed. These need local data on the current state of the cancer problem, as well as gaps in the existing cancer control plan and ongoing activities, which this study aims to provide.

To summarise, little focus has been placed in Ethiopia on determining 1) the incidence of HCC and how it affects the population over time; 2) the burden of HCC risk factors among HCC patients; 3) cancer awareness among the general public, including HCC; and 4) infrastructure, financial, and education gaps in HCC control. Four projects of research in the following thesis were designed to address this.

Project One- systematic review and meta-analysis

Two systematic reviews were conducted to identify gaps in the following main areas: 1) the incidence and risk factors of HCC in Ethiopia; and 2) the combined roles of HCC risk factors in the development of HCC worldwide.

Project Two – data audits

Considering the gaps identified by systematic review in Project One, Project Two looked at the incidence and trends of HCC in Addis Ababa using eight years of retrospective data from the Addis Ababa City Cancer Registry, the country's first and only cancer registry. Project Two also assesses HBV and/or HCV infection among HCC patients in Addis Ababa. This is the first study to assess the incidence and trend of HCC in Addis Ababa, and the findings will aid in the development of effective HCC prevention and control strategies/plans.

Project Three – surveys

Given the incidence and trend of HCC and the prevalence of HBV and/or HCV infection among HCC patients in Addis Ababa, in Project Three, a cross-sectional survey was conducted to assess Addis Ababa residents' awareness of the signs, symptoms, and risk factors of HCC as well as all cancer types. This study was important because it provides important baseline data on HCC

awareness for the first time in the country for future cancer prevention and control efforts. Previous cancer awareness efforts in Ethiopia have paid little attention to a variety of cancers, including HCC (117). Thus, this study can assist policymakers in recognizing HCC during the design and implementation of cancer awareness programs.

Project Four – a qualitative study

Using qualitative interviews, Project Four investigated liver cancer clinicians' perceptions of Ethiopia's current educational, infrastructure, and finance needs in HCC control. This project is critical to the public health initiatives required in Ethiopia to meet the WHO cancer control planning approach because it identifies infrastructural, educational, and financial gaps in HCC control in the country that should be considered in future control planning (16).

1.7 Research questions, aims, and objectives

1.7.1 Research questions

1. What is known about the prevalence of HCC in Addis Ababa?
2. What is the epidemiology of HCC risk factors among HCC patients in Addis Ababa, Ethiopia?
3. What is the available evidence on the combined role of HBV and HCV in HCC development?
4. What are liver cancer clinician's perceptions of the current infrastructural, educational, and financial needs to control HCC in Ethiopia?

1.7.2 Aims and objectives

Aim 1: To review the available evidence on the burden of HCC and its associated risk factors.

I. To report the best available evidence on the burden of HCC and its risk factors in Ethiopia

II. To identify the best available evidence on the combined roles of HCV and HBV in the development of HCC

Aim 2: To determine the epidemiology and correlates of HCC in Addis Ababa, Ethiopia

I. To determine incidence and trends of HCC in Addis Ababa, Ethiopia, from 2012 to 2019
II. To determine the positivity rates of HBV and/or HCV among HCC patients in Addis Ababa, Ethiopia

Aim 3: To determine public awareness of HCC signs, symptoms, and risk factors in individuals aged 18 and older in Addis Ababa, Ethiopia

I. To determine whether there are any sociodemographic differences in public awareness of cancer, particularly HCC, signs, symptoms, and risk factors among adults in Addis Ababa, Ethiopia

Aim 4: To explore liver cancer clinicians' perceptions of the current educational, infrastructure, and financial needs to control HCC in Ethiopia

I. To explore the perception of liver cancer clinicians on educational, infrastructure, and financial gaps in HCC control in Ethiopia
II. To explore liver cancer clinicians' recommendations on how to address educational, infrastructure, and financial gaps in HCC control in Ethiopia

1.8 Thesis significance and originality

The findings of this thesis provide an opportunity to raise community and government awareness of HCC as a public health concern in Ethiopia, and of the relevant risk factors which need to be addressed. This is required to aid in earlier HCC detection and improve health-seeking behaviour, thereby reducing HCC incidence and death and improving patient survival.

The study's findings may also help public healthcare institutes in Addis Ababa to strengthen their efforts to reduce the burden of HCC in the city. Ethiopian public health institutes, as discussed in depth in the other sections of this chapter, integrated cancer education programs for the public into their daily operations (104, 132, 136, 173). Identifying socio-demographic differences in public HCC awareness in this study will, therefore, support institutes in identifying those in the city with

the lowest HCC awareness and tailoring cancer education to them. Identifying socio-demographic differences in public awareness of HCC in Addis Ababa also aids cancer advocates in their efforts to raise HCC awareness in the city. Stakeholders may hold forums and launch advocacy campaigns to assist decision-makers in understanding the issue and responding appropriately.

Cost, effectiveness, and disease burden are some of the factors that affect cancer intervention selection, including preventative intervention (103, 104). Therefore, to prioritize the scale-up of interventions in Ethiopia, the availability of local epidemiological data on HCC and other types of cancer is necessary (104). Thus, the findings of this study have the potential to help prioritize the scaling-up of interventions in Ethiopia. Moreover, future researchers will use the findings of this study as a baseline to evaluate the efficacy of future cancer control and prevention efforts in Addis Ababa. This thesis represents Ethiopia's first study into 1) trends in HCC incidence; 2) public awareness of HCC signs and risk factors; and 3) liver cancer clinicians' perceptions of current educational, infrastructure, and financial needs in HCC control.

1.9 Thesis structure

The thesis has eight chapters. Following this first chapter (introduction, background, and statement of the problem), the second chapter reviews the burden of HCC and its risk factors globally, in sub-Saharan Africa and Ethiopia, and the mechanism by which HBV and/or HCV increases the risk of developing HCC. The methods used in the thesis are summarized in Chapter Three. The fourth chapter presents the results of two systematic reviews on the independent and combined effect of HCC risk factors on and the development of HCC, as well as the results of a systematic review on the incidence of HCC and its risk factors in Ethiopia.

Chapter Five summarizes the results, discussion, and conclusion of a retrospective study on the incidence and trends of HCC across eight years (2012–2019) in Addis Ababa, Ethiopia. This chapter also presents the results, discussion, and conclusion of a retrospective study on HBV and/or HCV infections in HCC patients in Addis Ababa, Ethiopia. Chapter Six summarizes the findings from a cross-sectional survey on public awareness of HCC and overall cancer signs, symptoms, and risk factors in Addis Ababa, Ethiopia.

Chapter Seven presents the findings from a qualitative study on liver cancer clinicians' perceptions of the current public policy needs to control HCC in Ethiopia. Chapter Eight synthesizes all the findings of the thesis, conclusions, and recommendations and discusses the implications of the project for policy, research, and program.

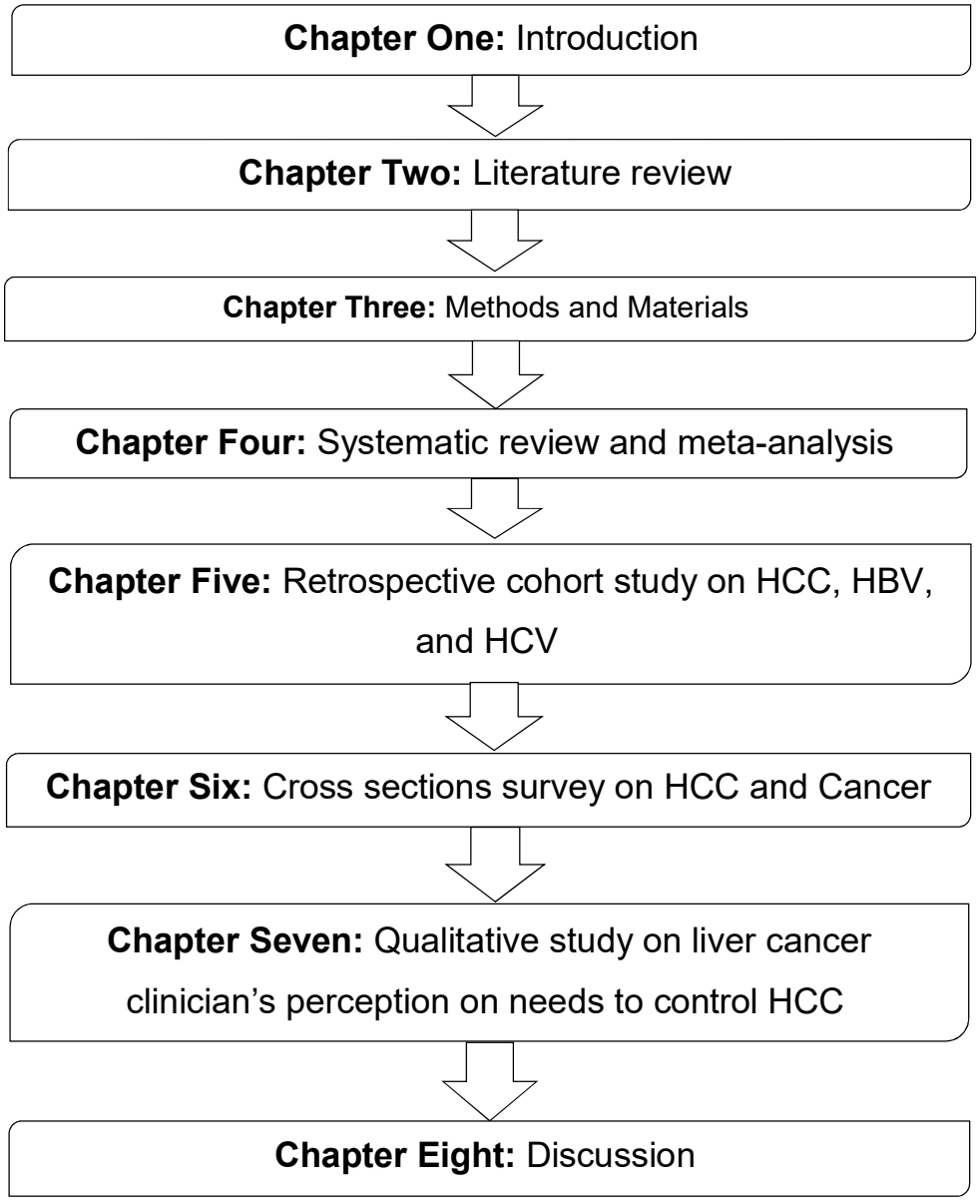

Figure 1-8: Flowchart showing the structure of the thesis.

CHAPTER TWO: LITERATURE REVIEW

2.1 Hepatocellular carcinoma (HCC)

HCC is a form of primary liver cancer that develops in the liver tissues (174, 175). Several mechanisms have been proposed for the development of HCC (176); these are summarised visually in Fig. 2-1. One of the primary mechanisms is the interaction between HBV or HCV and the host (177, 178). T-cell immune responses are elevated during HBV infection to eliminate the virus (177-180). The increased T-cell immune response causes necrosis, inflammation, and, eventually, hepatocyte regeneration (177, 181). Continuous replication of hepatocytes allows oncogenic lesions to propagate, leading to genetic instability and, eventually, the development of HCC (Fig. 2-1) (177, 181). HCV also follows the same steps as mentioned above, but employs a different mechanism (Fig. 2-1) (177, 182). The physical interaction between HBV and the endoplasmic reticulum (ER) creates ER stress, which leads to mutations that induce genetic instability, which finally leads to HCC (Fig. 2-1) (35, 183). HCV inhibits P53-regulated pathways or inactivates the P53 gene (a tumour suppressor gene), resulting in a lack of control over cell growth and proliferation and the development of HCC (184).

In addition to HBV and HCV infection, a range of additional pro-inflammatory pathways can contribute to HCC risk. For example, chronic alcohol consumption can cause an increase in the production of pro-inflammatory cytokines, inflammation, and necrosis, which can lead to HCC (185). Aflatoxin B1 inactivates p53, leading to a loss of control over growth and proliferation, genetic instability, and, eventually, HCC (186). Human liver cells contain a variety of immune cells, including CD8+ T cells, CD4+ T cells, B lymphocytes, and others (187). Lipid accumulation and oxidative stress in people with non-alcoholic steatohepatitis (NASH) may recruit and activate these immune cells, causing them to release molecules that cause inflammation, fibrosis, and HCC (Fig. 2-1)(188). Obesity has also been linked to hepatic inflammation, fibrosis progression, and the development of HCC (Fig. 2-1) (44). T2D causes pro-inflammatory cytokines and oxidative stress, increases cellular growth and proliferation, and inhibits apoptosis, all of which contribute to the development of HCC (Fig. 2-1) (189).

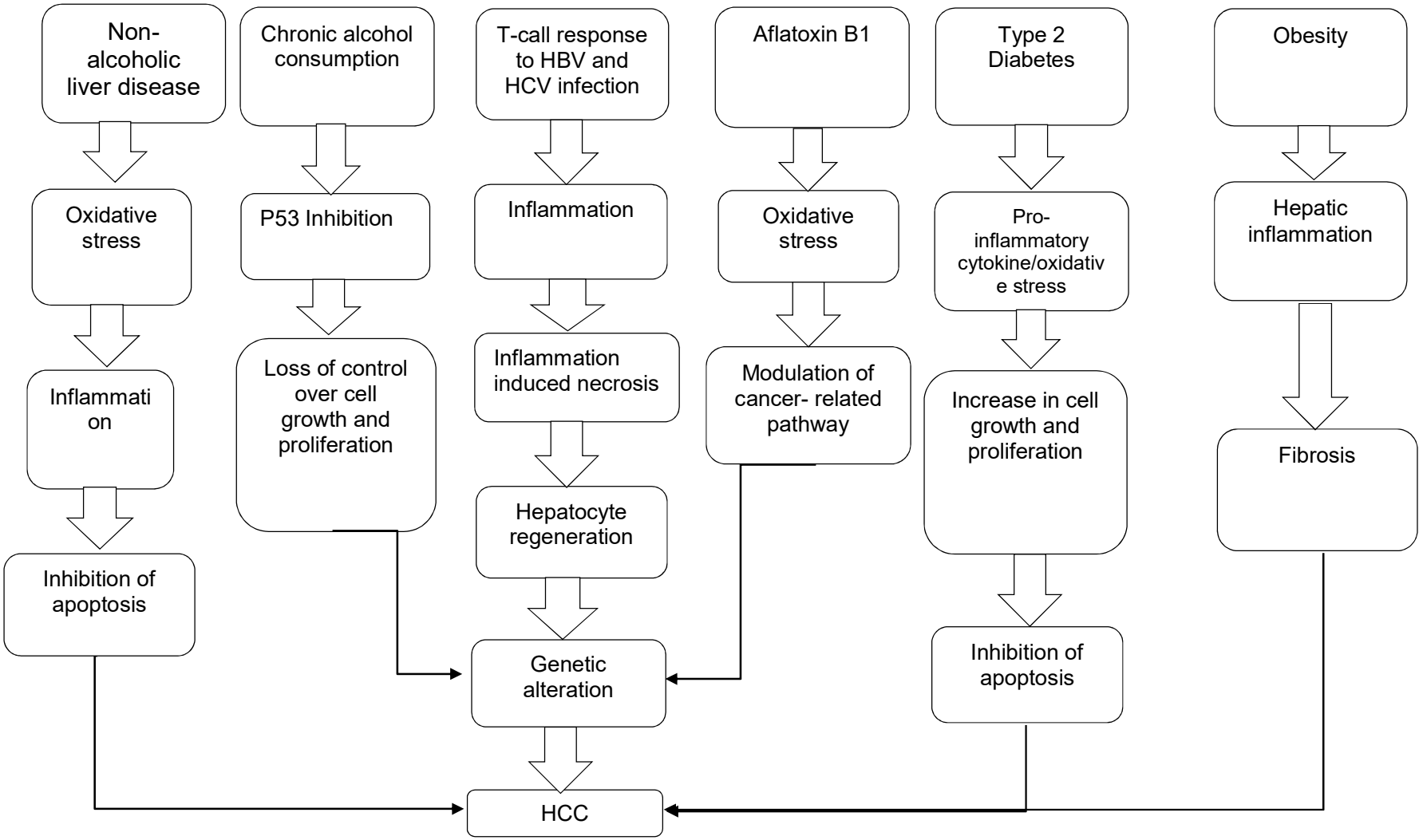

Figure 2-1: Hepatocarcinogenesis mechanisms (177, 182, 188, 189).

Several factors influence HCC treatment, including the availability of liver transplants, the stage of the disease at presentation, the patient's ability to tolerate surgery, and the availability and accessibility of other treatments such as radiotherapy, radiofrequency ablation, transarterial chemoembolization, and percutaneous ethanol injection (190, 191). HCC treatment can have at least four intents: curative, bridging, down staging, and palliative (192). Curative intent is when the cancer is limited to a few areas of the liver. In this case, surgical removal may be curative (192). In "bridging intention" cases, some patients may receive treatment for some or all of their tumours while waiting for an organ to become available (190). HCC treatment can also be used to downstage diseases that are too advanced for curative treatment (190). This stage is performed to qualify the patient for liver transplantation by reducing the number and size of active tumours (190). Palliative care is available for patients with more advanced diseases in order to alleviate symptoms and increase survival time (193). It also enhances patients' quality of life, which has been linked to increased patient survival (193, 194). A multidisciplinary team provides palliative care (195). Palliative care providers employ a multidisciplinary approach to help patients, including satisfying patients' practical needs and giving counselling (195, 196). Palliative care offers a support system that allows patients to remain as active as possible until death (197). Early HCC signs and symptoms are typically absent in most patients. When they occur, the following may be present: upper abdominal pain, unintentional weight loss, loss of appetite, general weakness, abdominal swelling, jaundice, nausea and vomiting, and fatigue (198, 199). HCC diagnosis may include a blood test for alpha-fetoprotein (AFP), an imaging test such as an ultrasound, A computed tomography (CT) scan, or magnetic resonance imaging (MRI), and a biopsy in which liver tissue samples are taken and examined under a microscope (198, 200). In Ethiopia, HCC can be diagnosed through clinical examination, the identification of specific tumour markers, cytology, and the histology of metastases (Appendix 2) (107). The gold standard for radiological imaging of HCC is comprised of computerized tomography (CT) and magnetic resonance imaging **(**MRI) (201).

2.2 Hepatocellular carcinoma prevention strategies

Prevention of HCC requires an understanding of the disease's pathogenesis and risk factors (202). There are three stages of prevention for HCC: preventing the disease from occurring by focusing on risk factor prevention, halting the course of chronic disease, and preventing recurrence (202, 203). Preventing risk factors includes vaccination, lifestyle changes, and environmental interventions such as aflatoxin B1 regulations (202). HBV vaccination has been shown to significantly reduce the occurrence of HCC globally (204-206). Direct-acting antivirals (DAAs) have also been used to treat chronic HCV (207, 208). DAAs, which target many steps in the HCV replication life cycle, are very effective and safe (207, 208). The main goal of DAAs is to maintain a sustained virological response (SVR) (207, 208), and second-generation DAAs not only had fewer adverse effects but also reduced the duration of therapy (209). Treatment with DAAs has also been linked to a lower relative risk of developing HCC (210). Antiviral medicines, which prevent the HBV from reproducing and hence reduce inflammation and liver damage, may be used to treat chronic hepatitis B (210). Several antiviral medications, including adefovir, lamivudine, telbivudine, and entecavir can aid in the fight against HBV and decrease its capacity to harm the liver (210). HCV prevention also includes avoiding intravenous drug use and screening blood products and medical equipment (75). Harm reduction interventions, such as needle syringe programs (NSP) and health education for injectable drug users, have also been shown to prevent HCV (211). The NSP provides injectable drug users with more needles and syringes while reducing the spread of hepatitis and other blood-borne diseases (211). Education regarding viral hepatitis among drug users can also help prevent new infections among those who are still susceptible, as well as assist those who are already infected in avoiding the disease's spread to others (212).Several preventative measures against Aflatoxin B1 contamination have been reported (103). Among the most effective ways to reduce Aflatoxin B1 exposure are measures aimed at preventing crop contamination in the field, as well as during post-harvest handling and storage (103). Several countries use a variety of mechanisms to prevent aflatoxin contamination, including the implementation of rules and regulations governing aflatoxin B1 in foods (213, 214). These include determining the maximum permissible or recommended levels of aflatoxin B1 in specific foods

(213, 214). Aflatoxin B1 exposure can also be reduced through agricultural and nutritional education (215).

According to a 2019 systematic review, avoiding alcohol consumption is the best way to prevent carcinogenicity (118). However, no threshold for the emergence of carcinogenic effects from alcohol was specified in the studies included in the review. A variety of tobacco-prevention strategies have also been reported (48). Policy-level tobacco-prevention measures are among the most effective (216). This includes raising taxes on tobacco products, putting restrictions on who can buy them, where they can be used, and how much advertising is allowed (217, 218). Mandatory health warnings must also be placed on packages (216). At the community or school level, tobacco smoking prevention programs are also possible (219). Educating potential smokers about the health risks can be helpful (220).

Several international liver societies recommend screening at-risk patients, which includes patients with cirrhosis and chronic HBV infections (8, 221-223). These recommendations are based on expert opinions, but they are backed up by several control trials and cohort studies. When compared to not screening, screening patients with chronic HBV improved early tumour detection (stage I, 60.5% vs 0%) and overall survival (37%; hazard ratio 0.63; 95% CI, 0.41-0.98) (224-228). However, no screening for HCC has been implemented in Ethiopia (117).

Preventing HCC from occurring by preventing its risk factors, such as HBV and HCV, has been recommended (229). Preventing its risk factors may include hepatitis B immunization and screening of blood donations (230). Prevention, which aims to halt the course of chronic disease, has also been recommended (203). Ideally, preceding illnesses (HCV and HBV) are eliminated, or the several stages of the carcinogenic process are suppressed using this approach (203). Chemoprevention medicines have to be widely available to help with this where cancer has already been diagnosed (58). Moreover, it has been suggested that almost all adult patients with cirrhosis and certain patients with chronic HBV should be engaged in HCC screening program due to their increased risk of HCC development (231). The other recommended prevention strategy is to prevent recurrence after 1-2 years of curative therapies (232). It has been reported that

immunotherapy following HCC resection significantly reduces HCC recurrence (233). Adjuvant interferon therapy has also been shown to reduce late-stage HCC recurrence (219).

In 1980, Ethiopia initiated the Expanded Immunization Program (EPI), which focused on women of childbearing age (15-49 years) and children under one year old (164, 234). The vaccination program targets six antigens: BCG, Diphtheria, Pertussis, Tetanus, Polio, and Measles (164). Hepatitis B was added to the standard EPI schedule in 2007, but little has been done since to assess the country's success with HBV immunization (164). The development of educational materials, standardization of diagnosis, care, and treatment in hospitals, and involvement in advocacy and awareness campaigns are also a few of the interventions for viral hepatitis in Ethiopia (234).

Limited efforts to prevent HBV infection and aflatoxin B1 exposure also jeopardize HCC prevention in developing countries (235). Despite the availability of an effective HBV vaccine, hepatitis B vaccination coverage remains low in developing countries (236). Most developing countries have no practical measures in place to prevent Aflatoxin B1 exposure (235). Because of poor sanitation, careless food handling, and ineffective food regulations, Aflatoxin B1 is more common in developing countries (90).

2.3 Hepatocellular carcinoma globally

Although several reasons have been proposed for the high incidence of HCC in developing countries, the high prevalence of the disease's two major risk factors, hepatitis infection, and dietary aflatoxin B1 exposure, have been reported to be the most important (235, 237). Moreover, in developing countries, financial and logistical constraints jeopardize efforts to prevent tumour development (235). Patients in developing countries with HCC have poorer prognosis than patients in developed countries (235). This is primarily due to several factors, including fewer cancer specialists, limited cancer diagnosis facilities, late-stage cancer presentation, and medication shortages in developing countries (235, 238, 239).

Several factors have been proposed to explain the gender and age disparities in the broader global incidence of HCC (240, 241). Gender disparities in the prevalence of HCC risk factors have

been identified as the most significant factor contributing to men's high HCC burden worldwide (34, 242). Several studies reported that males were found to be more likely than females to contract hepatitis B and C viruses (34, 242). Both alcohol abuse and aflatoxin B1 exposure are also said to be more prevalent in men than in women (34, 242). People's bodies become more susceptible to cancer as they age (243). As they grow older, they are exposed to more cancer-causing agents, such as viruses and tobacco smoke (243-246). The ability of immune systems to eliminate cells that have the potential to become malignant cells deteriorates with age (242). Moreover, immune function declines with age, making it more difficult to eliminate various cancer-causing agents (246, 247). The global incidence rate per 10,000 of primary liver cancer, which includes HCC in males younger than 30 years old, was 0.74 in 1990 and 0.52 in 2017, with a -2.63% change (Table. 2-1). For females under the age of 30, the corresponding rate was 0.42 in 1990 and 0.25 in 2019 (estimated average percentage change (EAPC) = -2.62) (Table. 2-1).

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Table 2-1: Global incidence rates of primary liver carcinoma and estimated average percentage changes among males and females (248).

Age (years)	Males					Females				
	1990		2017		1990-2017	1990		2017		1990-2017
	ASR/100,000	n[a]	ASR/100,000	n[a]	EAPC (95% CI)	ASR/100,000	n[a]	ASR/100,000	na	EAPC (95% CI)
<30	0.74	11.2	0.52	10.2	−2.63 (−3.20, −2.06)	0.42	6.21	0.25	4.77	−2.62 (−2.98, −2.25)
30-59	20.48	163.26	20.04	287.59	−0.49 (−0.65, −0.33)	6.88	53.30	5.01	72.18	−1.52 (−1.69, −1.35)
> 60	68.27	148.46	86.91	391.76	0.64 (0.52, 0.75)	33.28	89.90	34.44	186.59	−0.06 (−0.14, 0.03)

ASR; age-standardized incidence rate; EAPC, estimated average percentage change; n, number of cases; a, the numbers of cases are on thousand-scales.

There have also been reports of disparities in HCC incidence based on ethnicity/race. For instance, the incidence rate of HCC in the US is highest in Asians/ Pacific islanders (11.7/100,000) and lower in whites (3.9/100,000). It is intermediate in black persons (7.0/100,000), Hispanic (8.0/100,000), and American Indians/Alaska (6.6/100,000) (249). The disparities in incidence by race/ethnicity may have resulted from differences in the prevalence of HCC risk factors in each group (242).

Assessing the burden of cancer, including HCC, is poorly understood in developing countries (15, 250). Sub-Saharan African countries, including Ethiopia, are among these (110, 251). The two consecutive sections that follow discuss the burden of HCC, disparities in HCC burden by socio-economic factors, and challenges in estimating the burden of HCC in Sub-Saharan Africa and Ethiopia.

2.4 Hepatocellular carcinoma in sub-Saharan Africa

In SSA, HCC is a public health issue. HCC was first identified in SSA in 1879 (15), but a high incidence of the tumour among black Africans in the region was discovered in 1921 (252). Other studies have been conducted since those initial reports, and they have revealed that the tumour affects all Black ethnic groups in the subcontinent, albeit not equally (15). It was recently reported that 46,000 new cases of HCC are diagnosed each year in SSA (253). However, the lack of reliable data sources in the region made an accurate determination of the burden of the disease difficult. Table 2-2 shows the ASIR and incidence cases of HCC (primary liver cancer) in African countries in 2019 (254). Table 2-2 shows that males had a considerably higher ASIR than females in Guinea, The Gambia, Niger, and Cameroon, based on data from cancer registries collected by the GBD (255). This could be owing to the considerable disparity in the incidence of HBV, a major risk factor for HCC, between males and females in these countries. According to the GBD, the ASIR of HBV in Guinea in 2019 was 14.3 in males and 2.4 in females (255). In The Gambia, the corresponding ASIR for males and females in 2019 were 17.29 and 4.92, respectively (255). In 2019, the ASIR in Niger was 0.18 for males and 0.05 for females. Moreover, in 2019, the incidence of HBV in Cameroon was 0.23 in men and 0.07 in women (255). The high difference in HCC due to HBV between men and women may be owing to a difference in HBV exposure, with men being

more infected than women (256).

Table 2-2: Incidence cases and age-standardized incidence rates of primary liver cancer including HCC in Africa by region in 2019 (255).

Region/ Country	Incident cases		ASR per 100,000	
	Males	**Females**	**Males**	**Females**
West Africa				
Cote d'Ivoire	375	158	2.8	1.3
The Gambia	312	96	28.3	8.5
Guinea	1465	415	23.9	6.4
Mali	1078	282	9.9	2.6
Nigeria	1437	1348	1.4	1.2
Niger	3470	1649	0.3	0.1
Burkino Faso	112	120	1.0	1.1
Central Africa				
Congo	44	32	1.7	1.2
Cameroon	58	26	0.4	0.2
East Africa				
Kenya	367	296	1.5	1.2
Rwanda	151	127	2.5	1.9
Tanzania	324	275	1.2	0.9
Uganda	563	399	2.8	1.9
Southern Africa				
Malawi	143	97	1.6	1.0
Zimbabwe	518	513	7.2	6.6
Namibia	31	16	2.7	1.4
South Africa	1764	835	6.5	2.9

ASR; age-standardized incidence rate.

Few studies have been conducted to determine changes in the incidence of HCC in SSA nations, with conflicting results. Between 1990 and 2017, the ASIR in females aged under 30 years, 30-59, and ≥60 years decreased in all SSA regions (Table 2-1). The incidence rate also decreased between 1990 and 2017 in men aged 30 to 59 and those aged 60 and older in Central, Southern, and Western Sub-Saharan Africa (Table 2-1). The global decline in chronic hepatitis B in both

sexes was reported to be the primary cause of the global decline in ASIR of HCC diagnosed between the ages of 30 and 59 (248).

HCC is also reported to be more common in young people in SSA (15). Hepatitis infection during childhood or birth, and early aflatoxin B1 exposure are among the factors contributing to the increased incidence in younger people in SSA (257, 258). In several SSA countries, little attention has been paid to determining the burden of HCC, how it affects the population over time, and the factors that affect it (15). A lack of definite tumor diagnosis, a scarcity of cancer registries, a lack of appropriately trained personnel in cancer research, and no or low government financial support for cancer research are among the factors influencing HCC burden determination in SSA (15, 253). These and other challenges are also common in Ethiopia, a Sub-Saharan African country, making accurate HCC incidence determination difficult, as discussed in the following section.

2.5 Hepatocellular carcinoma in Ethiopia

To date, data on the epidemiology of HCC in Ethiopia, like data on all cancers in the country, has been neither complete nor always accurate (110, 117). Several factors have been identified as contributing to the country's lack of reliable data on the epidemiology of several cancers, including HCC. First, cancer care facilities are scarce in most parts of Ethiopia, and people must travel long distances to get cancer diagnosis and treatment, making them less motivated to seek medical help (132, 157). As a result, hospitals in the country record fewer cases of the disease, and using such records to estimate disease burden results in an underestimation of the true incidence (117, 132).

It has also been reported that incidence rates are better estimated using data from population-based cancer registries, which collect information on all new cases of cancer in a given area (15, 253). However, until recently, Ethiopia did not have a population-based cancer registry (103, 104, 157). In its capital city of Addis Ababa, a population-based cancer registry was established in 2011 for the first time (117, 172, 259). The registry only collects cancer incidence data from Addis Ababa residents, who account for 3.7% of Ethiopia's population according to 2017 population projections (104, 172). Since the cancer registry only collects cancer incidence data from Addis Ababa residents, accurate determination of the actual incidence of cancer in the rest of the country remains difficult (104, 172).

Another barrier to accurately assessing the burden of cancer/HCC in Ethiopia is a lack of properly trained cancer personnel (117). Epidemiologists, statisticians, and other professionals with the necessary training have been and continue to be scarce for establishing and staffing cancer registries, as well as conducting cancer research (105, 132). Despite the difficulties described above in determining the burden of HCC in Ethiopia, limited evidence suggests that the disease is a public health issue in the country (92-97, 115).

In Ethiopia, eight studies on HCC and its risk factors were identified. Six of the studies were conducted three decades ago, indicating that they do not reflect the country's current status of HCC and risk factors (92-97). All existing studies either have not considered all possible cases of HCC in the general population in the study area, or did not use appropriate sampling techniques, indicating that the sample they used was not representative (92-97, 115). Tsega et al. (96) conducted a retrospective cohort study in 1992 among 334 chronic liver disease patients and found 112 of them have HCC. Similarly, Pavlica et al. (94) found 38 HCC cases among 236 chronic liver disease patients in 1970. HCC was also identified in 19.2% of the 860 liver disease patients in 1989 (111).

Moreover, the majority of the studies to date have been conducted in a few hospitals in Ethiopia (92-97). Some of the studies looked at risk factor exposure in a small number of HCC patients admitted to a few hospitals around the country (93, 260). One study found hepatitis infection in 46 of 70 HCC patients (110, 113). Similarly, of the 100 HCC patients tested for hepatitis infection, 50% were found to be HBsAg positive (93). Mekonnen et al. (260), found HBV and HCV infection in 48% of the 51 HCC cases examined. The findings of the limited studies conducted in Ethiopia to evaluate the incidence of HCC are reviewed in depth in Chapter Four of this thesis. Moreover, to better understand the disease and reduce its burden in Ethiopia, the epidemiology of HCC in the general population must be investigated using a representative sample.

2.6 Hepatocellular carcinoma risk factors

HCC has several risk factors. Some of the factors include hepatitis B and C infections (261), aflatoxin B1 exposure (262), obesity (263), hemochromatosis (264), chronic alcohol consumption

(265), and NAFLD (266). Due to the high prevalence of some of these factors in Asia and SSA, these regions account for the majority of the world's HCC cases (267).

2.6.1 Hepatitis B virus infection

According to a WHO report, 269 million people were chronically infected with hepatitis B in 2019 (268). The distribution of chronic hepatitis B infection varies by region, with the Western Pacific (6.2%) and African (6.1%) regions being the most endemic, followed by the East Mediterranean (3.3%), Southeast Asia (2.0%), European (1.6%), and Americas regions (0.7%) (269).

The global distribution of chronic hepatitis B and HCC mirror each other (270, 271). Chronic HBV infection can cause liver injury (272). Necrosis will occur following hepatic injury, followed by hepatocyte proliferation (176). A continuous cycle of proliferation can result in chronic liver disease, which can progress to cirrhosis and, eventually, HCC development (86). Cirrhosis is characterized by collagen build up, liver scarring, and abnormal liver nodule formation (86). Cirrhotic hepatitis B patients have a significantly higher risk of developing HCC than non-cirrhotic chronic hepatitis B patients (273). In a systematic review conducted in Asian countries, the incidence rates of HCC were 0.6 in non-cirrhotic chronic hepatitis B and 3.7 in cirrhotic chronic hepatitis B (274).

Hepatitis D virus (HDV) has been reported to promote HCC development in patients with HBV (275). HDV causes hepatitis D, a liver infection (276). Infection with hepatitis D cannot occur in the absence of HBV (277). HDV infection can occur when persons are infected with both the hepatitis B and hepatitis D viruses simultaneously (co-infection) or when they contract hepatitis D after being infected with the HBV first (super-infection) (278). Although there are no specific hepatitis D prevention recommendations, preventing HBV effectively prevents it (279).

According to a 2017 meta-analysis (280), the prevalence of HDV among HBV-infected patients in Africa ranges from 26% to 0.05%. In Central Africa, the prevalence is 26%, 7% in West Africa, and 0.05% in Eastern and Southern Africa (280). In the overall HBV-infected population, high-prevalence spots were in Gabon (45%), the Democratic Republic of the Congo (5%), Cameroon (14–35%), Mauritania (19%), and the Congo (26%) (280). Anti-HDV antibody prevalence in

Ethiopia ranges from 5.8 to 9.6% in the general population (281). Moreover, it was found that 3.2% of blood donors, 8.0% of HIV patients, and 12.7% of patients with liver disease in Ethiopia had anti-HDV antibodies (282).

It is unknown whether HDV is an oncogenic virus and what role it plays in HCC (275). In contrast to HBV, there is little evidence to establish a direct oncogenic involvement of HDV in human hepatocarcinogenesis (283). The evidence thus far indicates that cirrhosis, which results in the development of HCC, is more common in individuals with chronic hepatitis D compared to those who are monoinfected with HBV, even though HDV has not yet been included in the list of oncogenic viruses (275, 283). Although HDV infection has been linked to increased fibrosis in HBV patients, it is rare and its role in HCC development is unknown in Ethiopia (284), preventing this thesis from discussing the risk factor's role in HCC development in the country.

2.6.2 Hepatitis C virus infection

In 2019, 58 million people were chronically infected with hepatitis C (285). The hepatitis C incidence rate is highest in the Eastern Mediterranean region (62.5 per 100,000) and the European region (61.8 per 100,000) (269). Chronic hepatitis C infection affects 75–85% of hepatitis C virus-infected people, with 60–70% developing chronic liver disease. Among those who developed liver disease, 5% to 20% developed cirrhosis, and 1% to 5% died from liver failure or HCC (286).

The link between hepatitis C and HCC is reported to be a combination of the hepatitis C virus's independent effect on hepatocarcinogenesis and cirrhosis's indirect effect (287). HCV, unlike HBV, is an RNA virus that does not integrate into the host gene. Thus, it primarily causes HCC by inducing inflammation and hepatocellular injury, which eventually leads to cirrhosis and then HCC. HCV patients with non-cirrhotic chronic hepatitis C can develop HCC, indicating that the virus is oncogenic on its own (100). Several viral proteins have been implicated in the development of non-cirrhotic HCC in both animal models and culture systems (100). One of them is the HCV core protein, which has been proposed to induce HCC in transgenic mouse models, though the mechanism by which this occurs is unknown. However, it has been proposed that the HCV core protein can bind to tumor suppressor proteins such as p53, which can lead to HCC (132). The

annual risk of HCC development in chronic hepatitis C patients with cirrhosis is 1–4%, and an estimated 1–3% of chronically infected hepatitis C patients will develop HCC after 30 years (287, 288).

Moreover, although HCC is caused by a variety of risk factors, the majority is caused by hepatitis B and C viruses; however, it is unclear whether co-infection by the two viruses increases the risk of HCC development. Co-infection is the presence of two or more replicating organisms in a single host. HBV and HCV co-infection can happen in two ways (289). The first way is that because HBV and HCV share the same route of transmission (intravenous drug use, blood transfusion, and vertical transmission), they can be co-transmitted at the same time (290). HCV-HBV coinfection, on the other hand, can occur through superinfection, which occurs when one virus is acquired in a patient who already has a chronic infection with the other virus (290, 291).

The global prevalence of HBV and HCV co-infection has been estimated to be between 1 and 15% (292). The vast majority of previous studies on HBV and HCV co-infection were carried out in areas where both viruses were common (292). A large study conducted in the United States discovered a rate of coinfection of 1.4% (293). This low rate could be attributed to the low prevalence of HCV and HBV in the US compared to high prevalence areas. Individuals with HBV and HCV co-infection are at a higher risk of developing cirrhosis and decompensated liver disease (294, 295), as well as HCC (55, 56).

Synergy between the two viruses has been proposed as a result of some studies that when both viruses were present, liver damage was increased compared to when only one virus was present (296, 297). However, the risk of HCC development in subjects with both infections has not been accurately estimated (56). Little attention has also been paid to determining the relative importance of the hepatitis B and C viruses in increasing the risk of HCC (56). Chapter Four of this thesis analyses articles on the independent and combined effects of hepatitis B and C infections on the development of HCC. Assessing the combined effect of HBV and HCV on HCC development can help identify subgroups of people who are at high risk of developing HCC and inform appropriate HCC prevention practices.

Expanding investigations beyond the univariate association between a disease and its risk factors is necessary to understand the background of the disease (298). Thus, it is critical to use risk factor interaction assessments to determine whether and how risk factors work together to increase the risk of disease development (298, 299). The goal of interaction analysis is to determine the magnitude of the combined effect of risk factors on disease causation (298). It aids in determining the magnitude of the effect that two or more risk factors have on disease risk as well as on each other (298, 299).

Although the causal link between HCC and HBV or HCV is well established, little attention has been paid to determining the magnitude of the combined effect of the viruses on disease causation (56). However, determining the magnitude of the combined effect of the viruses on HCC development helps in different ways. For instance, it aids in identifying individuals who are at high risk of developing HCC (298, 299). This, in turn, will help intervention to be targeted to individuals who are at high risk of the disease (299-301).

One goal of this thesis is to identify individuals who are at high risk of HCC or to analyse disparities in HCC risk. It did several analyses in different chapters to identify individuals at high risk of HCC. Chapter Four, for instance, sought to identify individuals at high risk of HCC by evaluating differences in HBV and HBV risk in HCC by socio-demographic characteristics, as well as the magnitude of the combined effect of the viruses on HCC development. In other chapters, it looked at disparities in HCC risk by socio-demographic characteristics. Identifying people at high risk of HCC gives various advantages, especially in countries with limited resources like Ethiopia.

The study of interaction has a number of significance. For instance, it can help identify those who are at high risk of developing a disease (299-301). As a result, interventions can be tailored to individuals who are at high risk of the disease. It also aids in identifying people who should be prioritized during HCC screening, especially in resource-constrained settings (299-301). Moreover, in some countries like Ethiopia where resource is limited, intervening on or treating the entire population may be impossible. This is because the available resources may not allow it. The resource may only allow for intervention or treatment of a subset of the population. In this case, it is critical to identify individuals who would benefit the most from the treatment or intervention (299-301). Even in well-resourced countries where it is possible to intervene on or treat the

entire population, some interventions or treatments may be harmful to some groups while being beneficial to others. In this instance, it is vital to identify individuals for whom the treatment is harmful and to refrain treating them (300). Ethiopia has a high prevalence of hepatitis C and B infections (302). According to recent studies, the prevalence of hepatitis C and B infections is 7.4% and 3.14%, respectively. In Ethiopia, chronic hepatitis C and B infections cause more than 60% of chronic liver diseases (161). Moreover, the country is one of the world's hepatitis-endemic countries, according to the WHO (303). Despite this, there is no national strategy for viral hepatitis surveillance, prevention, and control in the country (302, 304). Little emphasis has been placed on determining hepatitis B and C infections in HCC patients in Ethiopia. The findings of the few studies that assessed the role of hepatitis C and B infections in HCC development in Ethiopia are discussed in depth in Chapter Four of this thesis.

2.6.3 Alcohol consumption

Alcohol abuse has been linked to over 200 diseases and injuries (305). Around 53% of people aged 15 and older globally have used alcohol at some point in their lives, with 39% having done so in the previous year (306). However, no threshold for the emergence of carcinogenic effects from alcohol was specified in the studies included in the review. Alcohol has a synergistic effect with other carcinogenic agents, increasing their potency in causing cancer (307). Alcohol increases cancer risk through a variety of mechanisms, including lowering blood levels of antioxidants such as vitamins A and E and weakening the immune system (307, 308).

Several epidemiological studies suggest an association between alcohol consumption and cancers of the liver, throat, breast, rectum, and lung (309). Alcohol is responsible for one-third of all primary liver cancer cases worldwide, with incidence varying greatly by region (240, 310, 311). The percentage of incident cases of HCC with an alcoholic aetiology varies significantly between nations and regions, from 6% in the Middle East to 14% in North Africa, to up to 50% – 60% in Eastern Europe, where viral hepatitis is only a minor cause of HCC. Increasing levels of alcohol consumption often directly correlate with an increased risk of HCC (261, 312). When combined with metabolic changes and hepatitis virus infection, alcohol use has been shown to have a greater impact on HCC development (313, 314). Alcohol may cause HCC through a variety of

mechanisms, including causing liver cirrhosis (313, 314). The odds of developing liver cirrhosis rise with daily alcohol consumption of 30 to 50 grams (315-317), while the odds of developing HCC rise with daily alcohol consumption of 60 to 100 grams (318-320).

Alcohol is more prevalent than any other consumer good in Africa and contributes significantly to the continent's high rates of early mortality and disability (306). In Ethiopia, the prevalence of alcohol consumption has increased significantly over the past decades, and men are more likely than women to engage in risky drinking and develop alcohol dependence (119). A systematic review and meta-analysis in Ethiopia revealed that the pooled lifetime alcohol use was 44% (119). A 48% lifetime alcohol use prevalence was also reported in Gondar, Northwest Ethiopia (118). One retrospective study examined the history of alcohol consumption in 51 patients admitted to Tikur Anbessa Hospital in Ethiopia and found a history of alcohol in 45% of the patients (110). Due to a lack of sufficient evidence and data beyond these findings on the role of alcohol in increasing the risk of HCC development in Ethiopia, we are unable to discuss it in depth in this thesis.

2.6.4 Non-alcoholic fatty liver disease

NAFLD is characterized by fat accumulation (steatosis) in more than 5% of hepatocytes (321). The global incidence of NAFLD ranges between 6% and 35% (322). NAFLD can be either simple steatosis without excessive alcohol consumption or NASH, a type of NAFLD in which there is also liver damage and liver inflammation in addition to liver fat, with or without cirrhosis. NAFLD causes hepatocellular injury, necrosis, hepatic fibrosis, cirrhosis, and eventually, HCC (322). NAFLD is primarily caused by obesity and type 2 diabetes (323). Being overweight, metabolic syndromes and old age are also risk factors for NAFLD (323, 324). Weight loss, low carbohydrate or fat intake, and physical exercise have all been reported to be effective treatments for NAFLD (325-328).

NAFLD prevalence is reportedly increasing globally (329). According to reports, between 10% and 30% of Americans are thought to have NAFLD, and similar rates have also been found in Europe and Asia (330, 331). An increased risk of getting HCC has been associated with NAFLD (332). NAFLD is a risk factor for liver disease worldwide and is likely to overtake other risk factors to become the main risk factor for liver disease in the coming decades (333). Worldwide differences

in the epidemiology and demographics of NAFLD are often parallel to the prevalence of obesity (333). The involvement of NAFLD in the development of HCC is becoming increasingly common worldwide (333). It is projected that the burden of NAFLD-related HCC will keep rising along with the prevalence of obesity around the world (334, 335)

The effect of NAFLD on HCC development is stronger in patients with cirrhosis. Mittal et al. (336) found that NAFLD was one of the common risk factors for HCC in a study of 1,500 patients diagnosed with the disease between 2005 and 2010, with cirrhosis in more than half of the patients. A meta-analysis also revealed that NAFLD patients with no or minor cirrhosis have a low risk of developing HCC (337). The yearly cumulative HCC incidence among patients with NASH-cirrhosis was also found to be 2.6 % to 4% (338).

NASH, a type of chronic liver disease that ranges from basic hepatic steatosis to liver cell damage and inflammation, is a subtype of NAFLD (339). The global incidence of NASH-related HCC has increased considerably as the global prevalence of NASH has increased (340). NASH has been linked to advanced fibrosis and cirrhosis, which raises the chance of developing HCC (341-343). HCC is one of the leading causes of death in people with NAFLD or NASH (344). Globally, there is an increase in NASH, primarily due to an increase in obesity and diabetes mellitus, both of which contribute to NASH development and are important risk factors for HCC (345).The mechanism by which NAFLD increase the risk of HCC remains unknown. It has, however, been suggested that NAFLD progresses to non-alcoholic steatohepatitis (NASH), which is characterized by inflammatory cell infiltration and varying degrees of fibrosis which ultimately result in HCC (346, 347). NAFLD is also associated with oxidative stress, which causes mitochondrial dysfunction. Mitochondrial dysfunction, in turn, affects lipid metabolism, growth and development pathways, and the immune system, all of which contribute to the development of HCC (346-348).

2.6.5 Aflatoxin B1

AFB1 is an aflatoxin, a poisonous carcinogen produced by certain molds, particularly by the common aspergilli *Aspergillus flavus* and *Aspergillus parasiticus* (262, 349). Foods contaminated with mycotoxin include dried fruits, rice, and oil seeds that have been improperly stored in hot,

humid, and unsanitary conditions(349). Aflatoxin exposure can occur in a variety of ways, including the consumption of aflatoxin-contaminated food and the consumption of plant or dairy products from animals fed contaminated feed (350). It can also occur among agricultural workers, especially farmers, from inhaling dust formed during the harvest, storage, and processing of contaminated crops and feeds (350). According to reports, 4.5 billion people are at risk of aflatoxin exposure worldwide (351). The biological activities of AFB1, which include acute toxicity and carcinogenicity, are well-known (352). Aflatoxin distribution varies by region and other factors. In places like Southeast Asia and SSA, AFB1is very prevalent. AFB1is also a problem in the Middle East (353). The distribution pattern of AFB1 is also associated with socioeconomic status; as a result, AFB1 is more prevalent in low-income countries due to poor sanitation, careless food handling, and ineffective food regulations (90).

Several preventative measures against AFB1 contamination have been reported. Among the most effective ways to reduce Aflatoxin B1 exposure are measures aimed at preventing crop contamination in the field, as well as during post-harvest handling and storage (103). Several countries use a variety of mechanisms to prevent AFB1contamination, including the implementation of rules and regulations governing AFB1 in foods (213, 214). These include determining the maximum permissible or recommended levels of AFB1in specific foods (213, 214). Aflatoxin B1 contamination can also be reduced through agricultural and nutritional education (215).

Based on how they cause cancer, food mutagens are divided into genotoxic and non-genotoxic agents (90). Genotoxic agents, which include micronutrients such as aflatoxin B1, are defined as agents that cause genetic changes through a mechanism that begins at the DNA level (354). However, non-genotoxic substances are mainly macronutrients that are thought to indirectly affect cells through tumor promoters, though their exact mechanisms of action are less clear (354, 355). AFB1is a genotoxic hepatocarcinogen that induces DNA adducts, a piece of DNA that has been bound to a cancer-causing agent, which alters the genetic makeup of its target cells and results in HCC (356).

2.6.6 Tobacco use

Tobacco use has been associated with several cancers, including HCC (357-359). Geographic location and racial/ethnic background do not affect the link between cigarette smoking and the development of HCC (360, 361). Smoking has several negative effects on the liver, including the production of carcinogens in the liver (362, 363). Many recent studies have found links between cigarette smoking and poor prognoses in HCC patients (362-366). Despite the uncertainty, cigarette smoking has recently been promoted as a separate risk factor for the onset of HCC. It was also suggested that continuing to smoke after surgery was strongly associated with disease recurrence and jeopardized the survival of HCC patients with HBV (362, 363).

Smoking increases the risk of HCC in two different ways: directly and indirectly. In the direct pathway, it increases the production of pro-inflammatory cytokines which are involved in liver cell injury (363, 367). This injury leads to the development of cirrhosis which will eventually lead to HCC (368). Tobacco smoking also causes the production of substances with cytotoxic potential (363, 367). The substances generated cause oxidative stress and start fibrosis formation (363, 367). All these activities or changes will lead to the development of hepatocellular carcinoma. In the indirect pathway, smoking increases carboxyhemoglobin levels and lowers red blood cells' ability to carry oxygen, which causes tissue hypoxia (363, 367). Erythropoietin is produced in response to hypoxia, and it directs the hyperplasia of the bone marrow (363, 367). Due to the resulting secondary polycythemia and increased red cell mass, hepatocytes experience oxidative stress which will ultimately lead to fibrosis, cirrhosis, and finally HCC (363, 367).

2.6.7 Type 2 diabetes

Prevalence has been rising faster in low- and middle-income countries than in high-income ones (369). Diabetes ranked tenth in terms of the most common causes of mortality in 2019, with an estimated 1.5 million deaths directly attributable to the condition (370, 371). Type 2 diabetes and cancer are becoming increasingly common around the world (189). Type 2 diabetes has been linked to several cancers, including HCC (189). Type 2 diabetes increases cellular growth and proliferation, induces oxidative stress, suppresses apoptosis, and produces pro-inflammatory

cytokines, all of which aid in the development of HCC (189). It was found that people with type 2 diabetes had a 2.5-fold greater risk of developing HCC (189).

Type 2 diabetes has been linked to an increased risk of developing HCC in several countries around the world, including China (372), Denmark (373), and Sweden (374). It has also been linked to an increased risk of HCC when combined with other risk factors such as cirrhosis, hepatitis, and alcoholism (374).

2.6.8 Obesity

Obesity is a medical condition that occurs when body fat levels reach an unhealthy level. Over 4 million people died in 2017 as a result of the complications and risks of various diseases associated with being overweight or obese (375). Obesity and overweight are becoming increasingly common in both adults and children. Between 1975 and 2016, the global prevalence of overweight or obesity among children and adolescents aged 5 to 19 more than quadrupled, rising from 4% to 18% (376, 377).

Numerous cancers, including HCC, have been associated with obesity (378, 379). A meta-analysis of 21 prospective studies that included 17,624 cases of primary liver cancer found that HCC risk increased by 39% for every additional 5 units of BMI (kg/m^2) (376). Obesity is associated with a 2-fold increase in the chance of developing HCC (263). Obesity has been associated with hepatic inflammation. This, in turn, caused fibrosis. Fibrosis progression eventually leads to the development of HCC (44).

2.7 Hepatocellular carcinoma public awareness

Cancer is one of the world's leading causes of death (380). The majority of cancer deaths occur in low and middle-income countries, most likely due to delayed presentation (381). It has been reported that changing one's lifestyle or avoiding key risk factors like alcohol consumption, tobacco use, and physical activity can prevent 30% to 50% of cancers (380). Early cancer identification and effective cancer treatment and patient care are other ways to reduce the burden of the disease (380, 382).

Public awareness of cancer symptoms and risk factors is important because it helps to prevent delays in presentation, resulting in earlier diagnosis and treatment (383, 384). Unfortunately, most developing countries have low public awareness of disease symptoms and risk factors (385, 386). These countries also have low public awareness of the importance of screening, the possibility of preventing several cancers through screening, and the possibility of treating precancerous lesions (387, 388). However, research into cancer awareness is still in its early stages in many developing countries. Ethiopia, for instance, is one of the world's least developed countries, with an increasing cancer burden but few studies on public awareness of disease signs, symptoms, and risk factors (117).

Only a few studies on public awareness of cancer in Ethiopia have been conducted in recent decades, and these studies have focused on a few types of cancer such as colorectal, breast, and cervical cancer (166, 168-170). For instance, a study of adults admitted to Jimma University Medical Center's adult medical and surgical outpatient clinic with health conditions other than colorectal cancer found that 57.6% had no awareness of colorectal cancer (166). The study also found that colorectal cancer awareness is related to gender, income, and educational level (166). According to a meta-analysis in Ethiopia, the pooled prevalence of identifying at least one risk factor and one symptom of cervical cancer was 52% (95% CI: 39-64) and 43% (95% CI: 26-60), respectively (389).

A study of women who visited selected healthcare facilities in Addis Ababa for maternal and child healthcare found that 53% were aware of breast cancer screening (169). This study also found that those with primary and secondary education, as well as those with a high income, were more aware of breast cancer screening (169). This study, however, did not assess general public breast cancer awareness, and it is an institution-based study that did not assess HCC and other cancer awareness in the city. A cross-sectional study in Gondar also found low awareness of breast cancer risk factors in students of the university of Gondar, with the majority of the students participating in the study unaware of breast cancer risk factors such as first child after the age of 30 years (51%), early onset of menses (55.3%), and menopause after the age of 55 years (47.7%) (390). Moreover, a community-based cross-sectional study in Assella town, Oromia region, found

that higher educational and economic status were linked to increased awareness of cancer signs and symptoms (391).

However, no previous study has explored the public awareness of HCC signs, symptoms, and risk factors in Ethiopia. It is also difficult to generalize the findings of previous studies on all cancer types combined and some cancers in Ethiopia to HCC in the country because they are carried out in different contexts, situations, times, and regions. As a result, there is insufficient existing evidence related to public awareness of HCC in Ethiopia or Addis Ababa.

2.8 Infrastructure, education, and financial need to control hepatocellular carcinoma

Over the past few years, clinical guidelines have been developed for HCC treatment (392-394). For early HCC, the guidelines recommend curative treatment such as liver transplantation and surgical resection (392-394). Individuals with advanced HCC, on the other hand, have few treatment options. It has also been reported that best practice guidelines are needed because the guidelines developed thus far vary from country to country (395).

Studies also suggest that although clinical guidelines are important for standardizing care, addressing HCC requires a broader strategy (396). The strategy must ensure proper disease prevention, control, and management. In contrast to clinical guidelines, little attention has been paid to developing national policies for the control of HCC in various countries (397).

Assessing policy needs requires an understanding the current state of the cancer problem, as well as gaps in the existing cancer control plan and ongoing activities (16, 152). Understanding the current state of the cancer problem including identifying age and gender differences in cancer prevalence, incidence, mortality, survival, and stage at diagnosis is part of assessing the current state of the cancer problem. Identifying gaps in physical (e.g., infrastructure), human resources (e.g., health-care personnel), and financial resources in cancer control is also an important part of evaluating the existing cancer control plan and ongoing activities (16).

There is, however, a scarcity of research on assessing public policy needs to control HCC. In 2011, a study assessed the public policy need to control HCC on a global scale (13). According to

this study, there is a need for more financing for HCC surveillance, screening, and therapy. It also discussed the significance of raising government, public, and medical community awareness of the challenges caused by cancer. Moreover, it acknowledged the significance of encouraging prevention through early risk assessment, with an emphasis on viral hepatitis and other lifestyle variables. Although it has been reported that public policy needs for cancer control vary by country, little research has been done to understand how these needs differ across countries (16, 171). No study in Ethiopia to date has assessed infrastructure, education, and financial gaps in HCC control, which significantly limits discussion of the issues in the country in this review.

2.9 Summary

This review highlights, among other things, the scarcity of data on HCC incidence, the prevalence of HBV and HCV among HCC patients, public awareness of HCC, and current public policy needs to prevent HCC in Ethiopia. Further, determining the disease's incidence and how it affects the population over time has received little attention in many countries around the world, including Ethiopia. This review also showed that few studies were conducted in Ethiopia to determine the incidence of cancer, and no study assessed how the incidence affected the population over time. The studies conducted so far in Ethiopia to determine the incidence of cancer have been conducted on individuals who are at risk of developing the disease, such as those admitted to health facilities in the country with liver disease. Finally, it is apparent that previous studies have several limitations, such as a small sample size and the use of non-representative cases.

Despite the identification of HBV and HCV in Ethiopia as a public health problem, little attention has been paid to assessing HBV and HCV infections in HCC patients in the country. This review emphasized the importance of assessing public policy needs to control HCC in Ethiopia, as well as the scarcity of research on policy needs to control HCC in the country. It also showed that assessing public policy needs necessitates evaluating infrastructure, educational, and financial gaps in HCC control. Moreover, it highlighted that no study in Ethiopia assessed infrastructure, educational, and financial gaps in cancer control.

In general, this review found a dearth of research in Ethiopia on the incidence and trends of HCC, hepatitis B and C infections in HCC patients, public awareness of HCC, and the infrastructure, education, and finance needs to control HCC. These gaps, therefore, should be addressed to reduce disease burden, improve disease outcomes, and design careful HCC or cancer control planning.

CHAPTER THREE: METHODS AND MATERIALS

3.1 Study area

Ethiopia is a country in East Africa (398). Somalia borders it on the east and northeast, Eritrea and Djibouti on the north, South Sudan on the west, Kenya on the south, and Sudan on the northwest (398). Ethiopia has a population of 117 million people and a total land area of 1,100,000 square kilometers (399, 400). It is Africa's second most populous country, with rural areas housing 80% of the population (399, 401, 402). Adult literacy in Ethiopia was 28.92% in 2007 (403).

Addis Ababa has a population of 3,859,638 people, according to the 2017 population projection (404). It covers an area of 527 square kilometers and has more women (52.7%) than men (47.3%) in the population (404). The majority of the city's residents are Orthodox Christians (82%), followed by Muslims (12.7%) and Protestants (3.8%) (405). According to World Population Review, adult literacy in 2007 in Addis Ababa was reported at 80% for females and 93% for males (405); considerably higher than Ethiopia more broadly. The population of Addis Ababa is expected to exceed 5 million in 2037 (404). The city is divided into ten sub-cities that vary in size and house people of various ethnicities (Fig. 1) (403, 405). The ten sub-cities of Addis Ababa are Arada, Addis Ketema, Lideta, Cherkos, Yeka, Bole, AkakiKaliti, Nefas Silk, KolfeKeranio, and Gulele (403, 405).

Addis Ababa is Ethiopia's only city with a population-based cancer registry, making it an ideal location in the country for quantifying cancer incidence at the population level (103, 104). The city also has a higher concentration of cancer diagnosis and treatment facilities, as well as cancer-related health professionals, than other Ethiopian cities (117). The data for this study came from three sources in Addis Ababa:

1) the Addis Ababa City Cancer Registry, Ethiopia's first and only population-based cancer registry,

2) public and private healthcare facilities in Addis Ababa that provide cancer diagnosis and treatment, and

3) the general population of Addis Ababa.

3.2 Quantitative and qualitative research designs

This thesis employed both quantitative and qualitative research designs. Quantitative methods were used to 1) assess the incidence and trend of HCC in Addis Ababa over eight years; 2) identify HCC risk factors among HCC patients in Addis Ababa; 3) assess public awareness of HCC signs and risk factors in Addis Ababa; and 4) conduct a meta-analysis on the role of hepatitis B and C infections on HCC development. The project used qualitative methods to explore liver cancer clinicians' perceptions of current infrastructure, education, and finance needs in HCC control in Ethiopia. The findings of this study could also aid efforts to develop evidence-based national cancer control plans.

3.3 Methods for the quantitative studies

3.3.1 Study One: A systematic review and meta-analysis of the role of HBV and HCV infections in HCC development

This section describes the methods used to conduct a systematic review and meta-analysis on the effect of hepatitis B and C infections on the risk of HCC development.

3.3.1.1 Systematic search strategy

There were three stages to the search for articles for the systematic review and meta-analysis on the relationship between hepatitis B and C infections and risk of HCC development. In Stage One, the initial search was conducted using MEDLINE, Google Scholar, Scopus, and CINAHL. At this point, any articles on HCC were identified. The keywords in the abstract and title of the articles identified in these databases, as well as the index terms used to describe the articles, were then analysed. Boolean "OR" was used to connect terms that shared the same concepts, and "AND" was used to combine those terms with other elements of search terms. A combination of keywords and search terms were used to create the final search terms: "hepatocellular carcinoma" OR "liver malignancy" OR "malignant hepatoma" OR "liver neoplasm" OR Hepatoma OR "liver cancer" OR Hepatocarcinoma AND diabetes OR obesity OR smoking OR alcohol OR "hepatitis B virus" OR "hepatitis C virus" OR "alcohol-related disorder" OR Porphyrias OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism"

OR "metabolic syndrome" OR "glycogen storage disease" OR "chronic obstructive pulmonary disease" AND "causal interaction" OR "biological interaction" OR "additive interaction" OR "multiplicative interaction" OR "mechanistic interaction" OR "risk factors interaction" OR "sufficient cause interaction" OR synergism (Appendix 1.1).

In Stage Two, a literature search was conducted in PubMed, MEDLINE, Emcare, CINAHL, and Scopus databases using the combined keywords and search terms. Initial papers identified from the broad search terms which would be expected to appear in a search strategy were used to confirm that the keywords and search terms adequately captured the desired research topics. In Stage Three, a manual search of reference lists of the articles included was conducted. The literature search was limited to human studies and the date of publication, and only included articles published between 1998 and 2020 as another meta-analysis was conducted on data published before 1998 (56). The search strategy used in this study expanded on the article search strategy used in previous meta-analyses (55, 56) by including more terms and keywords to broaden the search and identify more articles.

3.3.1.2 Eligibility criteria and quality assessment

The systematic review and meta-analysis investigated the role of hepatitis B and C infections in the development of HCC. Reviews, study protocols, unpublished studies, grey literature, and conference abstracts were excluded. Studies were also excluded during data extraction if they lacked sufficient data for meta-analysis. Moreover, a previous meta-analysis included only articles conducted in China excluding articles published in other areas during the study period (55), making it difficult to apply the search strategy used in this study or include articles from previous meta-analyses in this meta-analysis. Another driving factor for this decision is that it has been more than two decades since the last paper on the role of HCV and HBV in HCC development was published, and there have been advances in the diagnosis and management of both HCC and its risk factors.

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the studies' quality (406). In the NOS, the maximum and minimum possible scores are 9 and 0 stars, respectively, and

studies with scores greater than 6 stars are included in the meta-analysis (406). Studies with more than six stars on the Newcastle-Ottawa Quality Assessment Scale are considered high quality (407). The Newcastle-Ottawa Quality Assessment Scale assesses the quality of studies from three main perspectives: study group comparability, study group selection, and ascertainment of either the outcome or exposure of interest (Appendix 3) (406, 408). The review, which included the quality assessment process, was a collaborative work.

Unpublished studies were not included in the systematic review, as locating all unpublished papers from different countries is difficult. Failure to include all unpublished studies can lead to bias (409). This is due to the fact that the few unpublished studies that can possibly be identified constitute an unrepresentative sample of all unpublished studies (409). Another issue is the willingness of investigators of unpublished research from different countries to disclose data (409). This may be determined by the study's conclusions, with more favorable results being supplied more readily (409). This could again bias the findings of a systematic review (409).

3.3.1.3 Data extraction and synthesis

The following data were extracted from each of the articles identified for the systematic review and meta-analysis on the effect of hepatitis B and C infection on HCC development when available: sex, mean or median, study design, study area, sample size, type of controls, odds ratio (OR) values along with their 95% confidence intervals (CI), and proportion. Odds ratio estimates were calculated by applying the Haldane-Anscombe correction when they were not reported due to zero values of hepatitis B and C co-infection cases (29). Briefly, a value of 0.5 was added to each of the cells, and then the odds ratio over these adjusted cell counts was calculated (29). Moran's I^2 was determined to assess heterogeneity using STATA software (Version 16, Texas, USA) (1). An I^2 from 0% - 40% indicates unimportant heterogeneity; 30 - 60% moderate heterogeneity; 50- 90% substantial heterogeneity; and 75-100% considerable heterogeneity (410). The odds ratio along with the 95% CI was used as the effect measure. Synergism between hepatitis B and C infections was determined using the additive scale according to Rothman (411). As part of the process for this systematic review and meta-analysis, which followed PRISMA guidelines, two authors (Nega A

and Alelign A), including the student, independently searched the publication and extracted data from the publications included in the study. Any disagreements on which articles should be considered for the review were resolved by a third reviewer.

Sub-group analysis was not done as there was no high heterogeneity among the publications included in the systematic review and meta-analysis. Moreover, given the nature of the studies used in the systematic review and meta-analysis, such as having the same design, using the same case and control groups, being from different regions or countries, not being possible to extract data from them by gender, having the same treatment and outcome variables, and many other factors, subgroup analysis was not possible.

3.3.2 Study Two: A systematic review of the burden of HCC and associated risk factors in Ethiopia

This section describes the methods used to conduct a systematic review of the burden of HCC and associated risk factors in Ethiopia.

3.3.2.1 Systematic search strategy

The systematic review article search was concluded in three stages in 2020. A few studies on HCC were first identified through searches on MEDLINE, Google Scholar, Scopus, and CINAHL. The studies found in any of these databases were used to generate keywords and index terms for the final search. After identifying the keywords and terms, they were combined using the Boolean operations "AND" and "OR" as appropriate (Appendix 1.1).

The following search terms were created using a combination of keywords and search terms: "hepatocellular carcinoma" OR "liver malignancy" OR "malignant hepatoma" OR "liver neoplasm" OR "hepatoma" OR "liver cancer" OR "hepatocarcinoma" AND diabetes OR obesity OR smoking OR alcohol OR "hepatitis B virus" OR "hepatitis C virus" OR "alcohol-related disorder" OR Porphyrias OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism" OR "metabolic syndrome" OR "glycogen storage

disease" OR "chronic obstructive pulmonary disease" AND "incidence" OR "prevalence" OR "epidemiology" OR "burden" OR "proportion" OR "clinical diagnosis "OR" treatment" OR "control" AND "Ethiopia" OR "Addis Ababa."

The combined keywords and search terms were used in Stage Two to conduct a literature search in the PubMed, Google Scholar, and Cochrane Library databases. A manual search of reference lists of the articles included was done in Stage Three. Two authors, including the student, independently searched the articles as part of the process for this systematic review, which was carried out in accordance with PRISMA guidelines. A third reviewer arbitrated any disputes on which articles should be considered for the review. To increase the chance of not missing data from the city where this thesis determines the burden of HCC, HBV, and HCV, the name of that city i.e., Addis Ababa is included in the search final search term.

This systematic review and meta-analysis used a broad systematic search for different reasons, which helped in the retrieval of relevant articles. The first reason is that, as described in Section 1.3 (Chapter 1), studies interchangeably use terms such as primary liver cancer, liver cancer, hepatocarcinoma, and HCC. As a result, using a specific search term, such as HCC alone, and ignoring the other terms is likely to result in missing relevant articles. Some studies do not focus solely on HBV and HCV in HCC development, but rather on the interaction between other HCC risk factors and HBV/HCV, with HBV and HCV interaction on HCC as a secondary goal. Thus, excluding the other HCC risk factors (other than HBV and HCV) from the search term is likely to overlook these studies. Moreover, as discussed in different sections of the thesis, little attention has been paid to HCC research in various parts of the world. Thus, rather than using a specific search strategy, employing a broad strategy increases the chances of identifying the very few relevant articles published on HCC. Due to these and other criteria, the systematic review and meta-analysis employed broader search terms to maximize the likelihood of identifying literature on HBV and HCV interaction in HCC development.

3.3.2.2 Eligibility Criteria

Epidemiological studies published in Ethiopia between January 1, 1970, and November 30, 2020, that reported on the burden of HCC and associated risk factors were included. Protocols, unpublished studies, conference abstracts, grey literature, and review were all excluded from the review. Given the scarcity of research on the burden of HCC and associated risk factors in the country, no limitations have been placed to include studies on particular groups, such as those of a certain age or gender. Studies were also excluded during data extraction if they lacked data on the prevalence or incidence of HCC and HCC risk factors in HCC patients.

3.3.2.3 Data extraction and quality assessment

The following data were extracted, when available, for the systematic review of the burden of HCC and associated risk factors in Ethiopia: study design, study area, sample size, year of publication, HCC risk factors (HBV, HCV and alcohol use), and study setting. The Systematic Review Data Repository was used for the extraction of data for the systematic review (412, 413). Data on study design, sample size, number of participants, and other variables for this study were extracted from each study using the Systematic Review Data Repository.

The studies' quality was assessed using NOS (Appendices 3 and 4). The maximum and minimum possible ratings on the NOS are 9 and 0 stars, respectively. Studies are regarded as high quality if they receive more than six stars on the NOS. However, because of their low quality, the identified articles were not eligible for meta-analysis.

3.3.3 Study Three: A retrospective study on the incidence and trend of HCC in Addis Ababa

This section presents the methods used to determine the incidence and trend of HCC in Addis Ababa, Ethiopia. It has four sub-sections.

3.3.3.1 Study design, study population, and eligibility criteria

A retrospective design time series analysis was used to assess the incidence and trend of HCC across eight years (2012-2019) in Addis Ababa, Ethiopia. The data for this study were collected from the Addis Ababa City Cancer Registry (AACCR). Since the AACCR was established in 2011 and began collecting cancer data in 2012, data on HCC incidence for this study were extracted from the registry beginning in 2012.

The source population consisted of all Addis Ababa residents, while the study population consisted of Addis Ababa residents diagnosed with HCC between 2012 and 2019 in any healthcare facility in Addis Ababa that provides cancer diagnosis and treatment. The AACCR used residence in Addis Ababa for at least six months as a criterion to distinguish residents from temporary visitors (107). Eligibility criteria included being diagnosed with HCC, residing in Addis Ababa, and having data on the date of HCC diagnosis, age, and gender. As a result, the analysis included all of the HCC cases extracted from the AACCR. HCC cases at private and public hospitals in Ethiopia are coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (103, 104).

3.3.3.2 Data source and quality assurance

Data on HCC incidence was extracted from the AACCR, which collect cancer data only from Addis Ababa residents (103, 104). During the study period (2012–2019), two public hospitals (St. Paul's Hospital and Tikur Anbessa Specialized Hospital) and eleven private health institutions (Myung Sung Christian Medical Center, Teklehaimanot General Hospital, St. Gabriel General Hospital, Hallelujah General Hospital, Landmark General Hospital, Bethzatha Hospital, Chechela Higher Clinic, United Vision, Lagar Hospital, Bethel Teaching Hospital, and Kadisco General Hospital) in Addis Ababa notified the HCC cases to the AACCR. During the study period, no HCC cases from other cancer institutes in the city were identified and reported to the cancer registry.

Individuals at various levels assist the Addis Ababa City Cancer Registry in data collection (107). Four people work at the Addis Ababa City Cancer Registry headquarters, where they manage data

and ensure quality control (103, 104). These individuals also train contact persons assigned to Addis Ababa-based health institutes that provide cancer diagnosis and treatment to assist the Addis Ababa City Cancer Registry with data collection and reporting (103, 107). The contact persons collect data on cancer patients of all ages from the inpatient/outpatient departments of the institutes daily and report it to the AACCR weekly (104). These contact persons use a standardized format (Appendix 6) developed by the International Agency for Research on Cancer to collect data on HCC patients from each health facility that provides cancer diagnosis and treatment services in Addis Ababa (103, 107). Once the contact person has manually completed the data collection form, it will be sent to the AACCR head office at Tikur Anbessa Specialized Hospital, where the data encoder and other staff will enter the data into the AACCR database. AACCR staff may also collect completed forms from contact persons in person.

CanReg5 is used by the AACCR for data management, analysis, and quality control. CanReg5 is an open-source tool for storing, checking, and analysing cancer registry data (104). It includes data entry, quality assurance, consistency checks, and basic data analysis modules (103, 104). The AACCR identifies and corrects duplicate entries and multiple notifications of the same cancer case from different healthcare facilities (103, 107, 414). Training and supervising the contact persons regularly are also among the methods used by the registry to maintain data quality (414).

3.3.3.3 Data collection procedure, safety, and confidentiality

The first step in data collection was obtaining permission from the AACCR to use data collected by the registry for research purposes. To accomplish this, an application letter, a thesis proposal, a letter of support from Addis Ababa University (Appendix 8), and a letter granting ethical clearance for the study from Addis Ababa University and Flinders University (Appendices 8 and 9) were submitted to the oncology unit of Tikur Anbessa Specialized Hospital in 2020, which was managing the AACCR. Following the hospital's approval, the approval letter was submitted to the AACCR for additional review. The AACCR approved the application in 2020. The application approvals process at the aforementioned institutes entailed signing the application letter and directing it to the appropriate body within the institute if further approval was required. As is standard practice at the institutes, no approval number was assigned to the applications. The data

management section staff then extracted the requested data from the registry and gave the de-identified data to the researcher. Because ethical and legal constraints prevent researchers or graduate students from accessing AACCR databases, the data were extracted from the AACCR database by staff from the AACCR data management section.

Permission was obtained from the appropriate authorities as because the data for this study were not available online. Data on gender, date of birth, HCC (ICD-O-3: C22.0) and date of HCC notification, morphology (ICD-O-3: 8170), means of diagnosis, and place of residence was extracted by the data management staff from the AACCR database when available for all of the 306 HCC cases notified to the registry between 2012 and 2019. Although the cancer registry's data collection form includes variables on mortality and stage of cancer diagnosis, no data on HCC mortality and stage at diagnosis were collected during the study period. Chapter Five's analyses included all cases of HCC reported to the AACCR in this timeframe, as only a few cases of HCC were reported to the cancer registry during the study period. The inclusion of all HCC cases reported to the cancer registry during the study period is likely to yield more reliable results with higher precision and power than using case samples. Power is the likelihood of identifying an actual effect as statistically significant if it exists, and when large samples are used, there is a better chance of detecting an effect (415, 416). Moreover, when the estimation of an effect is based on large amounts of data or cases, the precision or chance of detecting minute effects improves (417). The researcher took the following measures to ensure safety and confidentiality:

- Data extracted from the AACCR were entered into a password-protected personal computer and stored and maintained in a secured, password-protected environment with the password known only by the Ph.D. student.
- The researcher/student agreed to abide by the agreements made with the AACCR on data handling and processing.

3.3.3.4 Data analysis

HCC incidence rates were calculated according to age and gender. The crude cancer incidence rate (CIR) is the number of new cancer cases diagnosed in a population over a given period (418,

419). The age-standardized incidence rate (ASIR) is a calculation of individual age-specific rates using a standard population (38). The ASIR is the rate that would be observed if the population had the standard population's age structure, in this case, the WHO World Standard Population (420). Both the CIR and the ASIR are expressed in terms of new cases per 100,000 people.

The Central Statistics Agency of Ethiopia provided population estimates for Addis Ababa for the study periods (421). The age-standardized incidence rates were calculated using the direct method (422). The direct method entails applying age-specific rates in a population of interest to a standard age distribution to reduce variations in observed rates caused by variations in population composition (422). Piecewise linear regression was used to assess incidence rates, average annual percentage change (AAPC), and annual percentage change (APC) using joinpoint software (US National Cancer Institute; version 4.5.0.1) (423).

Piecewise regression, which is frequently used when there are obvious "breakpoints" in a dataset, was applied in this study (424, 425). The independent variable is divided into intervals in piecewise regression, and a separate line segment is fitted to each interval (426). Piecewise regression is based on the idea that if the data shows different linear trends across different regions of the data, the regression function should be modeled in "pieces" (424-426). Joinpoint software runs a series of tests that the software is capable of doing to determine whether the incidence is constant or fluctuates over time (427). A joinpoint is defined as a statistically significant change in the slope of the incidence over time (427). The number of joinpoints was limited to one because it is recommended to use one joinpoint for data with 7 to 11 data points (428). The average annual percentage change (AAPC) was calculated to determine the overall percentage change in HCC incidence rates from 2012 to 2019. For each separate linear section between two joinpoints, the APC was calculated. Due to the small sample size, the ASRs, AAPC, and APC by age were calculated by categorizing patients into three age groups: <35, 35-54, and 55+. Values were considered statistically significant when the p-value was less than 0.05.

3.3.4 Study Four: A retrospective study on HBV and HCV infections in HCC patients

This section describes the methods used to identify HBV and HCV infections in HCC patients in Addis Ababa, Ethiopia.

3.3.4.1 Study design, study population, and eligibility criteria

A retrospective design was used to identify HBV and HCV infections among HCC patients in Addis Ababa, Ethiopia. All Addis Ababa residents made up the source population, and those who had been diagnosed with HCC at Tikur Anbessa Specialized Hospital between 2012 and 2020 made up the study population. Eligibility criteria for the study include having data on HCC (ICD-O-3: C22.0) and date of HCC diagnosis, date of HCV and HBV diagnosis, residing in Addis Ababa, and having data on age, gender, and HCC morphology (ICD-O-3: 8170).

3.3.4.2 Data source and quality assurance

The research was carried out at the Tikur Anbessa Specialized Hospital's oncology unit in Addis Ababa, Ethiopia. The Tikur Anbessa Specialized Hospital is Ethiopia's largest public referral hospital (429). It is a health professional training facility for medical students, laboratory technicians, nurses, and other paramedics (430). The hospital employs a large number of medical professionals from various medical specialties. In 2014, the hospital had a total of 678 beds, 20 of which were set aside for the oncology unit (430). The Tikur Anbessa Specialized Hospital's oncology unit has provided patients with supportive and palliative care in addition to chemotherapy, radiation therapy, pain management, and other forms of care (429, 430). Patient information is initially recorded manually on paper at the Tikur Anbessa Specialized Hospital oncology unit. The majority of the data is then stored on a computer. The oncology unit collects clinical as well as non-clinical data. When there is missing data, a data clerk communicates with the various sections of the unit. The oncology unit also has a random data-checking system to ensure data completeness and trains its employees in data collection and storage. The institute uses these and other mechanisms to ensure data quality (429, 430).

3.3.4.3 Data collection process, safety, and confidentiality

As described in Section 3.5.1.2, the AACCR collects data on cancer incidence, mortality, method of diagnosis and treatment, and stage at diagnosis from Addis Ababa health facilities that provide cancer diagnosis and treatment. However, it does not collect data on cancer patients' risk factor exposure status (103, 107). As a result, we were unable to extract data from the AACCR on the risk factor exposure of HCC patients included in this study. Moreover, none of the HCC risk factors were notifiable diseases or conditions in Ethiopia; if they had been, it would have been possible to electronically link HCC cases reported to the AACCR to HCC risk factor data that could have been notified to any Ethiopian institutes. As a result, we manually reviewed the medical records of the study participants found at the Tikur Anbessa Specialized Hospital in Addis Ababa that notified the majority of the cancer cases to the AACCR during the study period (2012-2020).

The first step in data collection was to request permission from the oncology unit at Tikur Anbessa Specialized Hospital to extract data from the medical records of HCC patients diagnosed at the hospital between 2012 and 2020. An application letter, an ethical clearance letter from Addis Ababa University (Ref no. ALIPB IRB/28/2013/20) and Flinders University (Proj.no.8572) (Appendices 7 and 8), and a thesis proposal were submitted to the oncology unit for this purpose. The oncology unit approved the application and forwarded this to the oncology unit's data record section for further review. The data record section approved the application and then assigned staff to extract the necessary data from the medical records of HCC patients. Patients' data is provided to researchers or graduate students with their permission to be used for research by the institute or researchers/graduate students. The agreement between the institute and the patients is not disclosed to researchers or graduate students who wish to use patient data for research purposes.

The paper data, which included laboratory results, follow-up sheets, and medical reports, were extracted by the assigned staff. Sociodemographic data (i.e., age and gender), stage of diagnosis (i.e., stages I - IV), risk factor exposure status (i.e., HBV, HCV, alcohol use, and type 2 diabetes), and method of diagnosis were all reviewed from each HCC patient’s files. There were no data on

some of the aforementioned variables. For example, there were no data that would have been useful for the study, such as aflatoxin B1 contamination, type of alcohol consumed, and pack-year units for cigarette smoking. There was also no information on the specific serological tests used to diagnose hepatitis B and C viruses.

Data on the date and method of hepatitis B diagnosis (defined by ICD-9 code: 070.22, 070.23, 070.32, 070.33, V02.61, and ICD-10 code: B18.1, B18.0, Z22.51), hepatitis C diagnosis (defined by ICD-9 code: 070.41, 070.44, 070.51, 070.54, 070.70, V02.62, and ICD-10 code: B17.11, B18.2, B17.10, B18.2, B19.20, Z22.52), and stage at diagnosis was extracted from each HCC patients when available.

3.3.4.4 Data Analysis

Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Armonk, NY) was used to enter and analyse the data. The odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship of age and gender with HBV and HCV infections were calculated using logistic regression models. Statistics were considered significant when the p-value was < 0.05. Due to the small sample size, the age association with HBV and HCV infection in HCC patients was assessed by categorizing patients into two age groups: less than or equal to 50 years old and 50 years old and over. Moreover, the median age of HCC diagnosis in SSA is around 50 years (24), and dividing the small number of cases in this study into two at 50 years may help to see if there are differences in HCC by HBV and HCV exposure status.

3.3.5 Study Five: A cross-sectional survey on public awareness of HCC and cancer in Addis Ababa

This section describes the methods used to assess awareness of HCC and all cancer types combined signs, symptoms, and risk factors among individuals aged 18 and older in Addis Ababa, Ethiopia.

3.3.5.1 Study participants, study design, and eligibility criteria

A cross-sectional survey was conducted in Addis Ababa in 2021. The source population comprised people aged 18 and older living in Addis Ababa. The study population comprised individuals who were selected at random from the source population at the household level. Participants in the study had to be able to communicate in Amharic (one of the languages spoken by the majority of people in the study area), understand the study's purpose, give written consent, provide socio-demographic information, and provide information about their awareness of HCC and all cancers combined signs, symptoms, and risk factors. They also need to be age 18 or older and not be suffering from a serious illness at the time of data collection. Participants were informed about the purpose of the study and who was eligible to participate in the study before the interview. They were also informed that an Addis Ababa resident is someone who has a city identification card, which is legally issued to city residents who have lived there for at least six months. This study only included participants over the age of 18 because HCC is rare in children and adolescents and the chance of exposure to HCC risk factors, such as alcohol and tobacco, is lower in these groups (431-434). Parental consent is also required for minors under the age of 18. To accomplish this, it is necessary to speak or interact with two people in each household rather than one, as in traditional adult surveys. Interacting with two people increases the project's complexity. Moreover, in Ethiopia, there is low access to social media or the internet, where those who are under 18 can learn about cancer signs and risk factors, despite their low risk of the disease (435). Understanding HCC signs and risk factor awareness in those aged 18 or alder will help recommend appropriate intervention strategies for those at high risk of HCC.

3.3.5.2 Sampling technique

The survey used multistage sampling. The ten sub-cities of Addis Ababa (Arada, Addis Ketema, Lideta, Cherkos, Yeka, Bole, AkakiKaliti, Nefas Silk, KolfeKeranio, and Gulele) were first listed in a frame. Then, using the lottery method, four of the sub-cities (KolfeKeranio, Arada, Yeka, and Nifas Silk) were selected. The total number of Kebeles in each sub-city was then determined using an online source (436). A Kebele is Ethiopia's smallest administrative unit. The Kebele System

('kebele' – Amharic for 'neighborhood') is a tight and old system of neighborhood administration and control in urban Ethiopia (436). A Kebele has at least 500 families or 3,500 to 4,000 people (437). Every town with a population of more than 2,000 people has at least one Kebele (54, 55. There were a total of 39 Kebeles in the selected four sub-cities: 11 in the Yeka sub-city, 10 in the Arada sub-city, 8 in the Nifas Silk sub-city, and 10 in the Kolfe-Keraniyo sub-city (436).

After determining the total number of Kebeles in each sub-city, three Kebele were chosen at random from each sub-city using a lottery method. Using an online resource, the number of households in each Kebele was then determined (436). Because the number of households in the selected Kebeles was almost equal, the sample size was divided equally among the twelve Kebele selected, or 50 households were included in the study from each Kebele.

The spinning pen method was used in the centre of each Kebele (which was determined using a map) to define the direction and start of data collection (168, 438). The gap between each selected household (sampling interval) was calculated by dividing the total number of houses in each research site by the sample size. When there were two or more eligible people in a household, the lottery method was used to select one interviewee. A multistage sampling method was used because the population of the ten sub-cities in Addis Ababa was too large (>3 million people) to research every individual (404).

When a household is empty when surveyors visit, the location is checked out again later that day or the next day. When an eligible participant was not available for an interview after several attempts, the home is permanently vacant, the occupants decline to participate, or the home is permanently empty, the next closest house was visited. On a Household Visitation Log Sheet, which was provided daily to the Survey Coordinator, the number of non-respondent households was noted (Appendix 10).

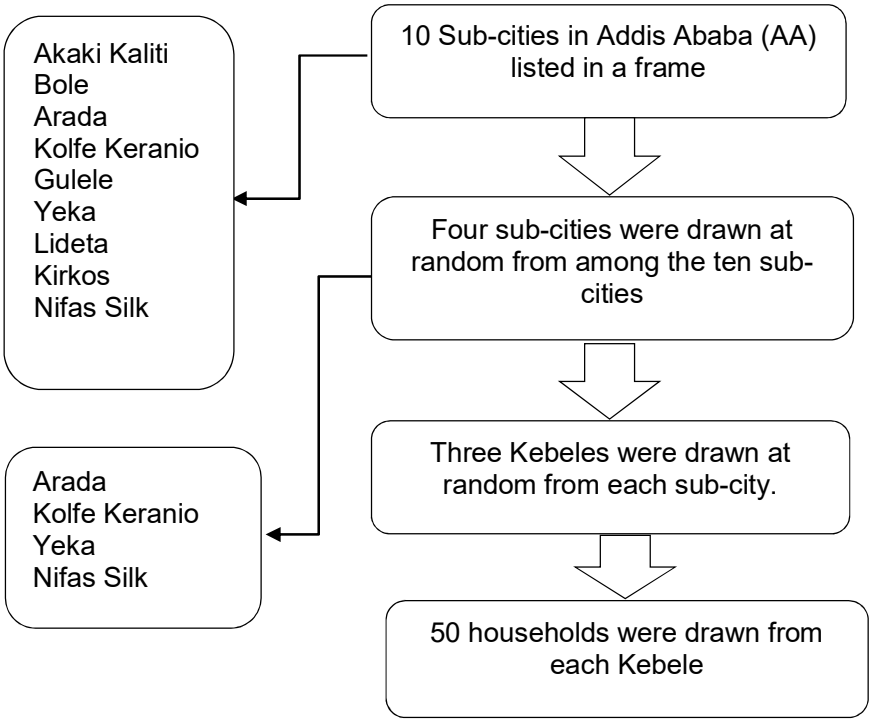

Figure 3-1: Flowchart showing the selection of households**.**

3.3.5.3 Sample size determination

The sample size was calculated using the Cochran formula (439), with a 95% confidence interval, a 5% margin of error, and a proportion of 52.2%, as follows:

$n = Z_{\alpha/2}^2$ ¬*p*(1-p) / d2,

$n = [(1.96)^2\ 0.5\ (1-0.5)]/\ (0.05)^2 = 384$

where,

d is the margin of error (0.05),

p is the population proportion (52.2%), and

Zα/2 is the normal distribution's critical value at α/2 (for 95% CI, α is 0.05 and the critical value is 1.96).

A population proportion is a percentage of the population that possesses particular characteristics, in this case, cancer awareness. This is frequently determined by using the results of a previous survey, as this study used a sample proportion of 52.2% from a previous study (391). Moreover, because the sampling process used at least two stages down to reach the final sampling unit, a design effect of 1.5 was used to determine the final sample size (169, 440). Considering a non-response rate of 5%, the total sample size was estimated to be 595 Addis Ababa residents (who lived in the city for at least six years) aged 18 and older. Cochran's single proportion formula is used to calculate the sample size for this study because it is the most efficient method for calculating a representative sample size from a large population like the population of Addis Ababa (439). This method has been recommended for cross-sectional surveys and has been used in several cross-sectional survey studies on cancer awareness (167, 390, 441-444).

3.3.5.4 Instrument development

The Cancer Awareness Measure (CAM) questionnaire was used to assess participants' knowledge of cancer symptoms and risk factors (445, 446). Cancer Research UK, University College London, King's College London, and Oxford University created the CAM, a validated standard questionnaire to assess awareness of cancer signs, symptoms, and risk factors (445, 446). The tool is freely available online and can be used and modified (2). However, the Ph.D. student made modifications to the previously validated cancer awareness measure (CAM) questionnaire to meet the study's objectives and to fit the local context. In this study, all of the stem questions from the original questionnaire that were designed to assess public awareness of cancer signs, symptoms, and risk factors were used. Questions were also added and removed as needed to meet the study's objectives and the local context. For instance, questions about living arrangements and postcodes were omitted because they did not fit with the context of the study area (Appendix 11).

The survey questionnaire translation team consists of experts familiar with the concepts the questionnaire intends to measure, language experts, and a naive/blinded translator who is unaware of the questionnaire's objective. The Ph.D. student began the translation process by translating the questionnaire from English (the original language) to Amharic (the local language).

A naive/blinded translator (Muse M) then translated the questionnaire into Amharic to detect subtle differences in the original questionnaire. The two translators discussed and resolved translation discrepancies. This is followed by back-translation (i.e., translating back from Amharic into the original language) by an expert to ensure the accuracy of the translation. Two experts reviewed both the Amharic and English versions of the questionnaire to ensure consistency.

During the translation process, cultural appropriateness was maintained. Some of the items used to collect socio-demographic data in the original study have been modified or omitted. For instance, Ethiopia is a country where same-sex activity is illegal and socially condemned (447, 448), so asking questions about sexual orientation in the country is inappropriate and offensive. Moreover, in some countries, certain minority groups are not legally recognized by the country, and asking questions about a person's ethnicity is considered offensive by some community members. A pilot test was conducted with 50 people living in Kebeles who were not part of the study sample and were not included in the actual survey. The pilot survey was conducted by the same survey team that conducted the final survey. Any issues discovered with the pilot survey were addressed before conducting the actual survey. During the pilot study, two minor issues with the survey administration procedures were identified. The first issue is related to the interpretability of the responses in terms of the required information. Respondents' responses to open-ended questions recorded by a few surveyors, in particular, were not easily interpretable in terms of the information required. They included a lot of information that was unrelated to the information needed for the study, making the responses of the respondents difficult to interpret. Some survey questions were also left unanswered or incomplete. These issues were addressed by retraining surveyors. However, the surveyors completed the survey within the time frame specified by the study, and there were no issues with the budget or logistics of conducting the survey. Face and content validity were determined prior to using the questionnaire, with a content validity index of 0.97. Two experts (Haregewoin T and Arage M) also evaluated the questionnaire's clarity and relevance. The experts using checklist evaluated whether the questionnaire measures what it claims to measure; is simple and easy to understand; whether any items are inappropriate, redundant, or missing; is likely to address the research objective; is relevant, has flow, and arrangement; and is wordy

(449). The validation process begins with the creation of a validation form and the selection of an expert review panel. This is followed by content validation and a review of the domain and items. Finally, assigning a score for each item followed by calculating the content validity index.

3.3.5.5 The recruitment and training of data collectors

The Ph.D. student developed criteria for the recruitment of data collectors. Calls for data collectors were announced by posting the recruitment criteria, the investigator's full address (phone number, email address, and mail address), and other information in various health and teaching institutes in Addis Ababa (Reference number: ALIPB IRB/28/2013/20). Those who contacted the Ph.D. student using the address posted or applied for the job were screened and scheduled for an interview.

The criteria used to recruit surveyors included being a health professional with a diploma or higher, having previous data collection experience, being available during the data collection period, living in Addis Ababa, and being available for two days of data collection training. The surveyors' responsibilities included systematically selecting households and administering the questionnaire.

Four interviewers, a data entry person, and a field coordinator were employed for this study. A survey field coordinator was employed to guarantee that questionnaires were complete and readable, as well as to handle any surveyor performance difficulties. A daily entry of completed questions into a survey database was assigned to one individual, enabling a speedy resolution of any issues that emerged. The data-gathering process and method were trained to data collectors and supervisors over two days. Flinders University, College of Medicine and Public Health, and Addis Ababa University have provided financial support for this study.

3.3.5.6 Data collection process

The interviewer introduced himself to the study participants before the interview and informed them about the purpose of the study, any potential risks associated with the study, as well as the fact that the study was entirely voluntary. The interviewer then gave the potential participants a letter of introduction (Appendix 12) and an information sheet that described the study's aim, purpose, and other details (Annex 12). Finally, the interviewer thanked the study participants for agreeing to

participate in the study, invited them to ask any questions they had about the study, obtained written consent (Appendix 14), and conducted 20 to 30-minute interviews with them.

The interviewer also explained to the study participant that the questionnaire is not a test but rather about their thoughts and opinions, so they should be as honest as possible in answering the questions and their answers will be treated confidentially. Some of the questions asked to each of the study participants are listed in the following sub-sections.

3.3.5.7 Data collection on cancer and HCC signs, symptoms, and risk factors

There were eleven questions about cancer signs and symptoms, ten closed-ended (recognize) and one open-ended (recall). The stem question for the closed-ended question was as follows: "The following may or may not be signs and symptoms of cancer. We are interested in your opinion." The participants were provided with a list of ten cancer signs and symptoms: coughing up blood, unexplained weight loss, shortness of breath, unexplained persistent pain, unexplained bleeding, a sore that does not heal, unexplained lump/swelling, tiredness all the time, persistent cough/hoarseness, and difficulty in swallowing. Responses for each cancer symptom and sign on the list included "Yes" ('1'), "No" (0), or "I don't know." The total score was determined by adding the responses (1/0) for each of the ten cancer signs and symptoms listed, with "don't know" responses being treated as "no." Therefore, the overall awareness rating for cancer symptoms and signs ranged from 0 to 10. The total score of signs and symptoms awareness (possible range: 0-11) was computed and dichotomized into poor and good awareness if less than the mean value and greater or equal to the mean value, respectively (391, 450).

Twelve closed-ended questions and one open-ended question were posed about cancer risk factors. The following is the stem question for the closed-ended questions: "These are some of the things that can increase a person's chance of developing cancer. How much do you agree that each of these can increase a person's chance of developing cancer? " Following that is a list of twelve cancer risk factors that are not specific to a specific type of cancer: alcohol consumption, older age, overweight (BMI= 25.0 - 29.9 kg/m2), eating red or processed meat, stress, not doing enough exercise/physical activity, obesity (BMI= 30.0 and above kg/m2), sunburnt/exposure to the

sun, family history/having a close relative with cancer, smoking, exposure to another person's cigarette smoke (passive smoking), and low intake of fruit/vegetables. Answers to the questions about cancer risk factors had three possible options: "Agree ('1'), "Disagree ('0'), and "Not sure ('0')." Not sure responses were interpreted as "disagree," and the sum of the responses (1/0) for each of the list's 12 cancer risk factors was used to determine the final score. The scores for the 12 potential cancer risk factors on the list were added to determine the overall awareness score for the risk factors. The total score of risk factors awareness (possible range: 0-12) was calculated and dichotomized into poor and good awareness if less than and greater than the mean value, respectively (391, 450)

Regarding hepatocellular carcinoma warning signs and symptoms, there were six closed-ended questions and one open-ended question. To determine how many signs and symptoms a respondent could recall without prompting, the open-ended question was used. The stem question for the closed-ended question was as follows: "The following may or may not be warning signs and symptoms of hepatocellular carcinoma. We are interested in your opinion." Following that is a list of six hepatocellular carcinoma warning signs and symptoms. The symptoms and warning signs of hepatocellular carcinoma were found using online resources (198). Responses included "Yes" ('1'), "No" ((0), or "I don't know" for each sign and symptom on the list. The total score was determined by adding the responses (1/0) for each of the six listed signs and symptoms. Responses of "don't know" were treated as "no." The overall awareness score for HCC signs and symptoms, therefore, ranged from 0 to 6. The total score of signs and symptoms awareness (possible range: 0-6) was calculated and dichotomized into poor and good awareness if less than and greater than the mean value, respectively (391, 450).

One open-ended and eight closed-ended questions were included in the survey regarding knowledge of hepatocellular carcinoma risk factors. The stem question for the closed-ended questions is as follows: "These are some of the things that can increase a person's chance of developing hepatocellular carcinoma. How much do you agree that each of these can increase a person's chance of developing hepatocellular carcinoma?" Following that is a list of eight hepatocellular carcinoma risk factors. The three response options were "Agree ('1'), "Disagree ('0'),

and "Not sure ('0')." The total score was calculated by adding the responses (1/0) for each of the eight HCC risk variables, and 'not sure' responses were considered 'disagree' (168). The total score of risk factors awareness (possible range: 0-8) was calculated and dichotomized into poor and good awareness if less than and greater than the mean value, respectively (391, 450).

Data were not collected from two or more people who took part in the study at the same time, or from the same family members. This is because one of the respondents' answers to the closed-ended questions prompts the other respondent to easily guess the answer to the open questions. As a result, data were collected from different individuals at different times. To reduce bias, open-ended questions were always asked before closed questions.

3.3.5.8 Data analysis

The data were cleaned and checked for outliers, missing values, and errors. The overall level of awareness about cancer/HCC symptoms and risk factors was classified as poor or good using the mean value, as described elsewhere (391, 450). Respondents with awareness scores higher than the mean were considered to have good awareness, as previously stated (173). The logistic regression models were used to estimate ORs and 95% CIs for the association between sociodemographic variables and cancer/ HCC awareness. The analysis helped in meeting the objectives in this section. However, the population of Addis Ababa, like the rest of the country, is divided into Kebele districts for administrative purposes alone. There was no suggested or reported basis for grouping the city's population, nor was there any indication of a significant socioeconomic disparity. However, if there was a known or suspected difference in the city's population grouping, it would have been ideal to do further analysis at different levels of resident groups.

For the logistic regression analysis, only complete samples were used. A few participants did not respond to one or more of the close-ended questions. The entire sample was used to analyse the responses to open-ended questions. However, for the regression analysis, only complete samples were used, and incomplete samples were removed using the deletion or list-wise deletion methods. The deletion method is one of the most widely used missing data handling methods. It

generates a simple complete data set, which enables the use of standard analysis techniques (451, 452). Moreover, because the majority of participants preferred not to disclose their monthly income, income was excluded from the logistic analysis. A complete case analysis for those who answered the income question yielded different results. *p*-values < 0.05 were deemed statistically significant. The data was entered and analysed using the SPSS version 26.0 (SPSS Inc., Armonk, NY) (453).

3.4 Method for the qualitative study

3.4.1 Study Five: Liver cancer clinicians' perceptions of the current educational, infrastructure, and financial needs to control HCC in Ethiopia

This section presents the methods used to explore liver cancer clinicians' perceptions of the current infrastructural, educational, and financial needs to control HCC in Ethiopia. There are four sub-sections in this section. The study design and population are presented in the first sub-section. The second sub-section presents the eligibility criteria and the recruitment of study participants. The third sub-section describes data collection. The data analysis is presented in the final sub-section.

3.4.1.1 Study design and population

A qualitative method in the form of an in-depth interview was used to explore liver cancer clinicians' perceptions of Ethiopia's current infrastructural, finance, and educational needs to control HCC. The phenomenological approach, an inductive qualitative research approach, was used to explore liver cancer clinicians' perceptions (454). The phenomenological approach seeks to identify phenomena by examining how participants in a situation perceive them (455). It entails using inductive, qualitative approaches like interviews to collect detailed data and perspectives (456). In phenomenological-based research, a variety of techniques such as interviews, discussions, action research, participant observation, analysis of personal writings, and focus meetings can be used (456). A relatively homogeneous group of participants is recommended for a phenomenological framework (457). Participants in a phenomenological study are recommended to be familiar with the same phenomenon. Before being allowed to participate in the

phenomenological study, participants were also recommended to have some experience with the topic under investigation (457, 458).

Purposive sampling was used to recruit participants with a variety of perspectives and firsthand knowledge of the research topic. Purposive sampling is a type of non-probability sampling in which researchers select members of the population based on their judgment to participate in their study (459, 460). It is one of the most commonly used qualitative research techniques for identifying and selecting information-rich cases (459). It entails the researcher purposefully selecting participants who are knowledgeable about the phenomenon. The researcher can determine whether or not the participants have knowledge of and experience with the phenomenon under investigation (460).

The target population consisted of Addis Ababa-based liver cancer clinicians involved in policy and/or the prevention, diagnosis, and management of liver cancer. Cancer care is provided in both public and private health institutions in Addis Ababa (132). Ethiopian clinics from both private and public cancer centres were included in this study. Although there were a few foreign physicians in Ethiopia working in a few cancer care centres, they were not included in this study since they are believed to have little knowledge about the financial, educational, and financial needs to control HCC in the country compared to Ethiopian clinicians. Some of the institutes in Addis Ababa that provide cancer diagnosis and treatment also train medical students and conduct health research (461-463). Staff at these institutes are involved not only in cancer diagnosis and management, but also in cancer research, education, and policy, making them ideal candidates for this study (461-463). Thus, liver cancer clinicians at these institutes were chosen as the target population because participation in such activities may provide them with firsthand knowledge of the country's infrastructural and educational gaps in HCC control. It was also assumed that enlisting individuals involved in such activities would aid in the generation of a diverse range of perspectives on the subject. Moreover, this study assumed that, rather than including only people involved in policymaking, including those involved in policymaking, cancer diagnosis and management, cancer research, and cancer education would yield more robust data on the topic.

3.3.6.2 Eligibility criteria and recruitment

The initial step in the recruiting procedure was to identify and compile a list of potential key participants in Addis Ababa, Ethiopia who were involved in policy and/or the prevention, diagnosis, and treatment of liver cancer, including HCC. The following criteria were used:

I) actively working on liver cancer or HCC in Ethiopia,
II) engagement in clinical practice, policy, or research related to liver cancer or HCC,
III) being a member of a national or international association for liver cancer or HCC,
IV) publication in peer-reviewed journals on liver cancer or HCC,
V) being able to communicate in Amharic,
VI) being willing to provide demographic information, and
VII) being willing to provide consent.

However, due to a lack of data, determining the exact number of liver cancer clinicians in health institutions that provide cancer diagnosis and treatment in Addis Ababa was difficult. As a result, the initial recruitment process included all clinicians working in the institutes, and further screening was performed during the recruitment process. Two different recruitment approaches were used. To begin, an information sheet with promotional text about the study, its eligibility criteria, and the researcher's contact information (phone number, email address, and student's home institute (i.e., Addis Ababa University) mailing address) was posted on locations/notice boards throughout all Addis Ababa hospitals that provide cancer diagnosis and treatment so that potential participants could see it. This is done after obtaining permission from the institutes, which entails submitting a letter of support from Addis Ababa University written directly to the institutes (Appendix 7). Participants who confirmed their interest to participate in the study by responding to the letter's contact information were scheduled for an interview.

In a second approach, the heads of oncology departments/units in hospitals throughout Addis Ababa that provide cancer diagnosis and treatment were given a letter containing promotional text about the study, its eligibility criteria, and the researcher's contact information (phone number, email address, and student's home institute (i.e., Addis Ababa University) mailing address) to

distribute to their staff during staff meetings. Participants who confirmed their willingness to participate in the study via the contact information provided was scheduled for an interview. Twenty-five people were invited for interviews from a population pool of 45 who met the recruitment criteria, and 13 in-depth face-to-face semi-structured interviews with liver cancer clinicians were conducted. Ethical clearance was obtained from the Institutional Review Board (IRB) of Addis Ababa University, Aklilu Lemma Institute of Pathobiology, and the Social and Behavioural Research Ethics Committee of Flinders University (Appendices 7 and 8).

3.3.6.3 Data collection

Before the interview, the interviewer introduced himself to the participants and handed out an information sheet outlining the study's objectives, purpose, and other details (Appendix 15). Following that, all study participants were informed of any potential risks associated with the study, as well as the fact that participation in the study was entirely voluntary. Finally, the interviewer thanked the study participants for agreeing to participate in the study, invited them to ask any questions they had about the study, had them sign the consent form, and conducted a 20-30 minute interview with them. The interview took place in quiet, secure, and confidential areas of the health institutes where the participants worked. The participants were first allowed to select the areas in which they wanted to be interviewed.

The interview focused on participants' perceptions of Ethiopia's infrastructure, education, and financial needs for liver cancer control (Appendix 16). The data was collected using a semi-structured interview guide. The interview guide was created in English first, then translated into Amharic by the researcher and double-checked by another expert (Degarege M). Amharic is a working language in Ethiopia and one of the languages spoken by the majority of the people in the study area (464). Pilot interviews were conducted, and any necessary modifications were made before the actual interview.

3.3.6.4 Data analysis

The data were analysed using a conventional content analysis approach as described in Erlingsson and Brysiewicz (465). Content analysis is one of the methods used in qualitative

research (465, 466). It looks for patterns in transcribed conversations and transforms a large amount of text into a highly organized and concise summary of key findings (465, 467, 468). By analyzing the semantic relationship and meaning of concepts and words, content analysis aids in the formation of qualitative inferences (468-470). Content analysis has several advantages, including the use of systematic approaches to data analysis that can be replicated by other researchers. It also makes use of reliable data, can be conducted at any time and in any location, and is inexpensive (465).

Conventional content analysis is said to be appropriate when there are no existing theories or research literature on a phenomenon and preconceived theories about the types of codes/categories of code to be used (471). There is a paucity of research on clinicians' assessments of infrastructure and education needed to control HCC in Ethiopia. Moreover, because there were no preconceived theories about the types of codes/categories of code to be utilized, this study took a data-driven approach (i.e., the codes were chosen based on a careful analysis of the data). The data in this study was examined using a content analysis approach, taking into account the aforementioned and many other factors.

The three main steps in content analysis are de-contextualization, categorization, and compilation (472). The de-contextualization process entails reading and re-reading the transcribed text to get a sense of the overall picture and to figure out "what is going on?" (472, 473). This step also entails dividing the transcribed text into small units known as meaning units. Meaning units are groups of phrases and sentences that contain aspects that are related to one another and contain the researcher's insights (470). This step also includes labelling the meaning units identified from the transcribed text (474). Depending on the study's design, coding can be developed inductively or deductively. If a deductive design is used in the study, the researcher should create codes before beginning the analysis. Otherwise, the list can be generated during the process (473).

The categorization process entails grouping codes that deal with the same issues. Themes will also be identified during the categorization step (475). Once the categories are established, the compilation step begins the analysis and writing-up process (472). The data in this study were

analysed in four major steps: formation of meaning units, condensation of meaning units, coding and categorization of meaning units, and development of themes, as described elsewhere (465, 472). In-depth interviews were audio-recorded to enable verbatim transcription. The first step in data analysis was to create a verbatim transcription of the interview.

Following the transcription process, there was data familiarization. Familiarization entailed reading and re-reading the transcribed interview to gain a sense of the whole, i.e., a general understanding of what the interviewees were discussing (465). Then the transcribed interview data was broken up into smaller parts known as 'meaning units ' after reading the transcribed interview many times while keeping the research questions and objectives in mind. Meaning units are phrases or sentences that contain elements that are linked to the same central meaning by content or context (470). Then, meaning units were condensed to create 'condensed meaning units. During the condensation process, the 'meaning units' were shortened while retaining their core meaning.

Following the condensing of the 'meaning units', codes were developed for each 'condensed meaning unit'. Codes are descriptive labels for 'condensed meaning units' that aid in the identification of connections between condensed meaning units. The codes that appeared to be dealing with the same issue were sorted. Depending on the study's design, coding can be developed inductively or deductively. If a deductive design is used in the study, the researcher should create codes before beginning the analysis. Otherwise, the list can be generated during the process. However, for this study, codes are generated during the process (465, 472). Following the categorization of the codes, an analysis was carried out, and themes were created by grouping two or more categories together. Figure 3-2 shows the step-by-step procedure used in the analysis.

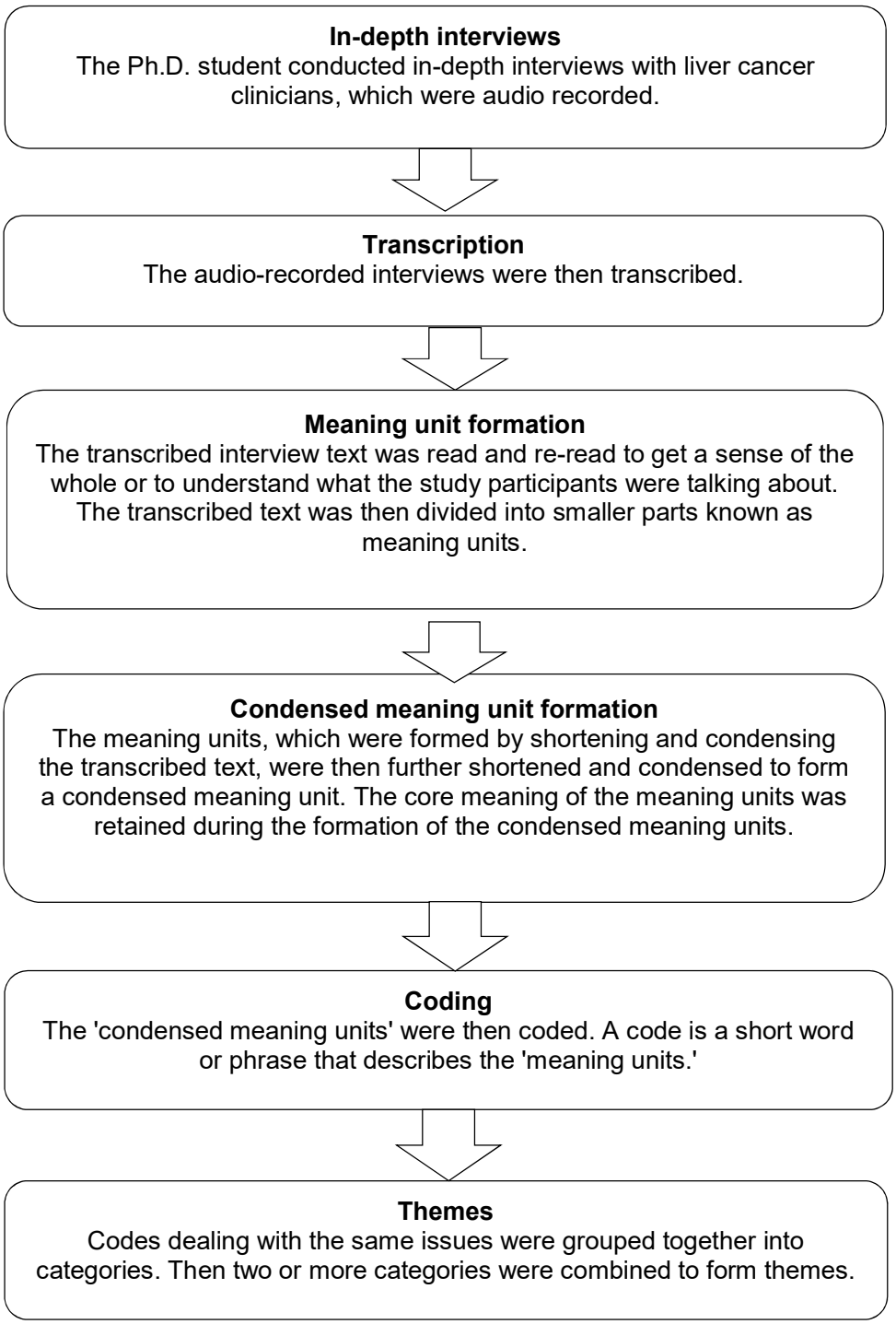

Figure 3-2: Flowchart showing the step-by-step procedure of the analysis.

3.5 Ethical considerations

This section aims to provide a summary of the ethical considerations discussed in the relevant chapters of this thesis. Project One was a systematic review and meta-analysis. As a result, no ethical approval was sought from any institute for this study. For Project Two to Four, ethical clearance was obtained in 2020 from the Institutional Review Board (IRB) of Addis Ababa University, Aklilu Lemma Institute of Pathobiology (Ref. no. ALIPB IRB/28/2013/20), and the Social and Behavioural Research Ethics Committee of Flinders University (Project no.8572) (Appendices 7 and 8).

For study Two, a retrospective study on the incidence and trend of HCC in Addis Ababa, de-identified data were obtained from the AACCR. Data for Project Three, a retrospective study on HCC risk factors in HCC patients in Addis Ababa, was manually extracted from HCC patients' medical records found at the oncology unit of Tikur Anbessa Specialized Hospital. The data for Projects two and three were stored on a password-protected computer, and the researcher had only the password. The researcher also agreed to keep the data for a set period (five years) as required by the data custodians (the AACCR and the oncology unit of Tikur Anbessa Specialized Hospital).

For the survey study (Project Four), study participants gave written consent. Study participants also provided written consent for the qualitative study (Project Five). Consent was sought from each of the study participants immediately before the start of the interview. Willingness to participate in the study was determined following the distribution of an information sheet outlining the purpose and process of the study to literacy participants or after the researchers verbally explained the purpose and process of the study to participants with literacy difficulties. Once study participants understood the study's purpose and process, they were asked to sign a written informed consent form (Appendix 14).

The study subjects were informed on the information page that their responses are completely anonymous and they cannot be identified by any of the information they provide. The anonymous

nature of the study was also indicated in all of the promotional materials (letters/introduction letters). Before undertaking the interview, participants acknowledged that their consent was given freely, they understood the purpose of the research project, and their involvement in the study may not be of any benefit to them. The filled-out consent form was kept in a filing cabinet with only the researcher's access.

The recruited data collectors were trained in the method of data collection and the rules of data collection. They were then asked to sign a contract outlining their duties and responsibilities. An acknowledgment was obtained from them about the confidentiality of data/information they have collected from the study participants. The signed forms were kept in a filing cabinet that only the researcher had access to. The study was conducted in conformance with the principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP), the Australian Code for the Responsible Conduct of Research (2007), and the National Statement on Ethical Conduct in Human Research (NHMRC, 2007). These codes for responsible research conduct adhere to the same ethical principles as the Ethiopian code of conduct, as stated in their working guidelines (476, 477).

CHAPTER FOUR: A SYSTEMATIC REVIEW AND META-ANALYSIS

Aim One: To identify the best available evidence on the combined roles of HCV and HBV in the development of HCC

4.1 A systematic review and meta-analysis of hepatitis B and C infections in hepatocellular carcinoma

HBV and HCV are major public health problems worldwide (478). In 2019, there were 269 million and 58 million chronically infected patients globally with HBV and HCV, respectively (479, 480). HBV and HCV are major risk factors for HCC, inducing HCC through a variety of mechanisms (176, 287). HBV, for instance, causes liver injury, which leads to necrosis and, eventually, HCC (176). HCV can also induce liver injury, which can progress to cirrhosis and HCC (287). There have been meta-analyses examining the association between HBV or HCV infections and HCC development, but little attention has been paid to the association between dual infections and HCC (55). Thus, this sub-section aims to explore the role of HBV and HCV infections in HCC development. Using quantitative methods, this section assessed the combined roles of HBV and HCV infections in HCC development. This section aims to identify the best available evidence on the combined roles of HCV and HBV in the development of HCC.

4.1.1 Methods Summary

Search strategy

The detailed methodology for the systematic review and meta-analysis is covered in Chapter Three. This section summarizes the method used to analyse the role of HBV and HCV infection in HCC development. The search for articles on the role of HBV and HCV in the development of HCC was conducted in three steps. The initial search was conducted to find keywords and index terms, which were then combined using the Boolean operators "AND" and "OR" to build the final search terms.

"hepatocellular carcinoma" OR "liver malignancy" OR "malignant hepatoma" OR "liver neoplasm" OR "hepatoma" OR "liver cancer" OR "hepatocarcinoma" AND diabetes OR obesity OR smoking

OR alcohol OR "hepatitis B virus" OR "hepatitis C virus" OR "alcohol-related disorder" OR Porphyrias OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism" OR "metabolic syndrome" OR "glycogen storage disease" OR "chronic obstructive pulmonary disease" AND "incidence" OR "prevalence" OR "epidemiology" OR "burden" OR "proportion" OR "clinical diagnosis "OR" treatment" OR "control" AND "Ethiopia" OR "Addis Ababa."

The initial search was conducted using MEDLINE, Google Scholar, Scopus, and CINAHL databases. In Step Two, the combined keywords and index terms identified in the initial search were used to identify articles on the role of HBV and HCV infection in HCC development on PubMed, MEDLINE, Emcare, CINAHL, and Scopus databases. Finally, the reference lists of the papers included were manually searched.

Eligibility criteria, article selection, and article quality assessment

The systematic review and meta-analysis included studies published between January 1, 1998 and November 30, 2020 and looked at the combined roles of hepatitis B and C infections in HCC development. Unpublished studies, review protocols, grey literature, conference abstracts, and review protocols were excluded. The studies were selected for the meta-analysis based on inclusion and exclusion criteria. The following major steps were used to select the studies: first, the number of articles identified by the systematic search was recorded. The duplicate records were then identified and excluded. The titles and abstracts of the non-duplicate articles were then reviewed, and non-eligible studies were excluded. The papers retrieved from the title and abstract reviews were subjected to a full-text screening, and those found to be eligible following the full-text screening were included in the study (Fig. 4-1). The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the studies (406). Studies with more than six stars on the NOS were considered high quality (406).

Information sources

Three information sources were used to identify articles for this systematic review and meta-analysis. The first data sources were the databases MEDLINE, Google Scholar, Scopus, and CINAHL, which were used to identify keywords and index terms from HCC articles to generate final search terms to identify articles on the role of HBV and HCV in HCC development. The PubMed, MEDLINE, Emcare, CINAHL, and Scopus databases were then used to identify articles using the final search terms. The third source of information was the reference lists of the papers included in the systematic review and meta-analysis, which were manually searched for articles or titles on HBV and HCV co-infection in HCC development.

Data collection process

When available, data on the author name, year of publication, study country, study design, sample size, and odds ratio (OR) of HCC along with the 95% confidence interval (CI), were extracted from each of the articles included in the systematic review and meta-analysis. When the odds ratio was not provided, raw data for the odds ratio analysis was taken from tables, texts, summary data, or figures in the articles. Data for the systematic review and meta-analysis were extracted using the Systematic Review Data Repository (412, 413).

Data items and outcome/ exposure measures

The odds ratio (OR) along with a 95% confidence interval (CI) were used in the synthesis to determine the role of HBV, HCV, and HCV and HBV co-infections in HCC development. Individuals were classified as having HCC using the International Classification of Diseases (ICD-10/ICD-O-3), with the following ICD code: C22. Hepatitis B infection (defined by ICD-9 codes: 070.22, 070.23, 070.32, 070.33, V02.61, and ICD-10 codes: B18.1, B18.0, Z22.51) is defined as being positive for HBV markers or antibodies by serological or molecular testing. The presence of HCV markers or antibodies detected by serological or molecular testing confirms hepatitis C infection (defined by ICD-9 codes: 070.41, 070.44, 070.51, 070.54, 070.70, V02.62, and ICD-10 codes: B17.11, B18.2, B17.10, B18.2, B19.20, Z22.52).

Data extraction and synthesis

Stata software (Version 11, Texas, USA) was used to analyse the data (481). The following data were extracted from each of the articles identified as available: gender, mean age, study design, study area, sample size, type of controls, odds ratio (OR) values along with their 95% confidence intervals (CI), and proportion. Moran's I^2 was determined to assess heterogeneity (410). The odds ratio along with the 95% CI was used as the effect measure. An additive scale was used to assess the interaction between HBV and HCV in HCC, as described elsewhere (482, 483).

$$(p_{11}-p_{00}) - [(p_{10}-p_{00}) + (p_{01}-p_{00})]$$

This is derived to:

$$p_{11} - p_{10} - p_{01} + p_{00}$$

Where

p_{11} the effect of both factors together

p_{10} the effects of the first factor alone

p_{01} the second factor alone

p_{00} the effect of both factors absent

If $p_{11} - p_{10} - p_{01} + p_{00} > 0$, the interaction is positive If $p_{11} - p_{10} - p_{01} + p_{00} , < 0$, the interaction is negative

4.1.2 Results

4.1.2.1 Identification of studies

A total of 2,417 articles were identified from Medline (n = 906), PubMed (n = 477), CINAHL (n = 48), Emcare (n = 286), and Scopus (n = 700), of which 299 articles were found to be duplicates. Of the 2,118 publications screened, 2,029 were excluded after reading the abstracts and titles. Of the 89 full publications reviewed, 79 were excluded. One article was subsequently excluded during

data extraction as it lacked data for further analysis in the meta-analysis. A total of nine publications were included in the meta-analysis (Fig. 4-1). A manual search of the reference lists of the articles included yielded no results.

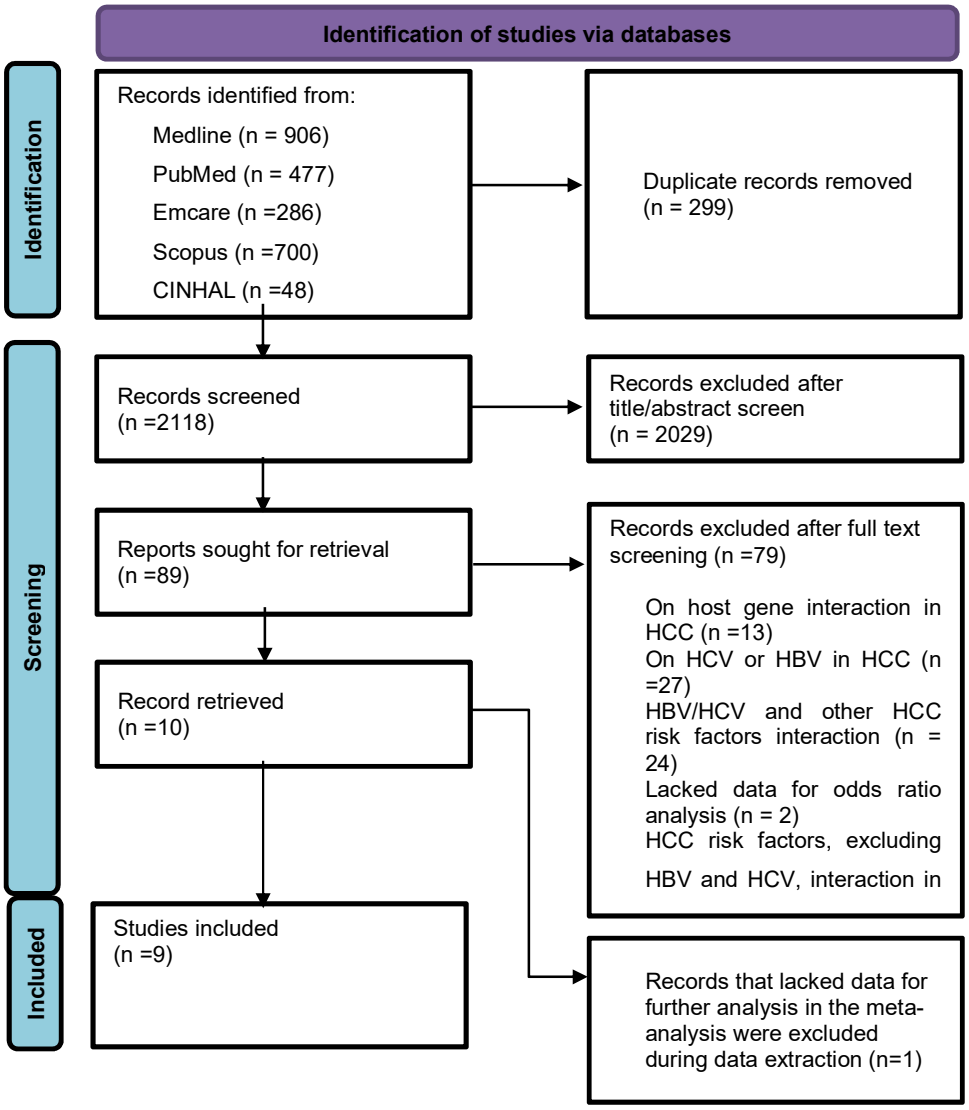

Figure 4-1: Flowchart showing study selection.

4.1.2.2 General characteristics of the studies

Table 4-1 and 4-2 show the key characteristics and main findings of the studies included in the systematic review and meta-analysis. It presents the design, sample size, and main findings of the studies. Except for one nested case-control study, all of the studies were case-control, with a total of 1855 cases and 3245 controls. Five of the studies were matched case-control studies. In the overall studies, men outnumbered women among cases (71.4%) and controls (77.8%). The proportion of men was also higher than women in both cases (60.7-84.9%) and controls (60.7-79.7%) in each study.

Four (44.45%) of the studies were conducted in Taiwan (484-487), while the remaining five (55.55%) were undertaken in five other countries: Japan (488), Greece (489), South Africa (490), Korea (491), and Saudi Arabia (492). The years of publication of the articles included in the meta-analysis range from 2000 to 2018, with the majority of them (66.67%) published after 2015. The included studies' data collection years vary. Jeng et al., 2009 collected data from 2003 to 2004 (485), Tsai et al., 2004 (8) from 1996 to 1997, Ohishi.,2008 (488) 1970 to 2002, Yun et al., 2010 (491) from 2002 to 2006, Mak et al., 2018 (490) from 2000 to 2012, Kuper et al., 2000 (4) from 1995 to 1998, Jeng et al., 2014 (484) from 2004 to 2005, and Tsai et al., 2001 (486) from 1996 to 1997.

The analysis of HBV and HCV infection in HCC in the studies resulted in a wide confidence interval. Some of the studies assessed the role of HBV and HCV infection in HCC development using small samples (484, 490, 492) which likely contributed to these wide confidence intervals. All of the studies used serological detection of HBsAg and anti-HCV antibodies to determine HBV and HCV infection or positivity. One study used molecular detection of HBV DNA and serologic detection of HBsAg (489). Another study included serologic anti-HCV antibody detection as well as molecular detection of HCV RNA (488). Males outnumbered females in both cases and controls in each study. The studies included in this meta-analysis are of high quality, with NOS scores of greater than 6 (Appendix 1.2).

Table 4-1: Characteristics of the included case -control studies on HCV and HBV infection in HCC.

		Cases				Controls				HBV and HCV co-infection
Author, year	**Country**	**Number**	**Mean or median age (year)**	**Male (%)**	**Female (%)**	**Number**	**Mean or median age (year)**	**Male (%)**	**Female (%)**	**OR (95% CI)**
Ayoola and Gadour., 2018 (492)	Saudi Arabia	118	58.1	96 (81.35)	22 (18.65)	118	57.6	96 (81.35)	22 (18.65)	14.60 (1.57–135.90)[3]
Jeng et al., 2014 (484)	Taiwan	200	59[#]	163 (81.5)	37 (18.5)	200	58[#]	163 (81.5)	37 (18.5)	206.74(11.74-642.21)[3]
Jeng et al., 2009 (485)	Taiwan	150	57[#]	115 (76.7)	35 (23.3)	150	55[#]	115 (76.7)	35 (23.3)	332.11(19.51–5654.40)[3]
Kuper et al., 2000 (493)	Greece	333	NR	283 (85.0)	50 (15.0)	360	NR	172 (63.2)	100 (36.8)	93.51 (5.46-1603.03)[3]
Mak et al., 2018 (490)	South Africa	150	46.1	111 (74.0)	39 (26.0)	438	45.7	324 (74.0)	114 (26.0)	3.15 (0.31,32.40)[1]
Ohishi., 2008 (488)*	Japan	224	66.4	136 (60.7)	88 (39.3)	644	63.7	387 (60.1)	257 (39.9)	32.17(6.07 -170.47)[3]
Tsai et al., 2001 (486)	Taiwan	263	59[#]	205 (77.95)	58 (22.05)	263	59[#]	205 (77.95)	58 (22.05)	37.89 (10.38–151.37)[3]
Tsai et al., 2004 (487)	Taiwan	210	58[#]	170 (80.95)	40 (19.05)	210	58[#]	170 (80.95)	40 (19.05)	78.50 (15.86–216.27)[3]
Yun et al., 2010 (491)	Korea	207	NR	165 (79.7)	42 (20.3)	828	NR	660 (79.7)	168 (20.3)	15.90 (0.75 – 335.51)[2]

NR; not reported, OR; odds ratio; * nested-case control; HBV, hepatitis B virus; HCV, hepatitis C virus; [#] median; [1] Adjusted for age group, sex, country and province of birth, number of years lived in urban area, place of birth, alcohol consumption, and HIV status; [2] Adjusted for gender, age, marital status, family income, lifetime alcohol intake, cigarette smoking, and body mass index; [3] crude odds ratio.

Table 4-2: Odds ratio values for HBV and/or HCV infection in HCC patients in the studies included in the systematic review and meta-analysis.

	HBsAg or HBV-DNA/anti-HCV status										
Author, year	**HCC cases**				**Controls**				**HBV OR (95%CI)**	**HCV OR (95%CI)**	**HBV and HCV OR (95%CI)**
	-/-	-/+	+/-	+/+	-/-	-/+	+/-	+/+			
Ayoola&Gadour., 2018**(492)**	29	10	75	4	106	3	8	1	34.3 (14.8–79.10)	12.2 (3.2–47.2)	14.60 (1.57–135.9)
Jeng et al., 2009 **(485)**	22	47	107	24	152	8	40	0	18.48(10.39-32.88)	40.59 (16.96-97.16)	332.11(19.51–5654.4)
Jeng et al., 2014 **(484)**	15	37	84	14	110	7	33	0	18.67(9.52- 36.59)	38.769 (14.67-102.40)	206.74(11.74-642.21)
Kuper et al., 2000 **(489)**	83	41	198	11	339	1	12	0	67.39(35.89- 126.56)	167.46 (22.70-1236.12)	93.51 (5.46-1603.03)
Mak et al., 2018 **(490)**	52	18	79	1	369	10	50	3	10.60 (4.33-26.00)	11.56 (7.10-18.85)	3.15 (0.31-32.40)
Ohishi.,2008 **(488)**	45	132	29	5	579	41	18	2	20.72(10.69-40.18)	41.42 (26.06-65.85)	32.17(6.07 -170.47)
Tsai et al.,2001 **(486)**	19	55	102	16	180	7	50	4	19.32 (10.42–36.17)	74.43 (27.65–209.70)	37.89 (10.38–151.37)
Tsai et al., 2004 **(487)**	8	33	105	12	157	5	34	3	60.60 (25.57–149.00)	129.52 (35.50–518.48)	78.50 (15.86–216.27)
Yun et al., 2010 **(491)**	23	23	160	1	777	4	46	1	158.66(83.00-303.30)	255.71 (64.71 –∞)	15.90 (0.75 – 335.51)

HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma;- , number of negative cases; +, number of positive cases.

4.1.2.3 Hepatitis B surface antigen (HBsAg) positivity and the odds of hepatocellular carcinoma development

The odds ratio (OR) and 95% confidence interval (CI) for hepatitis B surface antigen (HBsAg) positivity and anti-HCV negativity for the overall studies and each study is shown in Fig 4-2. A case-control study in Taiwan (487)and a nested case-control study in Japan (488) found that HBsAg positive anti-HCV negative subjects had higher odds of HCC than those who were negative for both markers. A case-control study in Korea also showed higher odds for HBsAg positivity anti-HCV negativity in HCC after adjusting for marital status, family income, lifetime alcohol intake, gender, age, and body mass index (adjusted OR: 158.66; 95% CI: 83.00-303.30) (491). Higher odds for HBsAg positivity anti- HCV negativity in HCC were also found in South Africa (490), Greece (493), and Saudi Arabia (492). The summary OR for anti-HCV negativity HBsAg positivity was 23.49 (95%CI: 13.76-33.22; Moran's I^2: 62.8%; p= 0.004) with moderate heterogeneity, indicating an association between HBV infection alone and an increased odds of HCC. The distribution of the OR of HCC vs. the standard errors of the studies that compared the odds of HCC between HBsAg-positive and anti-HCV-negative individuals and those negative for both viruses was symmetrical (Appendix 20). The meta-bias test for symmetry was also not significant (Bias = 219.0, p = 0.495) (Appendix 20).

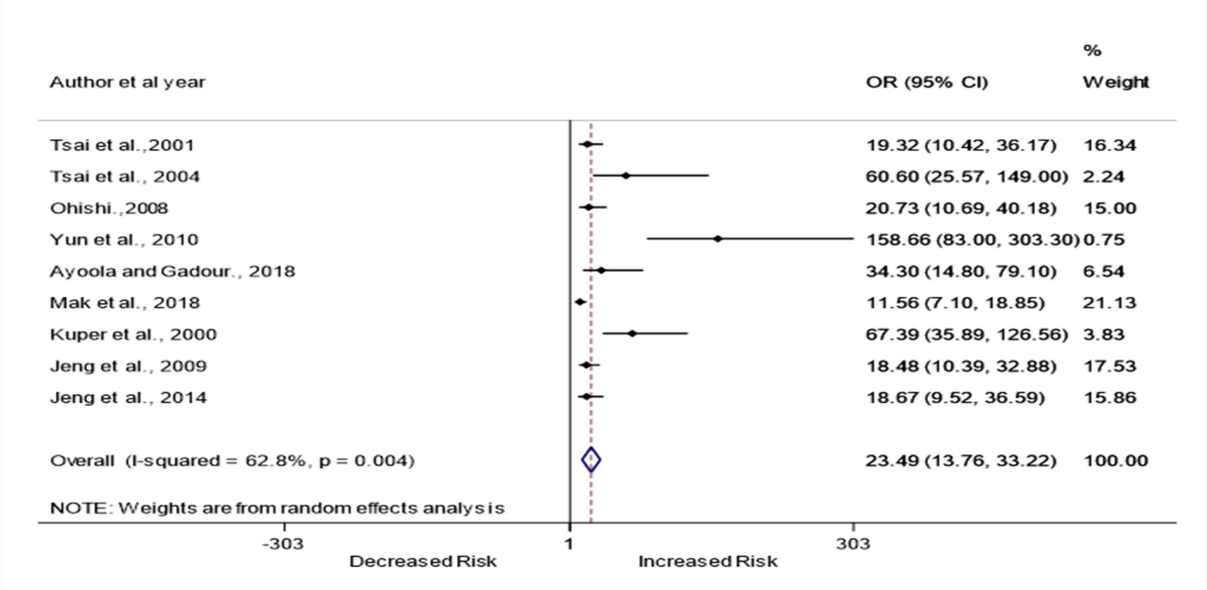

Figure 4- 2: Forest plot showing the odds ratio for HBsAg positivity and anti- HCV negativity in HCC.

4.1.2.4 HCV-positivity and the odds of hepatocellular carcinoma development

The summary OR and 95% CI for anti-HCV positivity HBsAg negativity in HCC are shown in Figures 4- 3. A case-control study of 1035 individuals in Korea showed higher odds for HBsAg negativity anti- HCV positivity in HCC than negativity for both markers (adjusted OR: 255.71; 95% CI: 64.71-1000.00)(491). The corresponding ORs were 41.42 in Japan (488), 167.16 in Greece (493), 12.20 in Saudi Arabia (492), and 10.60 in South Africa (490). A summary analysis revealed a higher odds of HCC among anti-HCV positive HBsAg negative patients compared to those not exposed to either marker with low heterogeneity (summary OR: 26.43; 95%CI: 11.45–41.42; I^2: 35.1%; p= 0.127). The distribution of the OR of HCC vs. the standard errors of the studies that compared the odds of HCC between anti-HCV-positive and HBsAg-negative individuals and those negative for both viruses was symmetrical (Appendix 21). The meta-bias test for symmetry was also not significant (Bias = 157.4, p = 0.113) (Appendix 21).

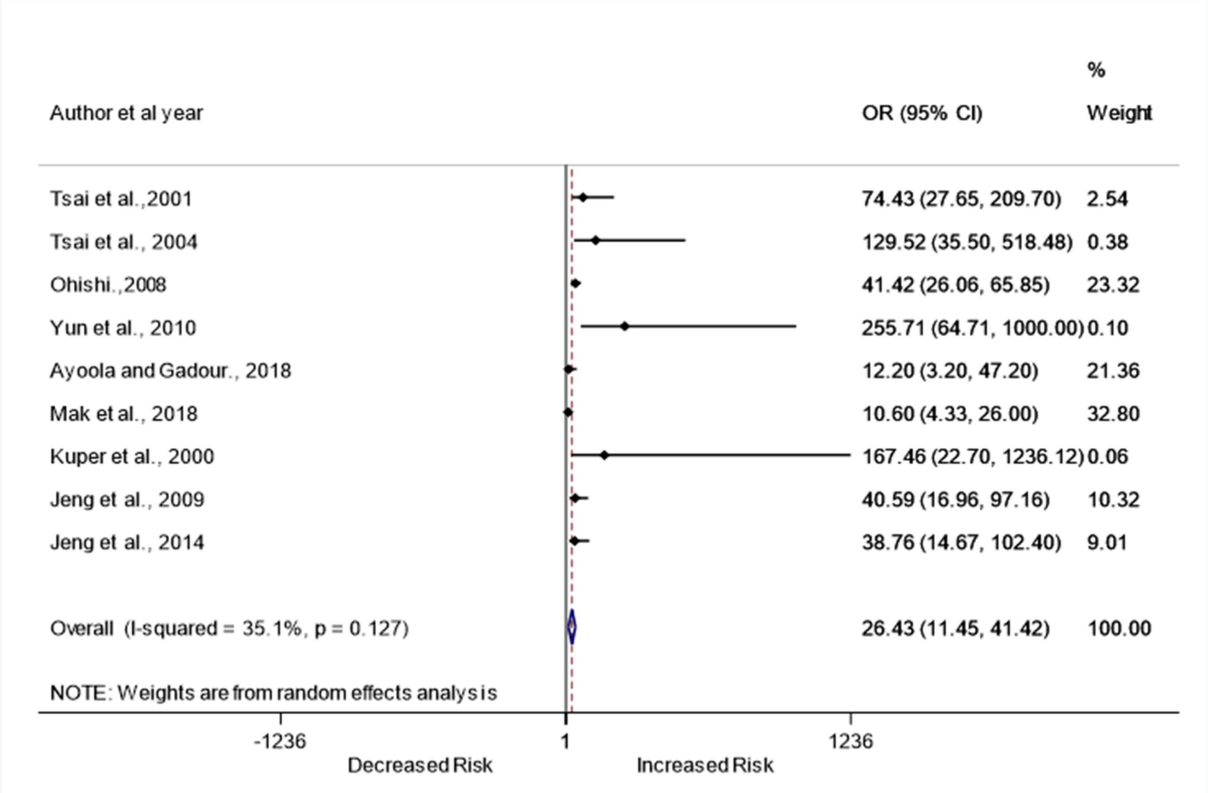

Figure 4- 3: Forest plot showing the odds ratio for HCV positivity anti- HCV negativity in HCC.

4.1.2.5 Positivity for both anti-HCV and HBsAg and the odds of hepatocellular carcinoma development

The summary OR for positivity for both anti-HCV and HBsAg from the analysis is presented in Figure 4-4. Nine studies investigated the odds of HCC in individuals being positive for both HBsAg and anti- HCV (484-492). All of the studies found a statistically significant association between positivity for both markers and increased odds of developing HCC (484-492). In Korea, Yun et al (491) reported higher odds for HBsAg positivity anti- HCV positivity in HCC than negativity for both markers (adjusted OR: 15.90; 95% CI: 0.75-335.51). The corresponding ORs were 16.60 in Saudi Arabia (492), 93.51 in Greece (493), 32.17 in Japan (488), and 3.15 in South Africa (490). The summary OR of HCC among anti-HCV positive HBsAg-positive patients was 8.01 and there was low heterogeneity (95%CI: -6.69-22.71; I^2: 0.0%; p= 0.94), suggesting the absence of association between HBV and HCV co-infection and HCC development. The distribution of the OR of HCC vs. the standard errors of the studies that compared the odds of HCC between anti-HCV-positive and HBsAg-positive individuals and those negative for both viruses was symmetrical (Appendix 22). The meta-bias test for symmetry was also not significant (Bias = 92.73, p = 0.303) (Appendix 22).

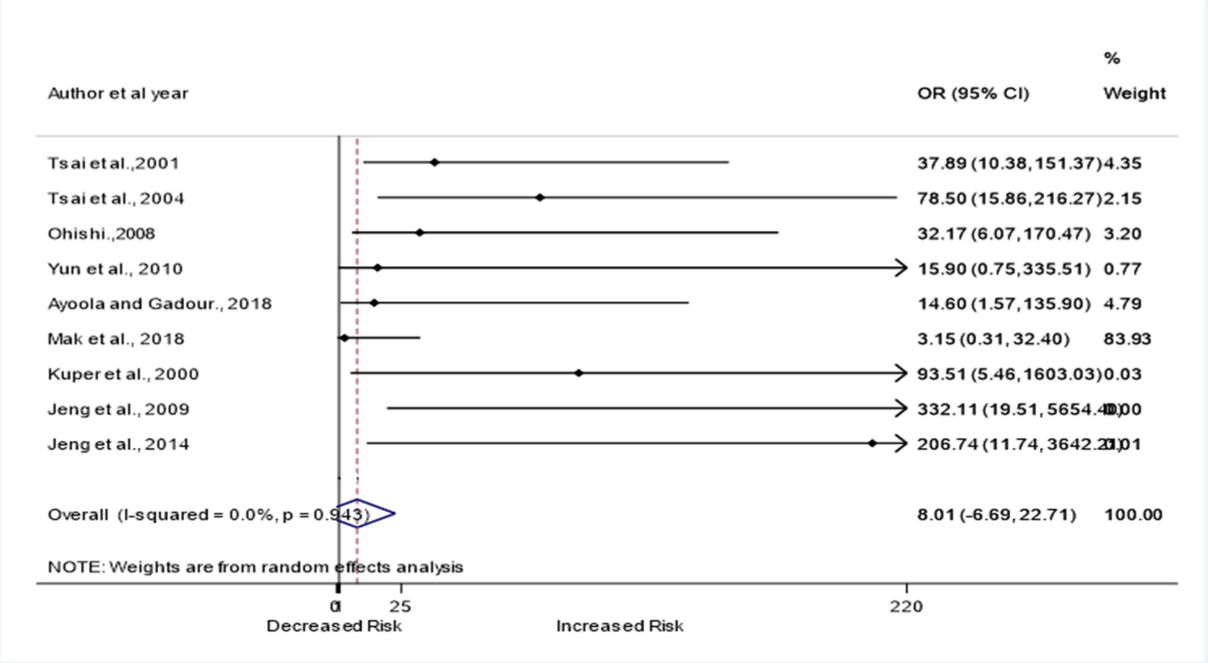

Figure 4- 4: Forest plot showing the odds ratio for positivity for both anti-HCV and HBsAg in HCC.

4.1.3 Discussion

This study provides an overview of the available data on the independent and combined effects of HCV and HBV on the development of HCC. It found increased odds of HCC in HBV-positive and HCV-negative individuals, as well as HBV-negative and HCV-positive individuals when compared to those who were negative for both viruses. The study also found no association between HBV and HCV co-infection and increased risk of HCC development. Four of the studies (44.45%) were conducted in Taiwan, while the remaining five (55.55%) were conducted in Japan, Greece, South Africa, Korea, and Saudi Arabia. Despite the high prevalence of HCC, HCV, and HBV in Africa, only one study has been conducted to assess the role of HBV and HCV infection in HCC development in the region (490). The greatest challenge in assessing the association between HBV and HCV co-infection and HCC is the paucity of HBV and HCV co-infected individuals who do not have evident liver disease (55). Thus, conducting such studies in Africa, where HBV and HCV are prevalent, may aid in understanding the relationship when there are more cases of HBV and HCV co-infection in people without clinically evident liver disease. Assessing the role of HBV and HCV infection in HCC development in Africa could aid in identifying individuals at high risk of HCC, which will be important when developing a strategy to reduce the region's HCC burden.

The sample sizes in some of the studies included in this systematic review and meta-analysis are small. There is also a high difference in the percentage of HCC cases classified under the different HBV and HCV infection statuses. Analysing small data and data with a high difference in the percentage of cases classified into two or more categories resulted in a wide confidence interval (410, 494). Moreover, high study variability or heterogeneity has been linked to a high confidence interval with a high margin of error (410, 494). The high heterogeneity among the studies included in this systematic review and meta-analysis may also explain the wide confidence interval.

The summary odds ratio for anti-HCV positive HBsAg negative subjects as compared to those unexposed to either marker in this study was 26.43 (95%CI: 11.45–41.42). Although this finding suggests an association between HCV infection alone and increased odds of HCC development,

the corresponding ORs in China and globally were significantly lower, at 17.3 and 8.0, respectively (55, 56).

Several mechanisms have been proposed to explain how HCV increases the risk of HCC. One of the mechanisms is to inhibit tumor suppressor genes (184). HCV, for instance, has been shown to inhibit p53, a tumor suppressor gene (184). Inhibiting P53 results in increased cell growth and proliferation (182). Continuous cell growth and proliferation cause genetic alterations, which eventually lead to the development of HCC (182). HCV can also cause HCC by inducing inflammation (178). HCV infection can cause an elevated T-cell response, and an elevated T-cell response causes inflammation. Inflammation, in turn, causes hepatocyte regeneration (177-180). Continuous hepatocyte regeneration may result in genetic alterations, which may eventually lead to HCC development (177, 182).

In this study, the summary OR for HBsAg positivity anti-HCV negativity was 23.49 (95%CI: 13.76-33.22), indicating an association between HBV infection alone and increased odds of HCC development. The corresponding summary ORs were 22.5 for studies from various parts of the world and 15.8 for studies from China (55, 56). This study supports previous studies' findings indicate that HBV infection is an independent risk factor for HCC (55, 56).

Previous research proposed several mechanisms for HCC development in HBV patients. The HBV HBx protein integrates into the genomes of liver cells. This will result in chromosome instability, which will eventually lead to HCC (495, 496). A robust response of CD4+ and CD8+ T cells has also been reported during acute HBV infection to clear the virus. HBV-specific CD8+ T lymphocytes either produce interferon (IFN) and tumor necrosis factor (TNF) and damage infected hepatocytes or directly destroy infected hepatocytes, both of which eventually lead to HCC (497-499). HBV can also interact with the ER and cause HCC (500). The interaction causes ER stress, which leads to oxidative stress (501). This, in turn, stimulates the cell growth pathway, which leads to mutation (35, 183). High mutation rates cause genetic instability, which eventually leads to the development of HCC (35, 183). The increased risk of HCC in HBsAg positive anti-HCV negative

individuals in this study could, therefore, be attributed to these and other HCV effects in the carcinogenic process.

The summary OR for positivity for both anti-HCV and HBsAg in this review was 8.01 (95% CI: -6.69–22.71), which is lower than findings from previous studies, though it suggests an association between HCV and HBV infection and increased odds of HCC development. A meta-analysis conducted in China found that the odds ratios for positivity for both anti-HCV and HBsAg were 39.5 and 44.9, respectively, when community and hospital controls were used (55). Donato et al. (56) found that using community and hospital controls, the overall OR for positivity for both anti-HCV and HBsAg was 420 and 34.6, respectively.

In this study, the summary OR for positivity for both anti-HCV and HBsAg was lower than the sum of the summary OR for HBsAg negativity anti-HCV positivity and HBsAg positivity anti-HCV negativity (49.92 vs 8.01) independently, indicating that HBV and HCV do not interact additively in HCC. Kuper et al. (291) also reported that coinfection had no additive effect on HCC development. In contrast, studies have found no evidence of HBV-HCV synergism in HCC (55, 56). Possible explanations for the lack of additive interaction between HBV and HCV in HCC were proposed. HCV and HBV interfere with each other's replication (295, 502-505). Although the progression of fibrosis and liver activity is reported to be higher in those co-infected with HBV and HCV, an inverse relationship between the replication of the two viruses in those co-infected with the two has been found (506, 507). The suppression of HBV replication in chronic HBV patients following acute HCV infection has been reported (295, 508). Similarly, HCV replication inhibition has been reported in chronic HCV patients with HBV superinfection (295, 508). This could explain the reduced odds of HCC development in HBV and HCV-co-infected patients in this systematic review and meta-analysis.

It has also been reported that HCV inhibits HBV replication when the two viruses infect the same hepatocyte (509). HCV structural and functional proteins directly inhibit HBV replication and lower HBsAg antigen expression in hepatocytes (509). For instance, a Taiwanese study found low levels of viremia and HBsAg antigen expression in the livers of HBV and HCV-co-infected patients (510).

This could also explain the lower odds of HCC development in HBV and HCV-co-infected patients in this systematic review and meta-analysis.

With the advancement of molecular biology techniques in recent years, genotypic variants in HBV/HCV and their geographic distribution have been established (511). The genotype variation of the viruses has been linked to clinical outcomes and the advancement of liver disease (511, 512). The role of HBV and/or HCV infection in increasing the risk of HCC development has also been reported to depend on which genotypes of the viruses are involved (511, 513-515). HBV genotype C is associated with a higher risk of HCC than the other genotypes (516). It has also been reported that HCV genotype 1b increases the risk of HCC development more than the other genotypes (514, 517). The distribution of HCV and HBV genotypes varies by geographic region (517). HCV genotypes 1 and 4, and HBV genotypes A, D, and E are more common in SSA (77, 518). Unfortunately, there has been a paucity of studies in many countries, including SSA countries, to determine HBV and HCV genotype distribution, which could be used to develop country-specific preventive approaches to lower the burden of HCC (519). There is also a need to assess the independent and combined roles of HBV and HCV in different countries around the world, as their roles depend on the HBV and HCV genotypes involved, which vary by geographical region (517).To reduce the chance of reporting bias, this study should have been registered in databases such as PROSPERO (520, 521), a global registry of systematic reviews, from the onset. However, it wasn't until after the review had been completed that we decided to submit it for publication. Registration of the protocol seeks to reduce reporting bias, especially when methodologies have undergone considerable changes that could introduce biases. Fortunately, we did not change the methods for carrying out this review after the protocol was developed.

Another limitation is that this study only included articles published in English for a variety of reasons that could potentially affect the quality of the meta-analysis. One of the reasons is the researchers' inability to translate non-English articles. Online translation technologies, such as Google Translate, have been regarded as insufficiently accurate for non-English studies, and the accuracy of the algorithms varies depending on the type of language translated (522). The quality of most non-English publications has also been reported to be lower when compared to English

publications, and most non-English publishers publish their results in international English journals when they are statistically significant and are less likely to publish them in other journals (523). Egger et al. (523), for instance, assessed articles published between 1985 and 1995 and found that authors reported significant results in English journals and were less likely to publish them in German publications. Moreover, study design standards or higher report completeness rates have been reported to be higher in English language studies than in non-English studies (524, 525). Non-English publications were also excluded from the systematic review on the burden of HCC in Ethiopia for the same reasons. Future research should conduct comprehensive literature searches and use accurate translation to assess the contribution of all relevant studies, regardless of the language of publication.

4.1.4 Conclusions and recommendations

A meta-analysis of nine studies was conducted to better understand the role of HBV and HCV infections in HCC development. Unlike previous studies, this study covered current studies on the role of HBV and HCV infection as well as studies conducted in any region throughout the world to examine the role of HCV and HBV in HCC development. This systematic review and meta-analysis, which included recent data, supported previous studies that found that HCV and HBV infections are independent risk factors for HCC. However, this study did not show an additive interaction between HBV and HCV in HCC development. As controlling HBV and HCV could reduce the burden of HCC, people should be made aware of potential protective behaviours (e.g., avoiding needles and other injecting equipment sharing and avoiding unprotected sex). It is also suggested that hepatitis B vaccination be increased to prevent chronic HBV infection and the resulting chronic liver disease (526, 527). Incorporating HBV and HCV prevention and control activities into existing HCC prevention and control plans/strategies may also aid in reducing the effect of HBV and HCV infections on increasing HCC development. Moreover, people must be made aware of the role of HBV and HCV infections in the development of HCC. However, because meta-analyses are based on published articles, there may be confounding factors and bias, necessitating additional similar research for more accurate results.

Moreover, the absence of additive interactions between HBV and HCV infections in HCC patients contradicts previous research and should be investigated further in future studies. This will help to clarify the conflicting reports and identify individuals at high risk of HCC.

Aim Two: To report the best available evidence on the burden of HCC and its risk factors in Ethiopia.

4.2 A systematic review of hepatocellular carcinoma burden in Ethiopia

HCC is a major public health problem in the world (11, 528, 529). It has major and less common risk factors (530). Its major risk factors include alcohol consumption, tobacco use, HBV, HCV, and NAFLD. In many countries around the world, particularly in SSA, little attention has been paid to determining the burden of HCC and the role of its major risk factors in HCC development (103, 104). In Ethiopia, a SSA country, little attention has been paid to determining the burden of HCC and its risk factors in the general population (105). Knowledge of the prevalence of HCC in the country, until recently, was largely based on the work of a few researchers who described the disease's burden based on sociodemographic variables such as age and gender in patients attending Ethiopian hospitals (92, 93, 109-113). There has also been little attention on identifying gaps in previous studies to design new studies to better understand the actual burden of HCC and related risk factors in the country. Thus, this chapter aimed at analysing the best available data on the burden of HCC and its risk factors in Ethiopia to address the second objective of this thesis, i.e., to identify the best available evidence on the burden of HCC and its risk factors in Ethiopia.

4.2.1 Method Summary

Systematic search strategy

The detailed methodology for the systematic review and meta-analysis is covered in Chapter 3. This section summarizes the method used to analyse the HBV and HCV infections in HCC patients in Ethiopia. The systematic search was carried out in three steps. First, searches on MEDLINE, Google Scholar, Scopus, and CINAHL were conducted to identify a few studies on HCC. The

articles in these databases were used to generate the final search's keywords and index terms. Following the identification of the keywords and terms, they were combined using the Boolean operations "AND" and "OR" as needed. In Stage Two, a literature search was done in the PubMed, Scopus, Google Scholar, and Cochrane Library databases using the combined keywords and search terms. In Stage Three, relevant reference lists of articles included were manually searched.

Eligibility criteria, article selection, and article quality assessment

The systematic review included all publications on the burden of HCC and its risk factors published in English between January 1, 1970 and November 30, 2020. Protocols, unpublished studies, conference abstracts, grey literature, and review protocols were all excluded from the review.

The studies were selected using inclusion and exclusion criteria. The selection process begins with the systematic search and recording of articles, followed by the exclusion of duplicate records, the review of titles and abstracts of non-duplicate articles, and the exclusion of non-eligible studies. The articles that passed the titles and abstract screening were then subjected to a full-text screening, and those found to be eligible following the full-text screening were included in the study (Figure 4-5).

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the studies' quality. If a study receives more than six stars on the NOS, it is considered to be of high quality. However, the identified articles were not eligible for meta-analysis due to their poor quality.

Information sources

This systematic review relied on three sources of data. The first data sources were MEDLINE, Google Scholar, Scopus, and CINAHL. These databases were used to identify a few studies on HCC, which were used to identify keywords and terms to develop the final search terms. Once the final search terms had been developed using the identified keywords and terms, the databases PubMed, Google Scholar, and Cochrane Library databases were used to identify articles for the systematic review. The third source of information was the reference list of the included

publications, which was used to manually search articles or the titles of articles on HCC and its risk factors in Ethiopia.

Data collection process, data items and outcome/ exposure measures

The data gathered from the papers for the systematic review of the burden of HCC and associated risk factors in Ethiopia include: study design, study area, sample size, year of publication, and risk factor variables. Data for the systematic review were extracted using the Systematic Review Data Repository (412, 413). HCC and its risk factors were assessed using prevalence or incidence. Laboratory or clinical confirmation of exposure to any of the HCC risk factors has established risk factor exposure among HCC patients. The studies included in the systematic review, with the exception of one (94), assessed risk factor exposure.

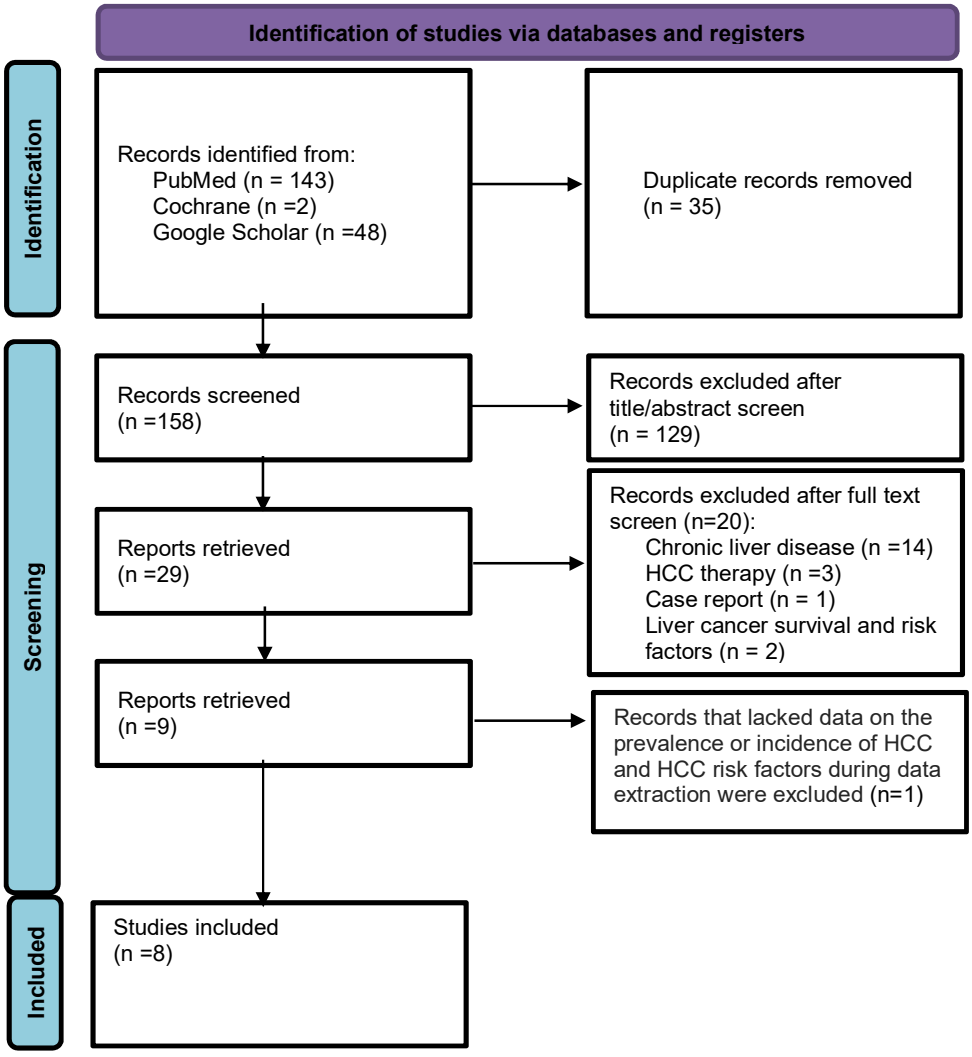

Figure 4-5: Flowchart detailing identification and selection of studies.

4.2.2 Results

4.2.2.1 General characteristics of the studies

This systematic review included eight studies that assessed the burden of HCC in Ethiopia. Except for two studies (110, 113), the studies were published between 1970 and 1995 (Table 4-4). In each of the studies included in this systematic review, men outnumbered women. Four of the studies included in this systematic review reported the mean or range of ages of HCC patients. Participants in these studies range in age from 18 to 70 years. One study reported that the 51 HCC patients it studied ranged in age from 18 to 65 (110). Another study (110, 113) found that the average age of the 70 HCC patients who took part in the study was 50. Pavlica et al. (94) reported that the 38 HCC patients assessed for HCC risk factor exposure ranged in age from 23 to 70 years old. Tsega et al. (97) studied HCV infection in 68 HCC patients with an average age of 49. The studies included in the systematic review were health facility-based studies conducted in Addis Ababa.

4.2.2.2 Quality of the included studies

Six of the studies included in this systematic review were retrospective or cross-sectional (110-113, 531, 532), and two were cohort studies (93, 94). While four studies looked at the burden of HCC in individuals with liver disease (92, 94-96), the remaining studies looked at the clinical and laboratory characteristics of HCC patients as well as their HCC risk factor exposure status. All of the studies, however, were ineligible for meta-analysis due to their low quality, with NOS scores less than or equal to 5 (See supplement tables in Appendix 1.2). All of the included studies used non-representative samples and no sampling technique (93, 109-113, 531, 532). The studies also didn't conduct any statistical analysis or provide a 95% confidence interval; they determined the number or percentage of HCC cases in patients with liver disease or the proportion of HCC risk factors in HCC patients (93, 109, 110, 113, 531). In two of the studies, the follow-up period for outcomes was not long enough (93, 94).

4.2.2.3 The burden of hepatocellular carcinoma in Ethiopia

Four studies of the studies included in this review looked at the burden of HCC among individuals with liver disease who were admitted to public hospitals in Ethiopia (92, 94-96) (Table 4-3). The studies determined the number or percentage of HCC patients diagnosed in hospitals in the country and reported it as the incidence or prevalence of HCC, which may not accurately reflect the disease's actual prevalence or incidence in the country. In one of these studies, 860 individuals with liver disease were recruited, and 704 liver biopsy specimens were qualified for testing for HCC; 19.2% of the samples tested positive for HCC (92). Another study in Ethiopia found HCC in 33.5% of 334 chronic liver disease patients admitted to a hospital (96). A retrospective study revealed that 5% of those hospitalized in three medical wards in Addis Ababa in 1977 had HCC (97).

Table 4-3: Studies which consider the burden of hepatocellular carcinoma in Ethiopia.

Study	Study design	Sample size and study setting/design	Main findings
Tsega et al.,1992 **(96)**	A hospital based cross-sectional study of adults admitted to a hospital with chronic liver disease.	334 adults admitted to a hospital with chronic liver disease.	HCC was found in 33.5% of the 334 chronic liver disease patients.
Fekadu et al.,1989 **(111)**	A retrospective study (chart review) of patients admitted to a hospital with liver disease.	860 individuals admitted to a hospital with liver disease.	Of the 860 patients, 704 biopsy specimens tested for HCC and HCC was found in 19.2% of them.
Tsega et al.,1977 **(92)**	A retrospective study (chart review) of patients admitted to three medical wards in Addis Ababa.	All individuals admitted to three medical wards in Addis Ababa in 1977. Sample size not reported.	5% of all medical admissions to the three medical wards had HCC.
Pavlica et al.,1970 **(94)**	A prospective cohort study of patients admitted to a hospital with chronic liver	236 persons admitted to a hospital with chronic liver disease.	HCC was found in 16.1% of the 236 individuals with chronic liver disease.

	disease.

HCC, hepatocellular carcinoma.

4.2.2.4 Hepatocellular carcinoma risk factors in HCC patients

All of the studies included in this systematic review determined HCC risk factor positivity in HCC patients admitted to a few public hospitals in Ethiopia (Table 4-4). None of the studies looked at the risk, or odds of, HCC risk factor exposure among the study participants. Instead, existing studies reported the number or percentage of HCC patients who tested positive for one or more HCC risk factors. One cross-sectional study of 70 individuals admitted to a hospital from January 1, 2013 to Dec. 31, 2015 with HCC found that 65.7% of them had HBV or HCV (110). Another similar study in 1995 assessed the HCC risk factor profile of 68 HCC patients in Ethiopia and found that 46% had anti-HCV and 82% had HBV (97). Tsega et al. (96) found one or more hepatitis B virus markers in 78% of 112 HCC patients admitted to a public hospital in Ethiopia between July 1986 and April 1989.

Another prospective cohort study, conducted in Ethiopia in 1977, found that half of the 100 HCC patients included had HBsAg (Table 4-4) (114). Viral hepatitis has also been found in 46 HCC patients in Ethiopia, with 41% having HBV and 45% having HCV (110, 113). A cross-sectional study of patients with a diagnosis of HCC on Computed Tomography examination at Tikur Anbessa Specialized Hospital from July 2016 to July 2017 also revealed that 59% had one or more hepatitis markers (533). Moreover, in another study in Ethiopia, HBsAg was found in the sera of 46 patients with HCC (534).

Table 4-4: Studies which explore hepatocellular carcinoma risk factors in HCC patients in EthiopiaHCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

Study	Study design	Number of HCC cases	Percentage of HCC, HBV or HCV
Getaneh F and Atnafu A .,2020 **(113)**	A hospital based cross-sectional study of patients with HCC.	70	HBV or HCV was detected in 65.7% of the 70 HCC patients.
Mekonnen et al., 2015 **(110)**	A retrospective study (chart review) of patients admitted to a hospital with HCC.	51	Among the 51 HCC patients, 48% had HBV and HCV, and 45% had a history of alcohol use.
Tsega et al.,1995 **(97)**	A hospital based cross-sectional study of HCC patients.	68	Anti-HCV antibodies were found in 46% of the 68 HCC patients.
Tsega et al.,1992 **(96)**	A hospital based cross- sectional study of adults admitted to a hospital with chronic liver disease.	112	Hepatitis B virus markers were detected in 78% of the 112 HCC patients.
Fekadu et al.,1989 **(111)**	A retrospective study (chart review) of patients admitted to a hospital with liver disease.	135	Of the 135 HCC patients, 25.4% had liver cirrhosis and 8.8% had HBV or HCV.
Tsega et al.,1977 **(93)**	A prospective cohort study of HCC patients admitted to a hospital.	100	50% of the 100 HCC patients were HBsAg positive.
Tsega et al.,1977 **(92)**	A retrospective study (chart review) of patients admitted to three medical wards in Addis Ababa.	All HCC patients admitted at three medical wards in 1997 in Addis Ababa. Sample size not reported.	50% of the HCC patients tested positive for HBsAg.
Pavlica et al.,1970 **(94)**	A prospective cohort study of patients admitted to a hospital with chronic liver disease.	38	Cirrhosis and HBV or HCV were found in 94.7% and 7.9% of the 38 HCC patients, respectively.

4.2.3 Discussion

This systematic review analysed studies on the burden of HCC and associated risk factors in Ethiopia. HCC incidence was found to range from 16.1% to 33.5% among liver disease patients. HBV, HCV, and alcohol consumption were found in HCC patients in the studies analysed in this systematic review. The percentage of HBV and HCV among HCC patients in this systematic review ranged from 7.9% to 65.7%. A history of alcohol consumption was also found in 45% of HCC patients in one study analysed in this systematic review.

According to the current systematic review, the incidence of HCC among individuals with liver disease admitted to hospitals in Ethiopia ranged from 16.1% to 33.5%. This is higher than reports from other East African countries (172). Lifestyle HCC risk factors in Ethiopia have risen in the general population in recent decades as a result of the country's rapid economic growth and globalization (117). Areas in the country that formerly had limited access to alcohol and cigarettes, for example, now have a greater access to both (117). As a result, the prevalence of alcohol and tobacco use in the country is rising (535). Moreover, injected drug use is becoming more common in Ethiopia, and users of injected drugs are reported to share drug-injecting needles and other equipment, potentially spreading HCC risk factors such as HBV and HCV (536). Alcohol has been shown to inhibit tumour suppressor genes such as p53 or cause a loss of control over cell growth and proliferation, which can contribute to the development of HCC (185). Tobacco has also been linked to an increase in pro-inflammatory cytokine production, which can lead to liver injury, cirrhosis, and, eventually, HCC (363, 367). Therefore, the aforementioned factors may have had an impact on the observed burden of HCC in Ethiopia.

A number of anticipated risk factors for HCC were observed in these studies of HCC in Ethiopia. Both HBV and HCV were found in HCC patients in the majority of the studies included in this systematic review. Cirrhosis has also been found in HCC patients in Ethiopia, according to this review. Ethiopia has urbanized more in recent decades. Due to these and other changes, body modification among adults and teenagers has increased in popularity throughout the nation (537). Teenagers and adults in the in rural and urban parts of the country are increasingly adopting tattoos and piercings as fashion statements. Ethiopia's tattoo market has also grown quickly (537).

To reduce or eliminate risks, no regulations have been set up for the tattoo and piercing industries. However, it has been noted that using tattooing and piercing tools repeatedly without sterilizing them can cause them to spread several bacterial and viral infections (538, 539). The viruses HBV and HCV, which are major risk factors for HCC, are among those spread by tattooing and body piercing (538, 539). The risk of HBV infection in Ethiopia has also been linked to body and gum tattooing (537). Moreover, Ethiopia has a high rate of multiple sexual partners among adults, and multiple sexual partners have been associated with HBV infection in the country (540). The aforementioned factors may explain the high burden of HBV and HCV in HCC patients in this review.

The prevalence of HCV and HBV in Ethiopia is reported to be 7.4% and 3.1%, respectively, and the country is classified as a hepatitis-endemic country (304, 541, 542). Despite these facts, little attention has been paid to studying the burden of HBV and HCV in the country. For instance, it has been reported that the country's viral hepatitis burden is underestimated, resulting in insufficient budgetary and organizational focus (172). There has also been less effort to raise public awareness of the role of HBV and HCV in increasing the risk of several cancer types, including HCC (172). Moreover, the WHO classifies the country as having no national strategy for viral hepatitis surveillance, prevention, and control (160-162). Thus, the high burden of HBV and HCV in the studies included in this systematic review may be due to a lack of data on the prevalence of viral hepatitis and a lack of emphasis on HBV and HCV in the country's health system.

The majority of the studies in this review focused on the number of new HCC cases discovered in specific cancer treatment facilities. Moreover, the majority of these studies (92-96) were conducted several decades ago, and none of them employed a representative sample (92-97, 115), a reliable data source (92-97, 115), or investigated trends in HCC incidence (92-97, 115). The findings of these studies do not accurately reflect the burden of HCC and its risk factors in the country (137). More research on the incidence of HCC and associated risk factors in the country is thus required.

This work was not registered in online registries such as PROSPERO (520, 521), a global registry of systematic reviews, since we did not decide to submit it for publication until after the review was

completed. Registration of the protocol of systematic reviews aims to reduce reporting bias, particularly when methods have undergone significant modifications that can induce biases. Following the development of the protocol, we didn't change the methods used for conducting this review. Given the small number of studies in the systematic review, the studies were not classified and discussed based on their study design.

4.2.4 Conclusions and recommendations

A high incidence of HCC was found in the studies included in this review, although these findings are limited and there is presently insufficient evidence to conclusively determine the incidence rate in Ethiopia. Regardless, these findings suggest there is a need to reduce the disease's burden in the country. As the majority of prior studies on HCC burden in Ethiopia were not recent studies, more contemporary studies are required to develop a better strategy to reduce the disease's burden in the country. Reducing the burden of the disease in the country may include screening the general public for HCC and, if resources are limited, screening those at high risk of the disease. Raising public awareness of the disease, which can improve their help-seeking behaviour, should also be implemented in Ethiopia. The incidence of HCC reported in this analysis was predominantly in individuals with liver diseases who were admitted to public hospitals in the country, suggesting that health facilities and health professionals in the country should prioritise identification of risk factors for HCC in people with liver disease who visit, or are admitted to, health institutes. This could take the form of a screening program. The high HBV and HCV seropositivity in HCC in Ethiopia seems to suggest that the two viruses were a major cause of the disease.

An effort should be made to raise public awareness about the disease's link to HBV and HCV infections in the country. This will encourage people to seek health care, resulting in a reduction in disease burden and risk factors in the country. There is also a need for ongoing health professional education on HBV and HCV early detection and screening, appropriate management, and early referral. The Ethiopian government integrated cancer public awareness into the daily operations of the country's public hospitals since 2016 (117). This program, on the other hand, focuses on modifiable cancer risk factors such as alcohol and tobacco use. The government should therefore emphasize raising public awareness of non-modifiable cancer risk factors in the

country, such as HBV and HCV, to reduce their role in increasing the country's cancer/HCC burden. Increased vaccination coverage can also help to reduce the burden of HBV, which in turn helps to reduce the burden of HCC. Tattooing and piercing regulations should also be established and implemented in Ethiopia. Moreover, body modification artists should have regular training opportunities to gain a more in-depth understanding of aseptic techniques.

CHAPTER FIVE: HEPATOCELLULAR CARCINOMA, HEPATITIS B AND C VIRUSES IN ADDIS ABABA, ETHIOPIA

Aim Three: To determine incidence and trends of HCC in Addis Ababa, Ethiopia, from 2012 to 2019

5.1 Incidence and trend of hepatocellular carcinoma in Addis Ababa, Ethiopia

5.1.1 Background

Primary liver cancer is one of the most commonly diagnosed cancers worldwide (7, 19, 261). Primary liver cancer includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and some rare disease types, with HCC accounting for the majority of cases (7, 19). Chronic hepatitis B or C virus infection, high alcohol consumption, aflatoxin B1 exposure, and NAFLD are the main risk factors for HCC (7, 19, 543-548).

In sub Saharan Africa (SSA), primary liver cancer is a public health problem (98). In 2020, there were 38,000 new cases of HCC in SSA, making it the world's fourth highest prevalence rate after South-Eastern Asia, South Central Asia, and North America (14). The majority of primary liver cancer cases in SSA (77%) are HCC cases, and HCC is the second leading cause of cancer death in the region (98). HBV (50%) and HCV (17%) cause the majority of HCC cases in SSA (549). Only about 3% of HCC cases in the region are caused by HBV and HCV co-infections (24, 549). Several other risk factors have also been identified as contributing to the burden of HCC in SSA (19). There is also evidence that the burden of HCC risk factors is increasing in SSA, which is expected to increase the region's disease burden (14, 175).

In Ethiopia, the prevalence of some HCC risk factors in the general population is increasing (105). Ethiopia, for instance, is experiencing rapid economic growth, urbanization, and increased globalization of unhealthy food and consumer goods markets, as are many other countries around the world (105, 124). These changes increased the prevalence of modifiable HCC risk factors, such as tobacco and alcohol use, expected to increase the burden of the disease in the country (105). Additionally, the WHO lists Ethiopia as a hepatitis-endemic nation, and more than 10 million Ethiopians have been reported to have HBV infection (160-162), one of the major risk factors for

HCC. Chronic hepatitis B and C viral infections are also responsible for more than 60% of chronic liver diseases in the country (163).

Despite the increase in the prevalence of some HCC risk factors in Ethiopia, no study has been conducted in the country to assess the incidence and trend of HCC in the general population (103, 105, 550). The majority of information about the incidence of HCC in Ethiopia originates from the work of a small group of researchers who determined the disease's burden in patients visiting a small number of Ethiopian hospitals. However, the studies conducted in the country thus far have several limitations. The majority of the studies looked at the disease's incidence in high-risk populations, such as patients with liver disease (92, 94-97). None of the studies looked at the trend in the incidence of HCC over time. The studies also failed to use reliable data, such as data from population cancer registries, to determine the trend in the incidence of HCC. Moreover, the majority of the studies were carried out decades ago (92, 93, 109, 111, 137, 260). These studies' findings are limited in their ability to accurately reflect the incidence and trends of HCC in the country (137). More study is, therefore, needed to accurately determine the disease burden in the country while also addressing the limitations of previous studies. Thus, this chapter assessed the incidence and trends in HCC in Addis Ababa over eight years (2012-2019) using data from the Addis Ababa City Cancer Registry (AACCR), Ethiopia's only cancer registry.

5.1.2 Method Summary

5.1.2.1 Registration population and registration criteria

The AACCR collects information from Addis Ababa residents who had lived in any of the city's 10 sub-cities (Akaki, Addis Ketema, Gulele, Lideta, Arada, Bole, Kirkos, Yeka, Nifas-silk Lafhto, and Kolfe Karanyo) for at least six months (107). Since all cancer care institutions in Addis Ababa are obligated to notify cancer cases to the AACCR, there is little chance that cases identified at a city cancer care facility will not be reported to the AACCR. The health institutes in Addis Ababa that provide cancer diagnosis and/or treatment use resident identification cards as evidence to confirm whether patients are from Addis Ababa. Only cancer cases from Addis Ababa that have been verified by the institutes are reported to the AACCR (107).

5.1.2.2 Source of information for the registry

The primary sources of data for the AACCR include various hospital units such as Gynecology, Surgery, Internal Medicine, Departments of Pathology, Haematology, Paediatrics, and radiotherapy centers in Addis Ababa.The other major sources are higher diagnostic clinics and diagnostic laboratories with pathology services in the city (107).

5.1.2.3 Data collection and quality control

The contact persons assigned in each health institute in Addis Ababa that provides cancer diagnosis and/or treatment used a standardized format developed by the International Agency for Research on Cancer to collect data on HCC (Appendix 6) (414). The contact person completes the data collection form manually and send it to the AACCR, and the data encoder at the AACCR head office will enter the data into the AACCR database. Each cancer case at the Addis Ababa City Cancer Registry (AACCR) was coded using the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) (103, 104).

The AACCR collects data from three public hospitals and fourteen private health institutions in Addis Ababa (107). However, during the study period (2012 -2019), the HCC cases reported to AACCR were from two public (St. Paul's and Tikur Anbessa Specialized Hospital) and eleven private health institutions (i.e. Myung Sung Christian Medical Center, Teklehaimanot General Hospital, St. Gabriel general hospital, Hallelujah general hospital, Landmark general hospital, Bethzatha hospital, Chechela higher clinic, United Vision, Lagar hospital, Bethel teaching hospital, and Kadisco general hospital) in Addis Ababa, Ethiopia, that provide cancer diagnosis and/or treatment services.

The team from the AACCR's Data Management Section extracted electronic data from the AACCR, including patient data for those with incident cases of HCC (defined by ICD-9 code 155.0 and ICD-10 code C22.0) between the period 1 January 2012 and 31 December 2019.

This sub-chapter analysed only patients identified as incident cases of HCC. Patients who had not lived in Addis Ababa during the study period were not included in the study since there were no HCC cases from outside Addis Ababa in the AACCR database, and the student did not get such data from the AACCR. For this analysis, gender, date of birth, HCC (ICD-O-3: C22.0) date of HCC

notification, HCC morphology (ICD-O-3: 8170), methods of diagnosis (Appendix 2), and place of residence were extracted.

CanReg5 is used by the AACCR for data management, analysis, and quality control. CanReg5 is an open-source tool for storing, checking, and analysing cancer registry data (551). It includes data entry, quality assurance, consistency checks, and basic data analysis modules. Duplicate entries/records are corrected using phone numbers, demographic information, and other information. Training and supervising the contact persons regularly are also among the methods used by the AACCR to maintain data quality (414).

5.1.2.4 Statistical analysis

HCC incidence and trends were analysed by age and gender. The number of newly diagnosed cases of cancer within a population during a specific period were reported as the crude cancer incidence rate (CIR) (103, 104). Individual age-specific rates are calculated using a standard population to produce the age-standardized incidence rate (ASIR). The ASIR is the rate seen if the population had the age structure of the standard population, in this case, the WHO World Standard Population (103, 104). The CIR and ASIR were both expressed in new cases per 100,000 people.

Ethiopia's Central Statistics Agency released population estimates for Addis Ababa (Appendices 18 and 19) (421). The direct technique was used to calculate the age-standardized incidence rates (standardized to the WHO World Standard Population) (Appendix 17) (420). Using joinpoint software (US National Cancer Institute; version 4.5.0.1), piecewise linear regression was used to evaluate incidence rates, average annual percentage change (AAPC), and annual percentage change (APC) (552, 553).

The Joinpoint software performs several tests to evaluate whether the incidence is constant or varies over time. A joinpoint is a statistically significant shift in the incidence slope over time. We used one joinpoint, as advised for data having 7 to 11 data points (552). To establish the total percentage change in HCC incidence rates from 2012 to 2019, the average annual percentage change (AAPC) was calculated. The APC was determined for each separate linear section between two joinpoints. Due to the low number of HCC cases when divided into different age

categories, the ASRs, AAPC, and APC by age were calculated by dividing patients into three age groups: <35 years, 35-54 years, and ≥55 years. When the p-value was less than or equal to 0.05, the value was considered statistically significant. In chapter three of this thesis, a detailed description of the methods and methodology used in this sub-chapter is provided.

5.1.3 Results

5.1.3.1 The general characteristics of the study participants

The general characteristics of the study participants, their treatment profiles, and the basis of their HCC diagnosis are shown in Table 5-1. From 2012 to 2019, a total of 306 HCC cases were reported to the AACCR. Study participants ages ranged from 14 to 95, with a median age of 57.00 (interquartile range (IQR) =20) years, and most (28.76%) were in the 55 to 64 age range. The 45-54 age group had the second-highest proportion of HCC cases (19.93%), followed by the 65-74 (17.33%), >75 (11.76%), 14-34 (11.44%), and 35-44 (10.78%) age groups.

Of the total HCC patients, 182 (59.48%) were men. Their age ranged from 16 to 95, and their median age was 58.00(IQR=23). The highest number of HCC cases 49 (26.92%) was seen in men between the ages of 55 and 64 years. Women made up 124 (40.52%) of the HCC patients in this study, with a median age of 56.00(IQR=19), which is younger than the average age of men in this study.

The highest number of HCC cases among women 39 (31.45 %) was seen in those who are between the ages of 55 and 64. There were 20 (10.99%) HCC cases in men in the 10 - 34 age group, 25 (13.74%) in the 35-44 age group, and 33 (18.13%) in the 65-74 age group. The proportion of HCC was 15 (12.09%) in the 10 -34 age group, 8 (6.45 %) in the 35 -44, and 30 (24.19 %) in the 45 -54.

The overall rate of HCC per 100,000 was 1.04 (95% CI: 1.16-0.92) in the total patients, 1.2 (95% CI: 1.37-1.03) in males, and 0.8 (95% CI: 0.94-0.66) in females. The highest and lowest incidence rates in total patients were 7.1 per 100,000 (95% CI: 9.42-4.78) and 0.1 per 100,000 (95% CI: 0.13-0.07) in those aged 75 and older and 10 to 34, respectively. The overall incidence rate in total

patients was 0.4 per 100,000 (95% CI: 0.54-0.26) in the 35-44 age groups and 1.5 per 100,000 (95% CI: 1.88-1.12) in the 45-54 age groups. In total patients, the incidence rate per 100,000 was 3.8 (95% CI: 4.59-3.01) in those aged 55-64, and 4.4 (95% CI: 5.58-3.22) in those aged 65-74.

Table 5-1: General characteristics of the HCC patients.

Characteristics	**Male n (%)**	**Female n (%)**	**Total n (%)**
Overall	182 (59.48)	124(40.52)	306 (100)
Age group (years)			
10-34	20 (10.99)	15 (12.09)	35 (11.44)
35-44	25 (13.74)	8 (6.45)	33 (10.78)
45-54	31(17.03)	30 (24.19)	61 (19.93)
55-64	49 (26.92)	39 (31.45)	88 (28.76)
65-74	33 (18.13)	20 (16.13)	53 (17.33)
>75	24 (13.19)	12 (9.69)	36 (11.76)
Basis of diagnosis			
Clinical	13 (7.14)	6 (4.84)	19 (6.21)
Clinical investigation	66 (36.24)	43 (34.68)	109 (35.62)
Specific tumor markers	3 (1.65)	5 (4.03)	8 (2.61)
Cytology	26 (14.29)	24 (19.35)	50 (16.34)
Histology of metastasis	2 (1.10)	0 (0.00)	2 (0.65)
Histology of a primary tumor	72 (39.59)	46 (37.10)	118 (38.56)
Treatment			
Chemotherapy	16 (8.79)	6 (4.84)	22 (7.19)
Radiotherapy	13 (7.14)	2 (2.42)	16 (5.23)
Surgery	1 (0.55)	13 (10.48)	14 (4.58)
Unknown (no data on therapy)	148 (81.32)	101 (81.45)	249 (81.37)
Combined therapy			
Chemotherapy - radiotherapy	0 (0.00)	2 (1.61)	2 (0.65)
Chemotherapy- surgery	3 (1.65)	2 (1.61)	5 (1.63)
Radiotherapy- surgery	1 (0.55)	0 (0.00)	1 (0.32)

Note: The basis of diagnosis listed may represent two or more methods of diagnosis (Appendix 2). Although all patients were treated, the method of treatment for some patients was unknown.

Twenty two (7.19%) patients received chemotherapy, 14 (4.58%) had undergone surgery, and 16 (5.23%) received radiotherapy. Five of the 22 patients who received chemotherapy had undergone surgery. Of the 16 patients who received radiotherapy, two patients received chemotherapy, and one patient had undergone surgery (Table 5-1). The majority of the HCC cases (38.56%) were identified by histology of the primary tumor and clinical investigation (35.62%). Cytology and clinical methods were used to identify 16.34% and 6.21% of the study participants, respectively. Only 2 (0.56%) of the participants had metastasis in their histology. Only 2 (0.56%) of the participants were identified based on metastasis histology (Appendix 2). There were no missing values in the AACCR data for age, gender, or date of HCC diagnosis, which were required for the incidence and trend analysis in this study.

5.1.3.2 Source of reported cases

Most of the HCC cases were reported to the AACCR from the Tikur Anbessa Specialized Hospital (51.9%) and Hallelujah general hospital (17.9%), and the lowest cases from Kadisco general hospital, Bethel teaching hospital, and Teklehaimanot General Hospital contributed 0.7% each (Table 5-2).

Table 5-2: HCC cases identified in the health institutes in Addis Ababa, Ethiopia between 2012 and 2019.

Health institutes	n	% of HCC reported to the AACCR
Tikur Anbessa Specialized Hospital	159	51.9
Myung Sung Christian Medical Centre	37	12.1
Teklehaimanot General Hospital	2	0.7
St.Gabriel General Hospital	4	1.3
Hallelujah General Hospital	55	17.9
Landmark General Hospital	7	2.3
Bethzatha Hospital	8	2.6
Chechela Higher Clinic	3	1.0
St. Paul's Hospital	14	4.6
United Vision	4	1.3
Lagar Hospital	9	2.9
Bethel Teaching Hospital	2	0.7
Kadisco General Hospital	2	0.7

HCC, hepatocellular carcinoma; n, number of HCC cases; AACCR, Addis Ababa City Cancer Registry.

5.1.3.3 Trends in hepatocellular carcinoma incidence in total HCC patients

The total number of annual HCC patients increased from 2012 (*n* = 25) to 2019 (*n* = 55), with an average annual percentage change (AAPC) of 6.70 % (95% CI: -10.40 -27.00; *p* = 0.47) (Table 5-3). For total patients, the age-adjusted incidence rate increased from 1.32 per 100,000 (95 % CI: 1.32 – 3.40) in 2012 to 4.09 per 100,000 (95 % CI: 2.84 – 5.34) in 2019 (P >0.05, Table 5- 3). The lowest and highest age-adjusted incidence rates were in 2012 (1.20 per 100,000) and 2018 (2.30 per 100,000), respectively (Table 5-3). Piecewise linear regression demonstrated an increase in incidence without any joinpoints for the total patients for 2012–2016 (APC 2.27%, 95% CI: -30.20 to 49.70; *p*= 0.86) and for 2016–2019 (APC 12.86%, 95% CI:-26.10 to 72.3; *p* = 0.43) (Table 5-4, Figure 5-1).

Table 5-3: Number of new HCC cases and age -standardised incidence rates per 100,000 by sex and year in Addis Ababa, Ethiopia 2012-2019

HCC,hepatocellular carcinoma; 95% CI , 95% confidence interval**.**

	Females		Males		All Patients	
Year	**Number of New Cases**	**Age-standardized Incidence (95% CI)**	**Number of New Cases**	**Age-standardized Incidence (95% CI)**	**Number of New Cases**	**Age-standardized Incidence (95% CI)**
2012	16	2.77 (1.32-4.22)	9	1.91 (0.48– 3.34)	25	2.36 (1.32-3.40)
2013	11	1.79 (0.67– 2.91)	21	4.15 (2.01-6.29)	32	2.98 (1.76– 4.20)
2014	17	3.30 (1.54– 5.06)	21	4.56 (2.42-6.70)	38	3.91 (2.52– 5.30)
2015	11	2.66 (0.88- 4.44)	12	2.16 (0.71-3.61)	23	2.38 (1.24- 3.52)
2016	10	1.40 (0.40- 2.40)	19	3.66 (1.92-5.40)	29	2.56 (1.54- 3.58)
2017	24	3.67 (2.06– 5.28)	24	3.90 (2.06-5.74)	48	3.79 (2.57– 5.01)
2018	21	2.91 (1.46– 4.36)	35	5.72 (3.56-7.88)	56	4.32 (3.01– 5.63)
2019	14	2.24 (0.87– 3.61)	41	5.93 (3.85-8.01)	55	4.09 (2.84– 5.34)

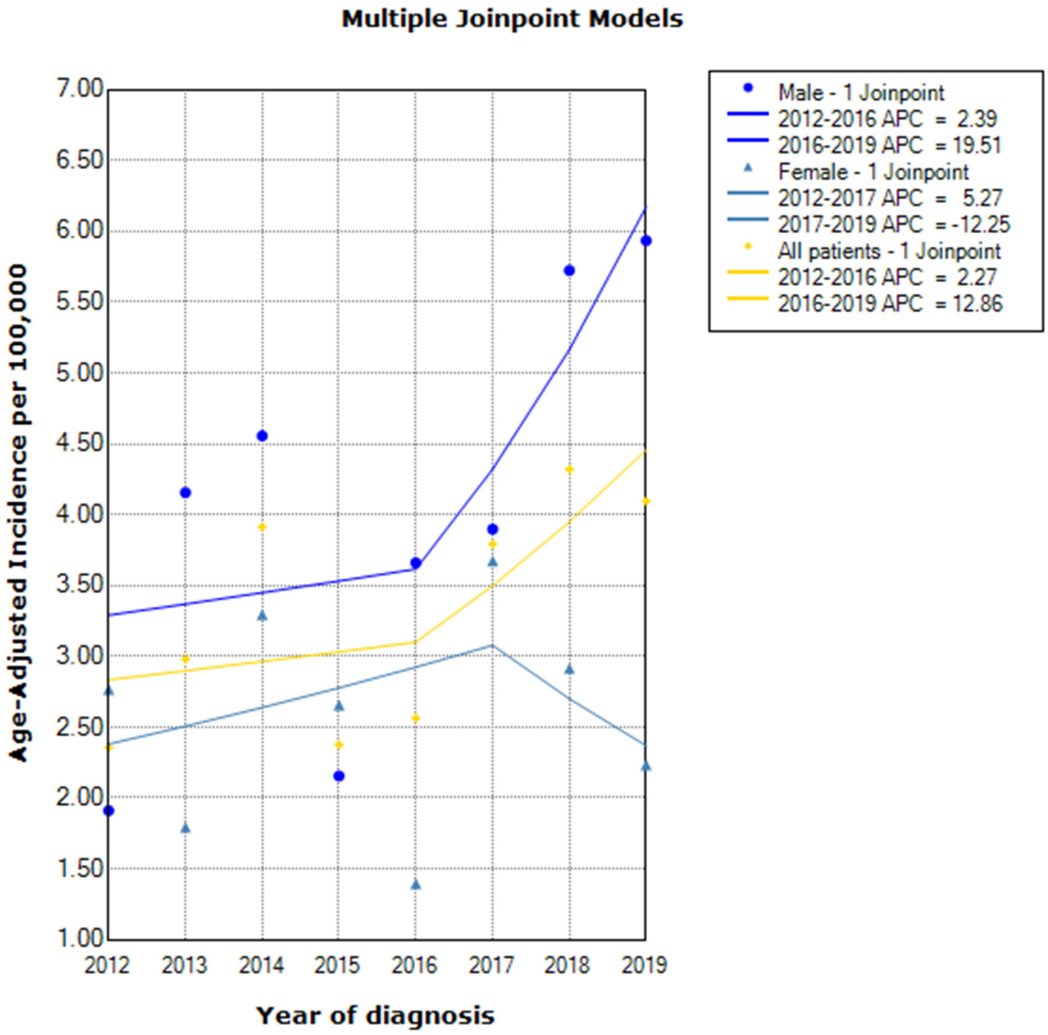

Figure 5-1: Age-adjusted incidence rates of HCC per 100 000 in Addis Ababa from 2012 to 2019 for females, males, and all patients.

Table 5-4: Annual percentage increases in HCC incidence from Joinpoint analysis by sex in Addis Ababa, Ethiopia 2012-2019**.**

Group	Joinpoint Segment	APC	95% CI	P-value
All Male	2012-2016	2.40	-50.50 to 111.70	0.92
	2016-2019	19.50	-40.1 to 138.5	0.47
All Female	2012-2017	5.30	-27.3 to 52.3	0.68
	2017-2019	-12.30	-80.50 to 295.30	0.80
All patients	2012-2016	2.30	-30.20 to49.70	0.86
	2016-2019	12.90	-26.10 to 72.30	0.43

APC, annual percentage change; HCC, hepatocellular carcinoma; 95% CI, 95% confidence interval.

5.2.3.4 Trends in hepatocellular carcinoma incidence in men and women

An increase in HCC incidence in men from 2012 to 2019 was observed (Table 5-3). The incidence rate in 2012 for men was 1.91 (95% CI: 0.48-3.34) compared with 5.93 per 100, 000 in 2019 (95% CI: 3.85-8.01) (p< 0.05) (Table 5-3). Piecewise linear regression identified non-significant positive APC without any joinpoints in men for the periods 2012-2016 (APC = 2.40%, 95% CI: -50.5 - 111.7; p= 0.92) and 2017-2019 (APC = 19.50%, 95% CI: -40.1 - 138.5, p = 0.47) (Table 5-4, Figure 5-1). There was no statistically significant increase in AAPC in men during the study period (AAPC 9.4 %, 95% CI: -20.1 - 49.8; p = 0.57) (Table 5-4, Figure 5-1).

In women, piecewise linear regression revealed a non-significant increase in incidence from 2012 to 2017 (APC = 5.27 %, 95% CI: -27.3 – 52.341.70, P = 0.80), followed by a decrease from 2017 to 2019 (APC = -12.25 %, 95% CI: -80.50- 295.30, P = 0.08) (Table 5-4, Figure 5-1).

5.2.3.5 Trends in hepatocellular carcinoma incidence by age

Overall, patients aged 55 and older had a significantly higher incidence of HCC (9.60 per 100 000; 95% CI: 5.97-13.23) than those aged 35-54 (2.70 per 100 000; 95% CI: 1.62-3.78) and under 35

(0.18 per 100 000; 95% CI: 0.00-0.36) in 2019 (Table 5-5). In males, the highest incidence rate was in 2018 among those over the age of 54 (16.13 per 100 000; 95% CI: 9.39-22.87), and the lowest was in 2012 among those under the age of 35 (0.1 per 100 000; 95% CI:-0.10-0.30). From 2012 to 2019, the incidence of HCC increased among males aged 35-54, under 35, or over 54. Similarly, the incidence of HCC increased in total patients aged 35-54, less than 35, or over 54 from 2012 to 2019. There was a decrease in the incidence of HCC among females aged 35-54 and over 54 between 2012 and 2019 (Table 5-5).

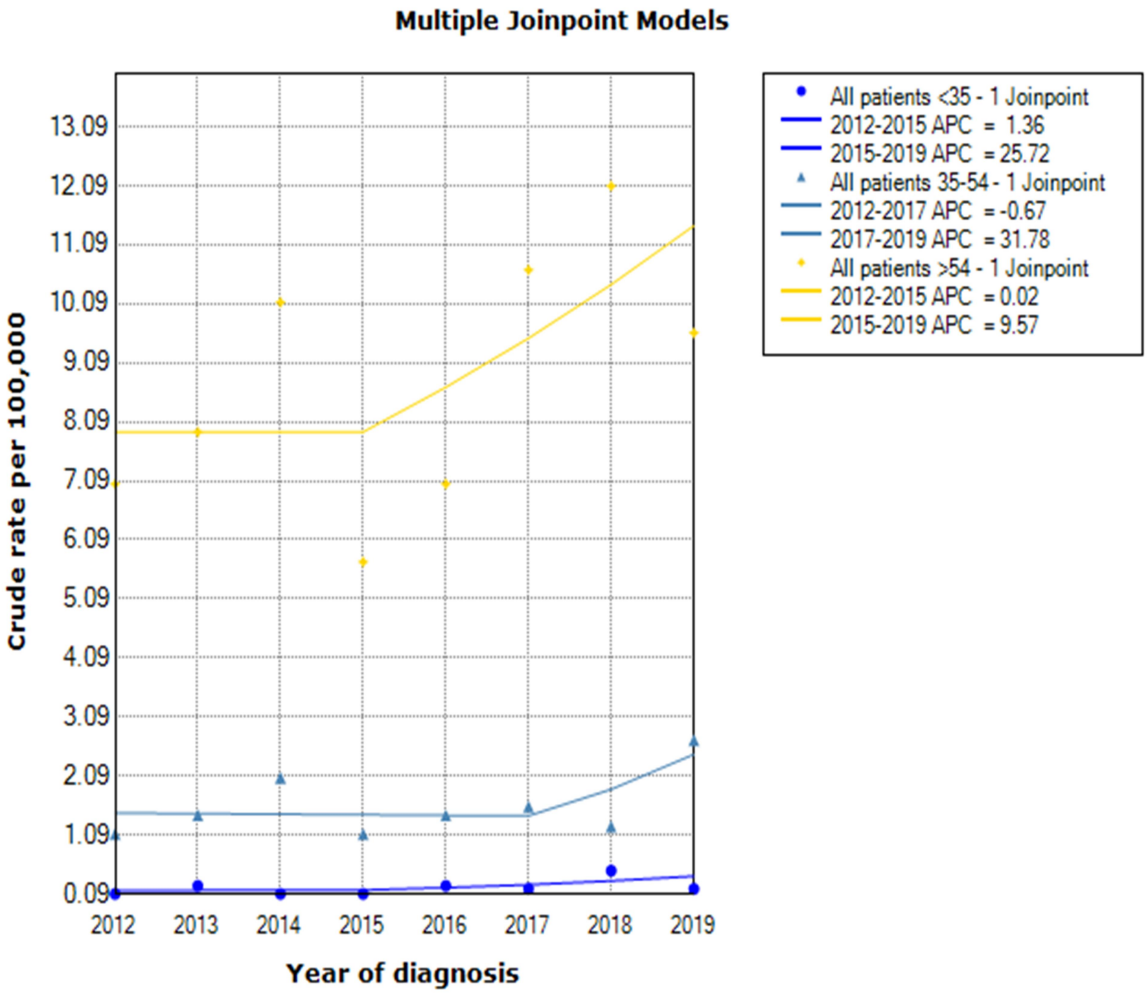

Figure 5-2: Crude incidence rates of HCC for all patients by age category 2012 to 2019. APC; annual percentage change

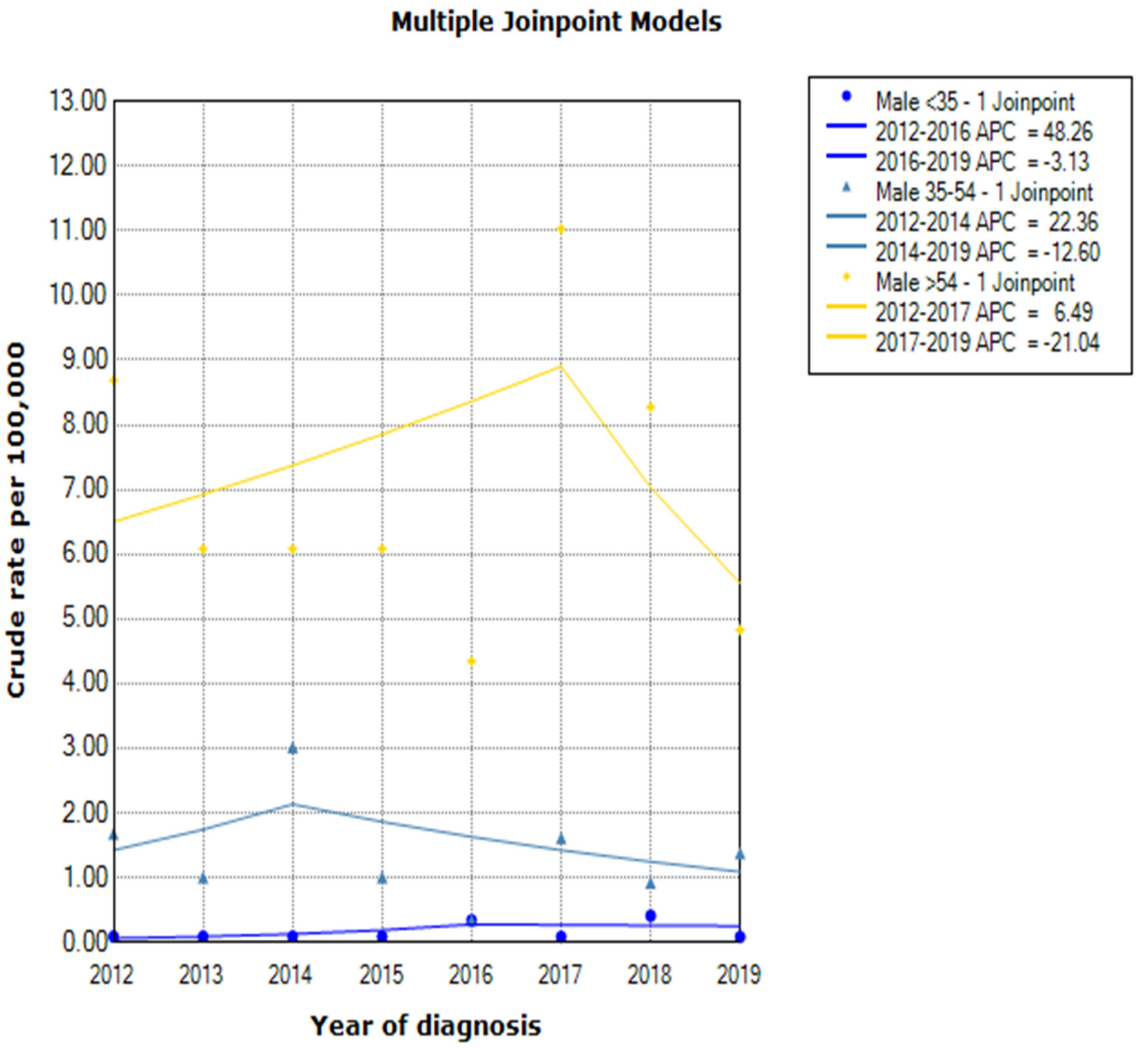

Figure 5-3: Crude incidence rates of HCC for males by age category 2012 to 2019. APC; annual percentage change

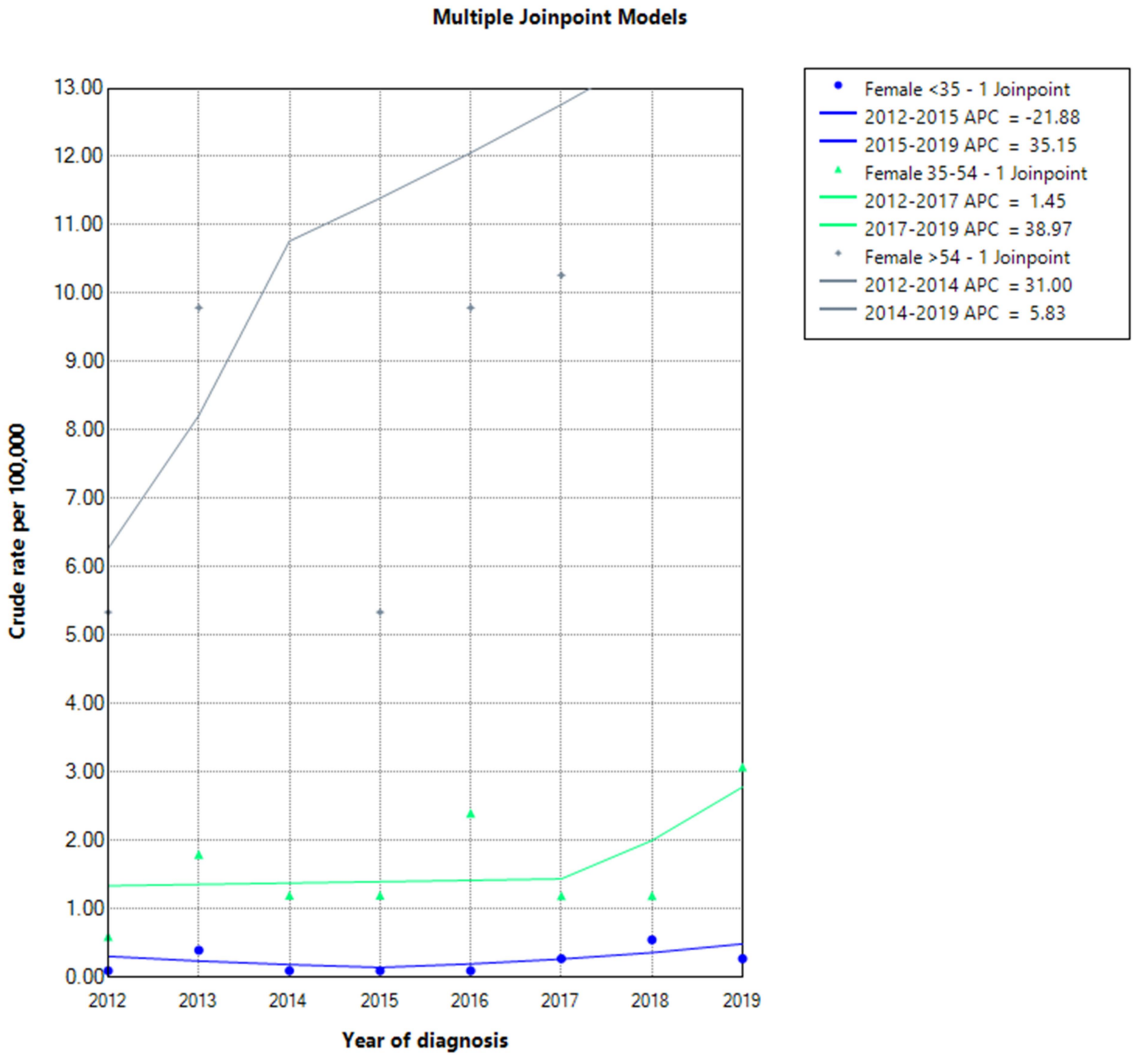

Figure 5-4: Crude incidence rates of HCC for females by age category 2012 to 2019.

Table 5-5: Number of HCC cases and incidence rates by age and year in Addis Ababa, Ethiopia 2012-2019

	All Patients <35y		All Patients 35-54y		All Patients > 54y	
Year	**Number of New Cases**	**Incidence (95% CI)**	**Number of New Cases**	**Incidence (95% CI)**	**Number of New Cases**	**Incidence (95% CI)**
2012	2	0.09 (-0.03 - 0.21)	7	1.11 (0.29-1.93)	16	7.04 (3.59-10.49)
2013	5	0.23 (0.03 – 0.43)	9	1.43 (0.49-2.37)	18	7.91 (11.58-4.24)
2014	2	0.09 (-0.03to 0.21)	13	2.06 (0.94-3.18)	23	10.11 (5.97-14.25)
2015	2	0.09 (-0.03to 0.21)	7	1.11(0.29-1.93)	13	5.72 (2.60-8.84)
2016	5	0.23 (0.03to 0.43)	9	1.43 (0.49-2.37)	16	7.04 (3.59-10.94)
2017	4	0.18 (0.00-0.36)	14	1.57 (0.75-2.39)	30	10.66 (6.84-14.48)
2018	11	0.49 (0.20-0.78)	11	1.24 (0.51-1.97)	34	12.08 (8.02-16.14)
2019	4	0.18 (0.00-0.36)	24	2.70 (1.62 – 3.78)	27	9.60 (5.97-13.23)

95% CI, 95% confidence interval**.**

In males, piecewise linear regression identified positive APC without any joinpoints in all age groups except for those under 35, where APC was negative for 2012-2015 (APC-21.9, 95% CI: -95.8 to 1353.7, P = 0.81; Table 5-6). Piecewise linear regression by age group showed non-significant positive APC in total patients aged under 35, 35-55, and over 54, except those aged 35-54, who showed a negative non-significant APC for 2012-2017 (APC -0.7%, 95 CI: -28.6 to 38.1, p= 0.95) (Table 5-6, Figure 5-3). Piecewise linear regression in females also identified a positive APC without any joinpoints in those aged less than 35 (2012-2016: 48.3, 95% CI: -69.5 to 620.3, P = 0.49), 35-54 (2012-2014: 22.4, 95% CI: -85.3 to 917.4, P = 0.78) and over 54 (2012-2017: 6.5, 95% CI: -6.2 to 21.0, P = 0.21; 2017-2019: 14.4, 95% CI: -52.7 to 31.7, P = 0.24), and a negative APC with no joinpoints in those aged less than 35 (2012-2016: -3.1, 95% CI: -92.0 to 1079.2, P = 0.97) and 35-54 (2014-2019: -12, 95% CI: -45.7 to 40.7, P = 0.43) (Table 5-6, Figure 5-4). A positive but non-statistically significant AAPC was found in all patients under the age of 35, 35-54,

and over 55, with those under the age of 35 having the highest positive AAPC (14.6%, 95 CI: -44.1 to 135.0, p=0.71; Table 5-6).

Table 5-6: Annual percentage increases in HCC incidence from Joinpoint analysis by age in Addis Ababa, Ethiopia 2012-2019

Age groups	Joinpoint Segment	APC (95% CI)	P-value	AAPC (95% CI)	P-value
All patients	2012-2016	2.50 (- 32.70-56.10)	0.90		
	2016-2019	14.40 (-28.40 - 82.80)	0.43	11.30 (-18.30 - 51.60)	0.49
<35	2012-2015	1.4 (-90.7 -1002.4)	0.99	14.6 (-44.1 - 135.0)	0.71
	2015-2019	25.7 (-52.7 - 234.2)	0.51		
35-54	2012-2017	-0.7 (-28.6- 38.1)	0.95	7.7 (-15.1 - 36.6)	0.52
	2017-2019	31.8 (-54.9 - 285.2)	0.47		
> 54	2012-2014	0.0 (-61.1 - 341.6)	0.99	5.4 (-10.6 - 24.1)	0.53
	2014-2019	9.6 (-15.2 - 32.2)	0.39		
All Males	2012-2017	5.40 (- 34.00 - 68.40)	0.70		
	2017-2019	27.50 (- 65.60 -372.50)	0.60	-0.40 (-0.00 - 29.10)	0.97
<35	2012-2015	- 21.9 (-95.8 - 1353.7)	0.81	23.5 (-47 - 192.8)	0.63
	2015-2019	35.1 (-64.2 - 410.0)	0.52		
35-54	2012-2017	1.5 (-33.0 - 53.6)	0.92	-3.8 (-37.3 - 47.5)	0.86
	2017-2019	39.0 (-60.2 - 385.4)	0.46		
> 54	2012-2014	31.0 (-61.1 - 341.6)	0.53	-2.2 (-12.1- 8.7)	0.66
	2014-2019	5.8 (-15.2- 32.2)	0.48		
All Females	2012-2017	3.30 (- 24.70 - 41.70)	0.80	-0.40 (-0.00 - 29.10)	0.97
	2017-2019	-8.90 (- 73.70 - 215.90)	0.80		
<35	2012-2016	48.3 (-69.5 - 620.3)	0.49	23.5 (-47 - 192.8)	0.63
	2016-2019	-3.1 (-92.0 - 1079.2)	0.97		
35-54	2012-2014	22.4 (-85.3 - 917.4)	0.78	-3.8 (-37.3 - 47.5)	0.86
	2014-2019	-12 (-45.7 - 40.7)	0.43		
> 54	2012-2017	6.5 (-6.2 - 21.0)	0.21	-2.2 (-12.1 - 8.7)	0.66

APC, annual percentage change; AAPC, average annual percentage change; HCC, hepatocellular carcinoma; 95% CI, 95% confidence interval.

5.1.4 Discussion

The study aimed to characterize the incidence and trend of HCC diagnosis in Addis Ababa, Ethiopia, from 2012 to 2019. This was accomplished through the AACCR, which collects data from all health facilities in Addis Ababa that provide cancer screening and treatment services. Except for data for 2012, the HCC incidence in Addis Ababa was higher in men than in women throughout the study period, and incidence rates increased significantly for men over the timeframe studied. This finding is consistent with other African countries' findings that the incidence of HCC is higher in men than in women (15, 554-556).

Men had higher HCC rates than women in this study, which could be due to a variety of factors. In SSA, men are more likely than women to have chronic HBV infection (roughly twice that of females) (557). A higher HBV infection was also reported in men than women in Ethiopia and Addis Ababa (31, 558). Men in SSA also have a higher consumption of iron-rich home-brewed alcohol and a lack of menstruation, contributing to dietary iron overload (15, 559, 560). This is one of the factors contributing to HCC in Africans and may explain the increased risk of HCC development in men in this and previous African studies. Moreover, in Addis Ababa, the vast majority of injecting drug users are men, and many share needles and other injecting equipment (536, 561). However, in general, injection drug usage is quite low in Ethiopia, contributing little to the country's hepatitis prevalence (562-564).This could lead to an increase in the spread of HCV in men, making them more susceptible to HCC than women (565, 566). Male sex has been found to be a significant predictor of alcohol consumption in many populations (567-569), and a meta-analysis in Ethiopia found that the prevalence of alcohol consumption was higher in men (11.58%) than in women (1.21%), which may have contributed to the higher HCC in men (119).

The study found a high incidence of HCC in adults over the age of 54, which contrasted with data from SSA studies, which found a higher incidence of HCC in younger age groups (15). According to one study, the incidence was highest in people aged 35 to 45 in Uganda, and between 30 and 50 in another study (570, 571). In a Kenyan study, the incidence was highest in those 35 to 45 years of age (572), while in a second study (573), it was highest in people 30 to 40 years of age. Why our findings indicate a rise in HCC incidence in adults over the age of 54 (which includes

adults in middle age, older age, and the elderly) is unclear based on the current data. This may be a function of truly increased incidence in older adults or a function of greater screening and diagnosis in this age group in Addis Ababa. Older individuals are disproportionately more susceptible to non-communicable diseases (NCDs), such as cancer. Obtaining medical assistance for NCDs and other illnesses among the elderly in Ethiopia, on the other hand, has never been simple (574). This is primarily because the vast majority of them cannot afford medications or transportation to medical facilities (138, 575, 576). The Ethiopian government has a free medical service system for the poor, but it is not functioning properly (577, 578). Historically, patients who seek treatment at public health institutions usually have to purchase medications from private pharmacies or are referred to private laboratories, which charge more than equivalent public facilities (576). This may have made them less likely to visit healthcare facilities, resulting in missed cancer education that could have helped them take preventive measures at a younger age or at an older age where they were able to reduce exposure to HCC risk factors and avoid disease occurrence. The government has subsequently incorporated routine health education in public healthcare facilities across the country (172). Moreover, it has also been noted that the risk of various cancers increases with age due to a range of factors, such as lower immunity and a greater possibility of exposure to cancer risk factors as one gets older (245, 247, 579). HCC risk has also been reported to increase with age, as has the risk of other malignancies, due to decreasing immunity and a higher chance of exposure to risk factors such as HBV, HCV, and alcohol (245, 580). This could be one of the reasons for the higher HCC incidence in men in our study.

The majority of Ethiopian elders also don't have reliable income streams or sufficient governmental pensions (581, 582), and this directly affects healthcare (583, 584). Unreliable income streams prevent older people from engaging in healthcare-seeking behaviours, leading them to turn to alternative therapies or traditional medicine instead of evidence-based medical care (585). Several traditional medicines in the country are unproven in terms of efficacy and safety (576, 586). Moreover, various causes of poverty and unemployment in Ethiopia, such as HIV and AIDS, are on the rise, and many elderly people are obligated to care for orphaned or abandoned children (576,

587, 588). The financial struggles that older persons have are worsened by the fact that these children are almost always their grandchildren (576). The elderly may have been less inclined to visit medical facilities as a result of these factors, which may have decreased their chance to benefit from the cancer awareness education offered in the nation's medical facilities and ultimately raised their cancer incidence.

The rising importance of modifiable cancer risk factors, poorly designed referral systems, inadequate cancer diagnostic and treatment services could all be contributors to the rising incidence of HCC over the period 2012-2019 in Addis Ababa (105). Alternatively, the increased rates observed in this study may also be a function of better diagnosis rates, rather than true increases in incident cases. However, due to a lack of data on the specific type of diagnosis method used to identify each HCC case, this study was unable to determine whether the observed rate was due to differences in diagnosis methods or rates. The focus on increasing health education since 2016 may have prompted more residents in Addis Ababa to seek healthcare for symptoms related to HCC. Ongoing monitoring of incident cases, and consideration of qualitative investigations in those who seek care for HCC, will help to better understand the help-seeking behaviours of residents in Addis Ababa for HCC symptoms.

For future cancer control initiatives to be successful, cancer registration quality and coverage must be improved. The Addis Ababa City Cancer Registry lacks information on several important variables, such as cancer diagnosis stage and cancer mortality, and calls for higher standards for cancer registration. The observed increase in the incidence of HCC in Addis Ababa further points to the need for the establishment of cancer registry sites throughout the country of Ethiopia to better quantify incident cases in the future. The establishment of cancer registries in various regions of Ethiopia will aid in accurately quantifying the disease's burden in various parts of the country, which is required for the development of effective cancer control plans. To accurately pinpoint the reasons behind the rising incidence of HCC and develop the most effective preventive measures, more research is necessary. This may include assessing the disease's risk factors, public awareness of the disease, and gaps in cancer policies or control plans. Furthermore, even though non-communicable diseases are on the rise in Ethiopia, the country's health system is

concentrated on containing communicable diseases. This contributes to a concealed epidemic of non-communicable diseases and adds to the nation's "double burden of disease" (105). Therefore, this might be a contributing factor to Addis Ababa's rising HCC incidence.

These findings should be considered in the context of some limitations. Accurately estimating cancer incidence depends on whether registration is complete. The AACCR gathers information from all medical facilities in the city that offer cancer diagnosis and treatment, however, some populations, especially the elderly, may have trouble accessing care for a variety of reasons, meaning registry data may not reflect true prevalence rates in the community or may be higher than what is observed in this study (576). Moreover, the registry lacks information on several factors, such as the stage of diagnosis that could aid in explaining the observed cancer incidence in the city. This study did not employ a sample size determination approach and instead took into account all cases due to the modest number of HCC cases that were reported to the cancer registry throughout the study period. The results of the non-significance tests and the broader confidence intervals for some of our estimations are likely explained by the small sample size. Any inferences made as a result of these findings should therefore be verified using a bigger sample size in the future. Some suggestions are made for future research into the incidence and changes in the incidence of HCC in Addis Ababa. Future research should look into the effects of various socioeconomic factors on HCC incidence and trends, the effect of the stage of diagnosis on HCC incidence, and how socioeconomic factors influence HCC diagnosis stage. Another suggestion for future research is to replicate this study using larger sample sizes in both rural and urban settings.

This study's higher prevalence of HCC among the elderly emphasizes the significance of bolstering community support, especially for the elderly. Traditional Ethiopian social organizations like “*mahber*”, a form of a religious organization, and “*iddir”*, a type of burial society, offer a range of community support services, including financial aid to older individuals who fall ill or experience other challenges (576). However, as a result of a variety of factors, including the community's inability to fund them, these institutions are becoming less functional (576). As a result, the government should encourage, and when necessary, engage in and guide income-generating activities for these institutions for them to function properly and provide better care for the elderly.

Therefore, to ensure that these institutions operate efficiently and can provide better care for the elderly, the government should encourage, participate in, and/or direct income-generating activities for them as needed. These organizations can also educate the elderly and other community groups about HCC and HCC preventive methods. Through these organizations, it may also be possible to educate the elderly and other groups of society about the link between HBV, HCV, alcohol, tobacco, and other risk factors for HCC and the risk of HCC. It is also possible to educate people using the organizations on the importance of early HCC detection and screening in disease prevention.

5.1.5 Conclusions and recommendations

This study examined the incidence and trends of HCC in Addis Ababa, Ethiopia's capital, over eight years. With the exception of 2012 data, men had a higher incidence of HCC than women in Addis Ababa throughout the study. HCC was also significantly more common in people over the age of 54 in 2019 than in those between the ages of 35 and 54 and under the age of 35. HCC incidence increased in men and total patients from 2012 to 2019, but decreased in women from 2012 to 2017 before increasing again from 2017 to 2019.

This study's high incidence of HCC among the elderly emphasizes the significance of focusing on HCC prevention and control, especially among Ethiopia's old population and men who are at high risk of developing the disease, which was not the case in the past (172, 576). Government efforts should include offering communities ongoing health education regarding age-related health risks, such as cancer. Aging populations should be considered in all cancer prevention and control programs, including those for HCC, by non-governmental organizations (NGOs) working on health in the nation. The government should also make an effort to solve the financial concerns that older people face because doing so indirectly solves their health problems. This includes supporting, participating in, and directing the aged in income-generating activities when appropriate.

Moreover, the government and NGOs in the nation could promote the medical needs of the elderly. This is crucial for decision-makers to understand the issue and act accordingly with appropriate public health interventions. Institutes in the nation that diagnose and treat cancer

should also pay close attention to NCDs, especially those that impact the elderly. Policies and plans for managing NCDs are appropriately put into practice. They should also put in place measures to increase the ability of their medical staff to care for the elderly, as well as make sure that essential drugs and medical supplies are accessible for NCDs.

The finding that HCC incidence was higher in men than in women in Addis Ababa also highlights the importance of raising men's cancer awareness, which will encourage them to seek medical attention or live a healthier lifestyle, lowering cancer incidence in men. Thus, it is recommended that professionals provide more cancer information and education to men in areas where men are more easily accessible, as men may not visit public hospitals as frequently as women. Increased HBV vaccination in men, as well as encouraging men to be tested and treated for HCV, not smoke or quit if they do, and avoid excessive alcohol consumption, may all help reduce HCC incidence in men. Screening and surveillance programs for HCC also help to reduce the disease burden in the country. Alpha-fetoprotein (AFP) testing in the blood, imaging tests such an ultrasound, computed tomography (CT or CAT) scan, or magnetic resonance imaging (MRI), are all possible screening options.

These findings have implications for community-based public health strategies to reduce prevalence. Improving HCC prevention and control, strengthening community support for the elderly, addressing the community's economic problems, particularly those affecting the elderly, raising men's cancer awareness, and advocating for the elderly's healthcare needs are all possibilities.

SSA has reported a high rate of hepatitis infection transmission through unsafe blood transfusions (589). For example, in SSA, the overall HBV and HCV risk from blood transfusion is estimated to be 4.3 and 2.5 infections per 100,000, respectively (590). HBV has been reported among blood donors (8.4%) in Ethiopia, a sub-Saharan country (591). Harmful traditional practices that could increase hepatitis transmission are also common in the country, including home dental extractions, unsterile barbershop shaving, and traditional surgery (592). Since the above- mentioned factors may result in hepatitis transmission, which plays a major role in HCC development; efforts should

be made to avoid hepatitis transmission through unsafe blood transfusions and harmful traditional practices, especially among the elderly.

Although a statistically high incidence of HCC was not found in this study's young participants, the number of HCC in this group is high. This could be attributed to perinatal HBV and HCV infection, aflatoxin exposure, a lack of HBV and HCV therapy, insufficient screening, and prophylaxis during pregnancy. Addressing these challenges is thus needed in order to lower the number of cases in these groups.

Aim Four: To determine the incidence of HBV and/or HCV among HCC patients in Addis Ababa, Ethiopia

5.2 Hepatitis B and C infections in hepatocellular carcinoma patients in Addis Ababa, Ethiopia

5.2.1 Background

The burden of hepatocellular carcinoma (HCC) is rising worldwide (35, 259, 593, 594). Several factors are said to have contributed to an increase in the burden of HCC on a global scale. One of the causes is the increase in the major HCC risk factors, including chronic alcohol use, NAFLD, and aflatoxin B1. Among the major risk factors for cancer, HBV and HCV were thought to be the main reasons for variation in HCC incidence between populations (54).

The processes through which HBV and HCV increase the risk of developing HCC have been the subject of various investigations in recent years. Studies show that HBV and HCV can cause HCC both directly and indirectly (595). They may directly damage the liver or may indirectly block or activate several host-related mechanisms that result in HCC. Direct liver damage from HBV and HCV causes severe fibrosis, cirrhosis, and eventually HCC (596). In the indirect pathway, HBV damages hepatocytes over time, causing inflammation and hepatocyte turnover. Overall, this leads to a build-up of potentially crucial mutations in the hepatocyte genome, which induces malignant

transformation and clonal growth and, ultimately, results in HCC (287, 597). Moreover, the DNA virus HBV can integrate its genes, including the hepatitis B virus X antigen (HBx), into the host genome, which can cause cirrhosis and hepatocarcinogenesis (598). Unlike HBV, which integrates into the host gene, HCV is an RNA virus. Therefore, it predominantly causes HCC by causing hepatic injury and inflammation, which ultimately results in cirrhosis and subsequently HCC. HCC can occur in HCV patients with non-cirrhotic chronic hepatitis C, proving that the virus is inherently carcinogenic (599).

The majority of cancer cases are connected to cirrhosis induced by chronic hepatitis B or C virus infection (273, 274). The type of hepatitis virus that is predominant in a community, the time the virus spreads, and the age of the persons infected by the virus impact the temporal trend of cancer as well as its age, gender, and race-specific rates (54). When a person has HBV or HCV infection, host genetics, viral factors, and environment can influence their risk of developing HCC. Other contributing factors include poor HCC prevention/control programs or policies and a lack of public awareness of HCC signs and risk factors (117, 600, 601).

The burden of HCC is also rising in low-income countries (LICs) due to the rise in the major risk factors of the disease. HCC is one of the three most prevalent malignancies in LICs, where 80% of all HCC cases worldwide are found (99, 235). Low-income areas with high HCC incidences include Eastern and South-Eastern Asia (except for Macau, Singapore, South Korea, Japan, Taiwan, and Hong Kong) and nearly all of SSA (99, 235). The burden of HCC is increasing in LICs mainly because two of its major risk factors in the world, namely, HBV and HCV, occur far more often in these countries (235, 237). The weak health system, scarcity of resources for optimal management of the disease, and the high burden of communicable diseases in these countries also contributed to the increasing HCC incidence (602, 603).

In Ethiopia, determining the burden of HCC/cancer and other risk factors including HCV and HBV in the country received little attention (117). Only a few non-recent studies with methodological and other flaws determined the burden of HCC and HBV/HCV among cancer patients in Ethiopia, and the current relevance of cancer risk factors in cancer development is unknown (110, 117).

However, Ethiopia, like LICs, has a weak health system, a paucity of resources for appropriate disease management, and a high burden of communicable diseases, all of which are likely to raise HCC incidence (117).

Moreover, over the last few decades, there has been an effort in Ethiopia to determine the burden of HBV and HCV on the general public. For instance, Ethiopia is classified as a hepatitis-endemic country by the WHO, and over 10 million Ethiopians have been reported to be infected with HBV (160-162). Chronic hepatitis B and C viral infections are also responsible for more than 60% of chronic liver diseases in the country (163). However, little attention has been made to determining the burden of HBV and HCV on HCC/cancer development, which could have aided the understanding of the disease and the development of cancer control planning in the country (117).

It has also been reported that body alteration that includes skin penetration, such as tattooing or piercing, puts persons at risk of getting blood-borne diseases (604, 605). Blood-borne illnesses are frequently connected with hepatitis B, Tetanus, hepatitis C, Septicaemia, and human immunodeficiency viruses (HIV) (606). Tattoo complications are believed to affect 2-3% of people(537). To reduce the risk of infection, strict adherence to infection control standards or guidelines is recommended during the tattooing and/or body piercing procedure (537). However, Ethiopia's population has been urbanizing steadily over the past few decades. Following this, among teenagers and young adults, body alteration has suddenly become trendy (537, 607). Teenagers' use of body piercing and tattoos as a fashion statement or to enhance their self-image has expanded in recent years. The tattoo and piercing industries have expanded quickly, but they are not systematically regulated. Hepatitis B and C infections were also linked to a history of body piercing and tattooing in Ethiopia (608, 609). This is also expected to increase the spread of HBV and HCV in Ethiopia, as well as increase the prevalence of HCC in the country (537).

Finally, in many regions of the developing world, injecting drug use contributes considerably to the spread of various infectious diseases, including HBV and HCV (610-612). The sharing of injection needles among drug users is one of the major routes for the spread of HBV, HCV, and other infectious diseases (613-615). In Ethiopia, the prevalence of injectable drug users is rising, particularly in Addis Ababa, the country's capital city (536, 561). The majority of injecting drug

users in Addis Ababa share needles and other types of injecting equipment (536). This may increase the spread of HCV and HBV making people more vulnerable to HCC.

Despite the high chance that the abovementioned and other factors increase the burden of HCC in Ethiopia by increasing the prevalence of HBV and HCV in HCC patients, little attention has been paid to determining the burden of the viruses in HCC patients in the country. However, such studies would have helped to reduce the burden of HCC in the country and also serve as baseline data for cancer control planning in the country. Therefore, this sub-chapter examined the incidence of hepatitis B and C virus infections in HCC patients in Addis Ababa, Ethiopia.

5.2.2 Method Summary

5.2.2.1 Study design, study population, and eligibility criteria

The methods employed in this sub-chapter are detailed in chapter three of this thesis. Briefly, this sub-chapter employed a retrospective design to assess the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) among hepatocellular carcinoma (HCC) patients in Addis Ababa, Ethiopia. The study population included all diagnosed with HCC at Black Lion Specialized Hospital between 2012 and 2020. The inclusion criteria for this study include having HCC (ICD-O-3: C22.0), residing in Addis Ababa for at least six months, HBV and HCV diagnosis status, the date and method of HCC diagnosis, age, gender, HCC morphology, and residency.

5.2.2.2 Study setting and data collection

The study was conducted in Addis Ababa, Ethiopia, at the Tikur Anbessa Specialized Hospital 's cancer diagnosis and treatment centre. Medical records of HCC patients diagnosed at this hospital from 2012 to 2020 were reviewed to determine the patients' HBV and HCV exposure history.

Due to data availability and collection limitations, we examined the positivity of HBV and HCV in HCC patients using data from Tikur Anbessa Specialized Hospital. However, many of the patients diagnosed at this hospital during the study period did not have their HBV and HCV exposure status recorded in their medical records. So, to increase the sample size and strengthen the power of our analysis, we included HCC patients diagnosed at the same hospital in 2020. This is why the

general characteristics of patients in this sub-chapter differ from those of patients in sub-chapter one of this chapter.

Accordingly, we collected data on the date and method of HBV (defined by ICD-9 code: 070.22, 070.23, 070.32, 070.33, V02.61 & ICD-10 code: B18.1, B18.0, Z22.51) and HCV (defined by ICD-9 code: 070.41, 070.44, 070.51, 070.54, 070.70, V02.62 & ICD-10 code: B17.11, B18.2, B17.10, B18.2, B19.20, Z22.52) diagnosis, as well as data on age, gender, HCC morphology/ topography, and place of residence from 198 HCC patients diagnosed at Tikur Anbessa Specialized Hospital from 2012 to 2020. The same safety and confidentiality procedure used in sub-chapter one of this chapter for HCC cases identified through AACCR was used in this section.

5.2.2.3 Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Armonk, NY) was used to enter and analyse the data. The odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship of age and gender with hepatitis B and C infections were calculated using logistic regression models. Statistics were considered significant when the p-value was <0.05. Due to the small sample size, the difference in HBV and HCV in HCC patients was estimated by categorizing patients into two age groups: less than or equal to 50 years of age and 50 years of age and over. Moreover, the median age of HCC diagnosis in SSA is around 50 years, and dividing the small number of cases in this study into two at 50 years may aid in determining whether there are differences in HCC based on HBV and HCV exposure status. Only HBV and HCV infection, as well as the age and sex of the participants, could be extracted from the study participants' medical records. These variables were included in the logistic regression analysis to determine HBV and HCV infection differences in HCC based on age and sex. It would have been preferable if data on other confounders had been extracted from participants' medical records and included in the analysis.

5.2.3 Results

5.2.3.1 The general characteristics of the study participants

The study population included 198 patients diagnosed with HCC in Addis Ababa, Ethiopia's capital, between 2012 and 2020. Their average age was 49.3 years, and 47.9% were 50 years or older. Disease stage was reported in 62.1% of cases, with 20.2% having an early-stage disease (stage I) and 24.2% had stage II (Fig 5-7). Moreover, more than half of patients had been diagnosed with advanced disease—that is, stage III and IV were 26.6% and 28.2%, respectively (Fig 5-7).

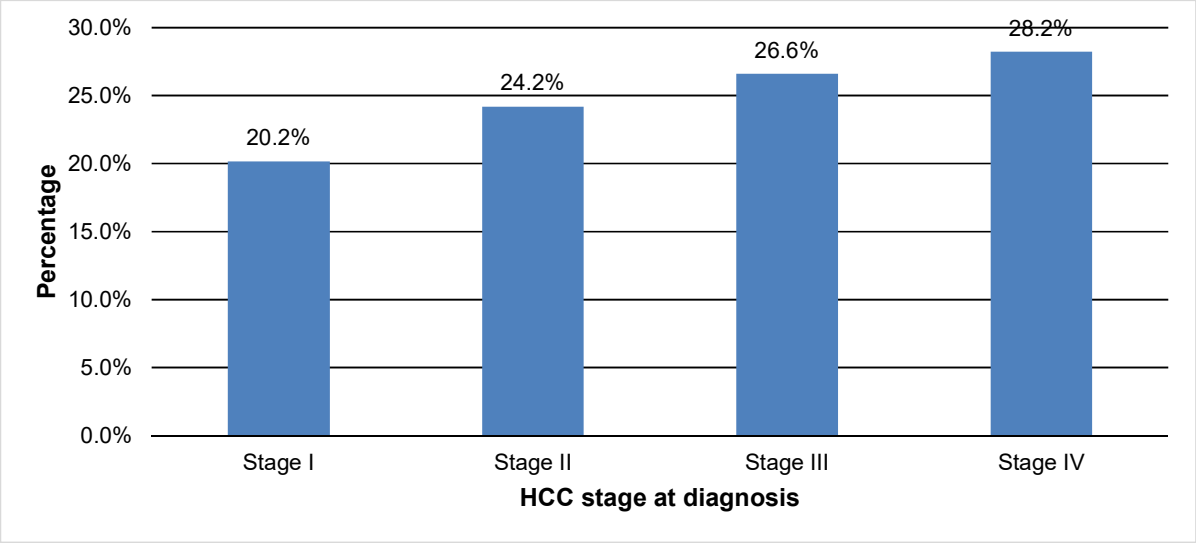

Figure 5-5: Distribution of hepatocellular carcinoma cases by stage at diagnosis.

HCC, hepatocellular carcinoma

5.2.3.2 Hepatocellular carcinoma and stage at diagnosis by gender

The sex distribution of HCC stage at diagnosis is shown in Figure 5-7. The proportion of male patients with stage III and IV was 15.3% and 21.0%, respectively. In females, 9.7% of patients were in stage III, and 3% were in stage IV. 12.1% and 15.3% of male patients were in stages I and II, respectively. The corresponding figures for females were 8.1% and 8.9%.

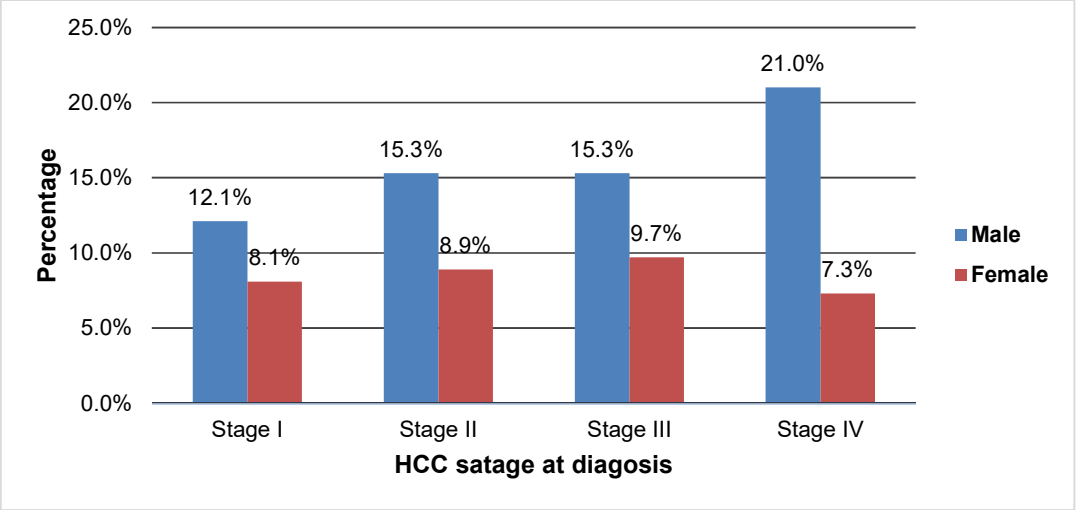

Figure 5-6: Distribution of hepatocellular carcinoma stages at diagnosis by sex.

HCC, hepatocellular carcinoma.

Figure 5-7shows the age distribution of HCC stage at diagnosis. Except for stage I, the proportion of patients in all stages was higher in those aged 50 and older than in those aged 50 and younger. For patients ≤50, the proportion of cases with stage III and IV was 50% and 39.0%, respectively. The corresponding figures for patients over the age of 50 were 8.9% and 19.4%. The percentage of patients under the age of 50 in stage I was 11.3%, and 19.4% in stage II. 23.0% of patients who are aged less than or equal to 50 were with stage I.

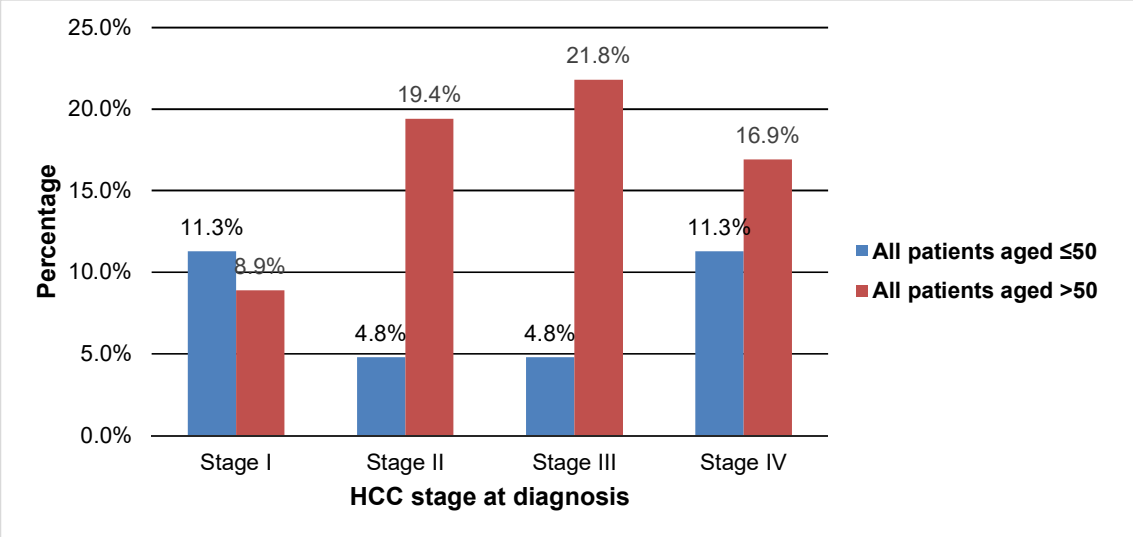

Figure 5-7: Distribution of hepatocellular carcinoma stages at diagnosis by age.

HCC, hepatocellular carcinoma.

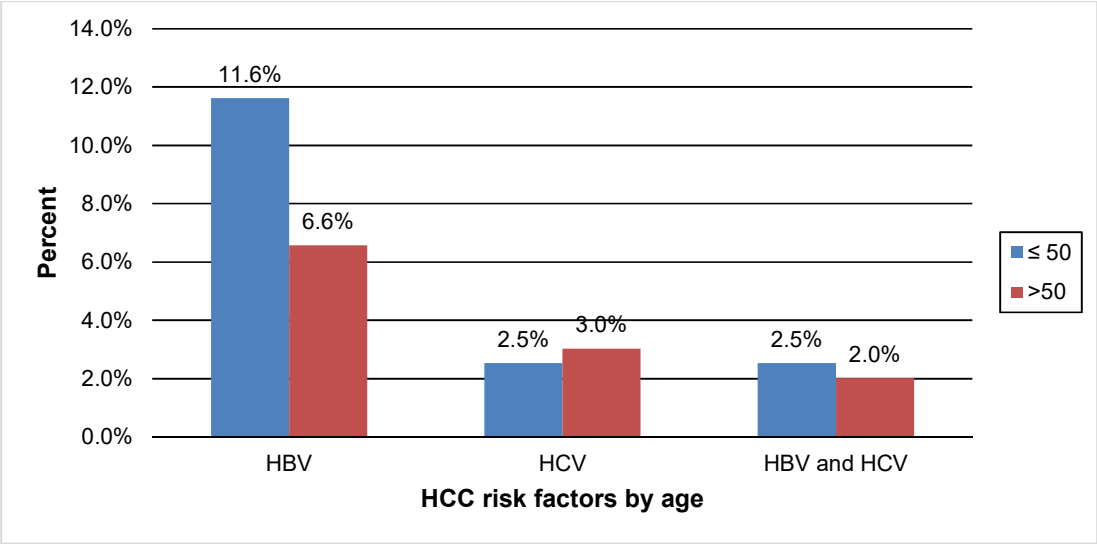

Figure 5-8: Positivity rate of HBV and/or HCV among HCC patients by age.

Note: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

A total of 65 (32.8%) HCC patients tested positive for anti-HBV, with 46 (23.2%) being men and the remaining 19 (9.6%) being women. Those who tested positive for anti-HBV had an average age of 46.42 years, with a range of 20-67 years. There were 18 (9.1%) men and 17 (8.6%) women among the 35 patients who tested positive for anti-HCV. Co-infection with HBV and HCV was found in 21 (10.6%) patients.

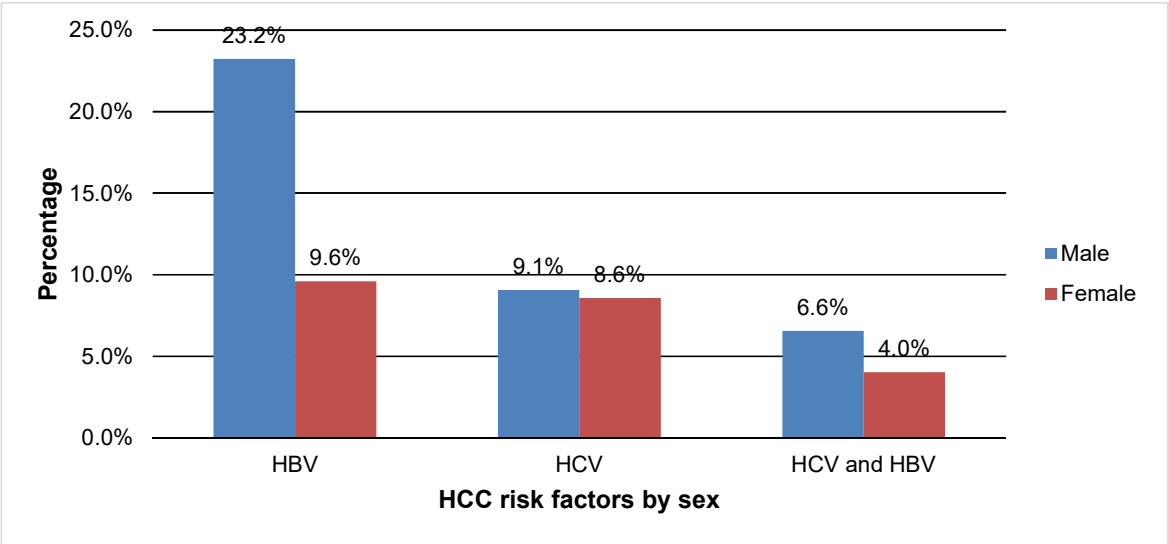

Figure 5-9: Incidence of HBV and/or HCV among HCC patients by sex.

Note: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

The percentage of HBV cases was higher in patients under the age of 50 (11.6%) than in those over the age of 50 (6.6%). In contrast, patients aged 50 and younger (2.5%) had slightly fewer HCV cases than those aged 50 or older (3.0%). HBV and HCV co-infection were higher in 2.5% of patients aged 50 and under, and 2.0% of patients aged 50 and over.

5.2.3.3 The odds of HBV and HCV in hepatocellular carcinoma patients by age and gender

Table 5-7 shows the odds of HCV and HCV infections in HCC patients based on age and gender. In men, the odds of HBV and HCV infection were 0.6(95 CI: 0.30-1.32, p=0.22) and 1.9(95 CI: 1.02-3.73, *p*=0.04), respectively, when compared to women. In comparison to patients aged 60 and older, the odds of HBV infection were 1.2 (95 CI: 0.43-3.46, p=0.69) in those under 30, and 1.6 (95 CI: 0.71-3.60, p=0.26) in those 30 to 60. In patients aged 30 to 60, the odds of HCV infection was 0.5 (95 CI: 0.25-0.99, p=0.04).

Table 5-7: The odds of HBV and HCV in HCC patients by age and gender.

		HBV		HCV	
Variables		**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
Gender					
	Female	1.00		1.00	
	Male	0.6 (0.30-1.32)	0.22	1.9 (1.02-3.73)	0.04*
Age					
	≥60	1.00		1.00	
	30-60	1.6 (0.71-3.60)	0.26	0.5 (0.25-0.99)	0.04*
	<30	1.2 (0.43-3.46)	0.69	1.7 (0.76-3.77)	0.19

95% CI, 95% confidence interval; AOR, adjusted odds ratio;* Significant difference; HBV hepatitis B virus; HCV, hepatitis C virus.

5.2.4 Discussion

HBV and HCV are common in Addis Ababa among patients diagnosed with HCC. More than half of the HCC patients in this study were diagnosed in the late stages—stages III and IV, and a higher prevalence recorded in males for both viruses.

In this study, 32.8% and 17.7% of study participants tested positive for HBV and HCV, respectively (616). In line with the findings of other studies conducted in different countries, this study found that male HCC patients had a higher percentage of HBV, HCV, or both viral infection than female HCC patients (617, 618). In this study, men were found to be 1.94 times more likely than women to have HCV. However, while there were more male HBV patients than female HBV patients, the difference was not statistically significant. Overall, rates of HBV and HCV are lower than findings from Zimbabwe, where up to 48.3% of participants with HCC were positive for HBV, and up to 24% for HCV (33, 34). Patients aged 30 to 60 were 0.5 (95% CI: 0.25-0.99) times less likely to have HCV than those over 60. Together, these findings suggest that public health measures and initiatives to reduce rates of HBV and HCV may be an important priority, as both HBV and HCV are known to precede incident cases of HCC (54, 619).

HBV and HCV co-infection was also found in 10.6% of the participants, which was higher than in another African study (620, 621). There was no statistically significant difference in HBV and HCV co-infection between male and female patients, or between patients aged 50 and over and those under 50. Previous research, on the other hand, found that HBV and HCV coinfection was more common in men and those aged 30-39 (622, 623). This could be due to the small number of cases of HBV and HCV co-infection. In other countries, patients with coinfection were found to experience an annual incidence of HCC of 6.4%, HBV mono-infection of 2.0%, and HCV mono-infection of 3.8% (291, 292, 624).

Several factors may have led to Ethiopia's higher proportion of HBV and HCV co-infections than in other countries. Ethiopia is classified as a viral hepatitis-endemic country, with a recent prevalence of 7.4% HBV and 3.1% HCV (541). HBV and HCV are also endemic in Ethiopia, though the prevalence varies by region (625-627). The prevalence of injectable drug use is also increasing in

Ethiopia, and drug users in Ethiopia's capital city, Addis Ababa, have been reported to share needles and other injecting equipment, which accelerates the spread of HCV and HBV in the city (536). The prevalence of hepatitis C and B infections in Ethiopia is 7.4% and 3.14%, respectively (161). Chronic hepatitis C and B infections account for more than 60% of chronic liver diseases in the country(161). Moreover, body alteration, such as piercing and tattooing, is becoming more common in Ethiopia, and this trend is linked to an increase in the prevalence of HBV and HCV in the country (537, 625, 628).

Although our data did not allow us to evaluate the effect of HBV and HCV co-infection in increasing the odds of HCC, there is conflicting evidence in the broader literature (54). To date, no single large-scale study has been conducted to determine the risk of HCC in patients infected with both HBV and HCV (54). However, three meta-analyses were carried out to determine the odds of HCC due to HBV and HCV coinfection and found an association between HCC and HBV and HCV coinfection, as discussed in Chapter Four. In contrast, other studies have found no evidence of HBV-HCV synergism in HCC (55, 56). HCV has been shown to suppress HBV replication and lessen the risk of HCC in patients infected with both viruses (508). Similarly, HCV replication inhibition has been observed in chronic HCV patients who are also infected with acute HBV (629). The inconsistent data on the role of HBV and HCV co- infection in HCC development implies that more research is needed to better understand the situation.

In our study, 20.2% of cancer participants were in stage I, while 54% were in stages III and IV. It has also been reported that the majority (85%) of cancer patients in Ethiopia are diagnosed at an advanced stage with few treatment options (172). A rigorous discussion, however, could not be explored due to a lack of comparable studies. It is plausible, based on the existing literature, that several factors may contribute to the majority of patients' advanced disease (stages III and IV). The problem is three prongs which encompass patient, clinician, and health system-related reasons. Patients may be unable to recognize cancer symptoms in themselves and come late for cancer diagnosis and care (630). The primary care physician may not recognize and treat patients with suspicious HCC symptoms, especially in young people (172). Secondary care patients with suspected cancer may not receive timely attention or may receive an inappropriate specialized

referral (631). There is also no screening program for HCC in the country (631). Thus, using various platforms or methods, it is necessary to increase public awareness of HCC and the importance of seeking timely medical attention. Primary care physicians must also be kept up to date on alarming symptoms of HCC and its risk factors. Moreover, the development of guidelines for identifying cancer signs could perhaps hasten detection.

The high HBV and HCV burden in Addis Ababa suggests that efforts to reduce the burden are required to reduce the burden of HCC, as HBV and HCV are the major risk factors for HCC. Several stakeholders, both governmental and non-governmental, should be involved in these efforts. They must devise strategies to reduce HCC through the reduction of HBV and HCV in the country. The government and non-governmental organizations must also promote early detection, as the majority of HCC patients in Addis Ababa are diagnosed at stages II and IV.

These findings should be considered in light of methodological limitations. The role of other risk factors for HCC development, such as alcohol consumption, aflatoxin B1 exposure, and NAFLD, could not be assessed in this study as almost all participants of this study's hospital records lacked this information. Moreover, in the majority of Ethiopian hospitals, HCC patients are routinely tested for HBV and HCV but not for other risk factors for HCC. For this reason, the analyses presented are predominantly descriptive. Future efforts to embed more biopsychosocial variable collection in cancer registry data or strong record-keeping in health facilities that allow data linkage for HCC would support stronger conclusions about the relationship between HBV, HCV, and HCC. This is particularly important for alcohol consumption, as although the cause of the higher prevalence of HBV and HCV in male patients is unknown, it has been hypothesized that this is because men are more likely to contract viral hepatitis and develop alcoholic cirrhosis.

However, while it would have been preferable to assess the HBV and HCV exposure history of HCC patients reported to the Addis Ababa city cancer registry (AACCR) from 2012 to 2019 to match the data in the first sub-chapter of this chapter, several factors hampered this. To begin, the AACCR collects data on cancer incidence, mortality, method of diagnosis and treatment, and stage at diagnosis when available from Addis Ababa health facilities that provide cancer diagnosis

and treatment. It does not collect data on cancer patients' risk factor exposure status. As a result, we were unable to obtain data from AACCR on the risk factor exposure of HCC patients included in this study. Second, none of the HCC risk factors were notifiable diseases or disorders in Ethiopia; if they had been, it would have been simple to electronically link the HCC cases reported to the AACCR to their HCC risk factor exposure history documented in any Addis Ababa health facility.

Moreover, we tried to review the medical records of HCC patients notified to the AACCR from 2012 to 2019 to determine their risk factor exposure status from the health institutes in Addis Ababa that notified the cancer cases to the AACCR. Our attempt, however, was not successful for the following main reasons: 1) Due to the weak data archive system of the majority of the health institutes that notified the cases or patients, it was impossible to extract the medical records of some of the HCC patients notified to the AACCR from 2012 to 2019; and 2) No data on the patients' risk factor status was found when the medical records of some of the patients were successfully obtained from the medical record archive from the health institutes that notified the AACCR of the cancer cases.

Only HCC cases with hepatitis serological data were included in this study's analysis. It would have been preferable, however, if all of the cases had hepatitis serology data and were included in the analysis. This is because using large data is more likely to generate reliable results for a variety of reasons (415, 416). For instance, the precision or chance of identifying minute effects increases when the estimation of an effect is based on large data or cases (415, 416). Using large data also increases the power or chance of finding an actual effect that is statistically significant if it exists (417). Not taking into account all of the HCC cases in this study may also reduce the generalizability of the conclusions.

5.2.5 Conclusions and recommendations

HBV and HCV are present in large proportion of patients with HCC in Addis Ababa, Ethiopia. A higher prevalence of both viruses was recorded in males. The following recommendations are made to reduce the impact of HBV and HCV on HCC development in the city, as well as the

incidence of late diagnosis. Ethiopian governments and non-governmental organizations (NGOs) should take the lead in advocating for the population's healthcare needs. Hosting forums and launching public awareness campaigns about the link between hepatitis infection and HCC, as well as the importance of early detection, could be a part of this.

The country's public and private health institutions should pay close attention to HCV and HBV, particularly their association with HCC. They should ensure that HBV and HCV, as well as their link to HCC, are addressed in their daily routine of raising public awareness of cancer. Ethiopian governments and non-governmental organizations should collaborate to increase hepatitis vaccination and reduce both the virus's direct and indirect effects, such as increasing the risk of HCC. It is also critical to raise public awareness of HCC risk factors and their links to the disease, as well as late-stage diagnosis and its consequences. Moreover, continuous training of health professionals in Addis Ababa on early detection of HCC cases is needed, particularly among those with HBV and HCV.

The World Health Organization (WHO) states that immunization against HBV is one of the most important and safest methods for its eradication (632). In 2007, the Ethiopian government launched immunization against hepatitis B (164). Efforts have been made in recent years to increase HBV immunization coverage in the country. However, due to some challenges, low vaccination coverage has been observed in several groups of people in the country, including children and healthcare personnel (633, 634). To reduce HBV and the diseases brought on by the virus, such as HCC, it is necessary to increase vaccination coverage among both the general population and those with low vaccination rates in Ethiopia.

Tattooing and body piercing have been practiced for decades and are becoming more popular in Ethiopia (537, 625, 628), which may have contributed to the increased frequency of HBV and HCV in HCC patients in this study. However, there are no guidelines or regulations in place in the country (537). There are also few possibilities for body modification artists to learn more than the fundamentals of aseptic methods (537). A more determined effort to set minimum standards for infection control in tattooing and piercing enterprises is required. Local governments, as well as

other concerned parties, should work to implement such standards. Regular monitoring of the quality of services provided in this industry may also help to lessen the burden of HCC by lowering the prevalence of HBV and HCV in the country.

In Ethiopia, injectable drug usage is increasing, and injecting drug users in the country's capital Addis Ababa have been reported to share needs and other injecting equipment, potentially increasing the transmission of HBV and HCV in the city (536, 561). Thus, there should be some form of effort to reduce injected drug usage and the sharing of needles and other drug-injecting equipment throughout the city. This may include raising public awareness of the negative effects of injectable drug use, the role of sharing needles and other drug-injecting equipment in HBV and HCV transmission, and the role of HBV and HCV infections in HCC development.

CHAPTER SIX: CANCER AND HEPATOCELLULAR CARCINOMA AWARENESS IN ADDIS ABABA, ETHIOPIA

Tekeste Z, Berhe N, Arage M, Degarege A, Melaku Y. Cancer signs and risk factors awareness in Addis Ababa, Ethiopia: a population-based survey. Infectious Agents and Cancer. 2023;18(1):1.

Aim five: To determine whether there are any sociodemographic differences in public awareness of cancer, particularly HCC, signs, symptoms, and risk factors among adults in Addis Ababa, Ethiopia

6.1 Background

The ability of an individual to obtain, interpret, and understand health information and services needed to make informed health decisions is defined as health literacy (635). Inadequate health literacy is said to be a serious problem in low-income countries (636). This is due to the link between health literacy and an inadequate health system, which is common in low-income countries (636). Moreover, demographic factors are said to influence health literacy. Level of education, marital status, gender, and income are some sociodemographic characteristics associated with health literacy (637-640). For instance, higher education attainment is linked to higher levels of health literacy (637-639). There are also reports that women have higher health literacy than men, primarily because they interact with the healthcare system more frequently due to their need for reproductive services related to pregnancy and childbirth (640). Health literacy improves health-seeking behaviour and early detection (641, 642).

Several types of cancer can be cured if detected and treated early, and survival improves when cancer is detected early (643). Delays in diagnosis and treatment cause cancer to progress to an advanced stage that is rarely treatable, resulting in severe morbidity and mortality. Cancers identified at advanced stages have a higher mortality rate than cancers that are localized and present earlier (644, 645). The foundation for improvements in cancer detection and prevention is the general public's health literacy, specifically basic knowledge and awareness of the disease (646, 647).

Cancer awareness assists patients in recognizing the early signs and symptoms of cancer, allowing them to seek treatment at an early stage (646, 647). Raising people's awareness of the main cancer risk factors would also help significantly reduce the disease's burden, as more than 30-50% of cancer cases might be avoided by changing their lifestyle or avoiding the risk factors

(382). Cancer awareness also helps to educate people on the necessity of routine screenings and check-ups (648, 649). Improvement in prevention also includes vaccination programs, changing risky behaviours (e.g. alcohol and tobacco use), screening before the onset of signs and symptoms, and managing disease after diagnosis to slow or stop disease progression (650). The aforementioned and other advantages of increasing cancer awareness imply that it is essential to implement interventions aimed at raising cancer awareness levels.

To raise cancer awareness, it is important to first determine the current level of public awareness, and the factors affecting it. It has been suggested that socioeconomic status, religious beliefs, and culture all affect people's knowledge and awareness of cancer signs and risk factors (651-653). However, assessing socioeconomic disparities in cancer signs and risk factor awareness generally in Ethiopia has received little attention, and no such study on HCC has been carried out (117).

Only a few studies on public awareness of cancer have been undertaken in Ethiopia over the last few decades (166, 168-170, 389). These studies, which were conducted in a few regions of Ethiopia, excluding Addis Ababa, reported varying levels of awareness and do not reflect actual public awareness of cancer in other parts of the country (110, 117, 166, 654). The majority of the study did not look at public awareness of the factors that increased the burden of cancer in the country (654). However, numerous socioeconomic characteristics, such as education level, gender, age, and income, have been suggested to influence cancer awareness elsewhere (655). Moreover, so far, research in Ethiopia has focused on determining public knowledge of a few cancer types, such as breast and cervical cancer (166, 168-170). To the best of our knowledge, no research is being conducted in Ethiopia, including Addis Ababa, to determine public awareness of the signs, symptoms, and risk factors of HCC.

To address this limitation, this study aimed to determine whether there are any sociodemographic differences in public awareness of cancer, particularly HCC, signs, symptoms, and risk factors among adults in Addis Ababa, Ethiopia.

6.2 Method Summary

6.2.1 Study design and participants

For detailed methods, please refer to Chapter Three. Briefly, a cross-sectional study was conducted in Addis Ababa in 2021. The source population comprised people aged 18 and older living in Addis Ababa. The study population comprised individuals who were selected at random from the source population at the household level.

6.2.2 Sampling technique

The study used multistage sampling. First, four (Kolfe-Keranio, Arada, Yeka, and Nifas Silk-Lafto) of Addis Ababa's ten sub-cities were chosen by lottery. Then, the number of Kebele (Amharic for neighbourhood) in each sub-city was listed in a frame. Following that, using the lottery method, three Kebele were chosen at random from each sub-city. Then 50 households were chosen from each Kebele in each sub-city. The spinning pen approach was employed in the middle of each Keble to determine the direction and start of data collection. The sampling interval was calculated by dividing the total number of houses in each research site by the sample size for each site.

6.2.3 Study tool

The Cancer Awareness Measure (CAM) questionnaire, a validated questionnaire for measuring cancer signs and risk factors awareness, was used to assess participants' awareness of cancer symptoms and risk factors (445, 446). For assessing HCC awareness, the survey modified pre-existing questionnaires used to assess cancer and hepatocellular carcinoma awareness to reflect the study's objectives and the local context (383, 445, 446, 656). The questionnaire was translated into Amharic, one of the most widely spoken languages in the study area. It was then back-translated into English. During the translation process, cultural appropriateness was maintained. Before the questionnaire was implemented, there was expert agreement on the Amharic and English versions. A pilot test was conducted with 50 people living in Kebeles who were not part of the study sample and were not included in the actual survey. The pilot survey was conducted by the same survey team that conducted the actual survey. Any issues discovered with the questionnaire were addressed before proceeding with the actual survey.

6.2.4 Data collection

There was one open-ended (recall) question and six closed-ended (recognize) questions about HCC warning signs and symptoms. The stem question for the closed-ended question was as follows: "*The following may or may not be warning signs and symptoms of HCC. We are interested in your opinion."* Following that is a list of six HCC warning signs and symptoms. Ten closed-ended (recognize) and one open-ended (recall) question about cancer signs and symptoms were used. The following was the closed-ended question's stem: "*The following may or may not be signs and symptoms of cancer. We are interested in your opinion.*" Following that, a list of ten cancer signs and symptoms was provided. Each cancer and HCC sign and symptom on the list was answered with "Yes" ('1'), "No" (0), or "I don't know." "I don't know" responses were interpreted as 'no,' and the total score was computed by adding the response (1/0) for each of the ten cancer and HCC signs and symptoms listed.

There was one open-ended question and eight closed-ended questions about HCC risk factor awareness. The following is the stem question for the closed-ended questions: "*These are some of the things that can increase a person's chance of developing HCC. How much do you agree that each of these can increase a person's chance of developing HCC?*" A list of eight HCC risk factors is provided. For cancer risk factors, there was one open-ended question and thirteen closed-ended questions. The stem question for the closed-ended questions is as follows: "*These are some of the things that can increase a person's chance of developing cancer. How much do you agree that each of these can increase a person's chance of developing cancer?*" A list of twelve cancer risk factors was then provided. There were three options for responses: "Agree ('1'), "Disagree ('0')," and "Not sure ('0')." 'Not sure'' responses were considered ''disagree,'' and the total score was calculated by adding the response (1/0) for each of the eight HCC risk factors assessed (168).

6.2.5 Data analysis

The data were cleaned and checked for outliers, errors, and omissions. Using the mean value as a cut-off point, the overall degree of awareness regarding cancer and HCC signs and risk factors was rated as poor or good as described elsewhere (391, 450). Respondents with awareness scores higher than the mean were regarded to have good awareness (173). Logistic regression

models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sociodemographic factors and cancer or HCC awareness. For the logistic regression analysis, only participants with complete data were considered. Moreover, because the majority of participants decided not to disclose their annual salary, it was excluded from adjusted models as a covariate. Statistics were considered significant for p-values < 0.05. The data were entered and analysed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Armonk, NY).

6.3 Results

6.3.1 General characteristics of respondents who responded to HCC and general cancer awareness questions

Table 6-1 displays the general characteristics of the study participants who responded to HCC and general cancer awareness questions. Six hundred Addis Ababa residents aged 18 and up were surveyed on their awareness of cancer symptoms and risk factors. The majority of participants in the study (67%) were between the ages of 18 and 39. Approximately 48% of participants were female, 48.7% were married, and 52.2% had completed post-secondary education. 332 participants disclosed their income, and 30.8% and 24.5% of the total participants earned more than 5055 and less than or equal to 5055 Ethiopian birr per month, respectively, with a mean monthly income of 6802 Ethiopian birr (I USD ≈ 55.73 Ethiopian birr).

Table 6-1: General characteristics of the study participants (N=600).

Socio-demographic characteristics	Number	%
Age in years		
18-29	224	37.3
30-39	178	29.7
40-49	97	16.2
50-59	53	8.8
≥ 60	48	8.0
Gender		

Men	315	52.5
Women	285	47.5
Marital status		
Married	292	48.7
Single	247	41.2
Divorced	33	5.5
Prefer not to say	28	4.7
Education level		
Primary	61	10.2
Secondary	138	23.0
Diploma	105	17.5
Degree and above	208	34.7
Unable to read and write	42	7.0
Prefer not to say	46	7.7
Employment		
Governmental organization	120	20.0
Non-governmental organization/private	309	51.5
Retired	25	4.2
Unemployed	87	14.5
Prefer not to say	59	9.8
Monthly income		
>5055 ETB	185	30.8
≤ 5055 ETB	147	24.5
Prefer not to say	268	44.7

ETB; Ethiopian birr.

6.3.2 Awareness of cancer signs and symptoms

Table 6-2 describes cancer awareness as measured by recognize (prompted) and recall (unprompted) questions. The most frequently recalled sign, without prompting, was unexplained bleeding, which was mentioned by 23.8% of those surveyed. Unexplained weight loss was recalled by 23.2% of those surveyed. Persistent cough and difficulty swallowing were recalled by 23% and 13% of respondents, respectively. The percentages of study participants who remembered being

tired all the time and coughing up blood as cancer symptoms and signs, respectively, were only 3.5% and 0.8%. For each cancer sign and symptom, the percentage of unprompted awareness was lower than prompted awareness.

Table 6-2: Percentage of participants who recalled and recognized general cancer signs and symptoms (N = 600)

	Unprompted awareness	**Prompted awareness**
Cancer Signs and symptoms	**Number of participants (%) who recalled cancer signs and symptoms**	**Number of participants (%) who recognized cancer signs and symptoms**
Unexplained weight loss	139 (23.2)	414 (69.0)
Unexplained lump/swelling	7 (1.2)	460 (76.7)
Unexplained persistent pain	58 (9.7)	453 (75.5)
Unexplained bleeding	143 (23.8)	308 (51.3)
Persistent cough/hoarseness	138(23.0)	209(34.8)
Difficulty in swallowing	78(13.0)	410(68.3)
Sore that does not heal	4(0.7)	426(71.0)
Coughing up blood	5(0.8)	248(41.3)
Shortness of breath	35(5.8)	465(77.5)
Tiredness all the time	21(3.5)	484(80.7)

6.3.3 Awareness of general cancer risk factors

The awareness of cancer risk factors among study participants is presented in Table 6-3. Smoking was recalled by 24.2% of respondents as a cancer risk factor, followed by alcohol consumption (18%), old age (4.3%), and not doing enough exercise/physical activity (3.4%). When prompted, the most frequently recognized risk factor was smoking, with 86.3% of respondents recognizing it. The percentage of respondents who recognized passive smoking and alcohol consumption as cancer risk factors were about 82.3 and 82.5, respectively. Only 34.5% of survey participants recognized being overweight as a cancer risk factor.

Table 6-3: Percentage of participants who recalled and recognized cancer risk factors (N = 600)

	Unprompted awareness	**Prompted awareness**
Cancer Risk factors	**Number of participants (%) who recalled cancer risk factors**	**Number of participants (%) who recalled cancer risk factors**
Smoking	145 (24.2)	518 (86.3)
Exposure to another person's cigarette smoke (passive smoking)	2 (0.3)	494 (82.3)
Low intake of fruit/vegetables	0 (0.0)	360 (60.0)
Alcohol consumption	108 (18.0)	495 (82.5)
Overweight	17(1.2)	207(34.5)
Obese	10 (1.7)	288 (48.0)
Sunburnt/exposure to the sun	10(1.7)	310(51.7)
Older age	26(4.3)	365(60.8)
Eating red or processed meat	3(0.5)	429(71.5)
Stress	17(2.8)	290(48.3)
Not doing enough exercise/physical activity	23(3.8)	363(60.5)
Family history/having a close relative with cancer	8(1.3)	320(53.3)

Obesity; BMI= 30.0 and above, overweight; BMI= 25.0 - 29.9.

6.3.4 Awareness of cancer signs, symptoms, and risk factors

The odds of being aware of cancer signs, symptoms, and risk factors by socioeconomic status as measured by closed questions are shown in Tables 6-4 and 6-5. Table 6-4 and 6-5 show the results of a model with all predictors included simultaneously. Those with primary (aOR =4.5; 95% CI, 1.72- 11.79; p = 0.02), secondary (aOR =4.6; 95% CI, 1.87-11.42; p = 0.001), and tertiary (aOR =7.5; 95% CI, 3.04-18.56; p< 0.01) education were more likely to recognize cancer signs and symptoms than illiterate respondents. Those aged 60 and older (aOR =0.3; 95% CI, 0.62-2.88; p=0.003) were less likely than those aged 18 to 29 to be aware of cancer symptoms and signs. Respondents with primary education were 4.8 (95% CI, 1.08- 21.03; p=0.03) times more likely to be aware of cancer risk factors than those who were illiterate in adjusted analyses. The odds of awareness about cancer risk factors was 0.2 (95% CI 0.83–0.58; $p = 0.002$) times lower among individuals aged 60 and older than those aged 18 to 29.

Table 6-4: Logistic regression model to determine the socio-demographic differences in public awareness of cancer risk factors in Addis Ababa, Ethiopia.

	Level of awareness for cancer risk factors		AOR [95% CI]	p-value
Study Variables	**Good n (%)**	**Poor n (%)**		
Gender				
Male	175(35.1)	90(18.0)	1.00	0.41
Female	161(32.3)	73(14.6)	0.74[0.37-1.49]	
Marital status				
Single	144(28.9)	71(14.2)	1.00	
Married	172(34.5)	85(17.0)	1.31[0.33-5.16]	0 .70
Divorced	20(4.0)	7(1.4)	1.16 [0.61- 2.21]	0.65
Education				
Illiterate (can't read and write)	14(2.8)	24(4.8)	1.00	
Primary	38(7.6)	20(4.0)	4.8 [1.08-21.03]	0.03*
Secondary	76(15.2)	46(9.2)	0.9 [0.34- 2.87]	0.97
Higher Education	207(41.5)	73(14.6)	1.5 [0.51- 4.58]	0.45
Employment				
Unemployed	55(11.0)	28(5.6)	1.00	
Governmental organization	84(16.8)	30(6.0)	0.6 [0.12- 3.13]	0.55
Non-governmental organization/private	182(36.5)	96(19.2)	0.6 [0.14- 2.97]	0.57
Retired	15(3.0)	9(1.8)	0.6[0.12- 2.62]	0.46
Age in years				
18-29	99(19.8)	34(6.8)	1.00	
30-39	55(11.0)	20(4.0)	0.7 [0.37- 1.49]	0.41
40-49	35(7.0)	14(2.8)	0.8 [0.33-1.91]	0.61
50-59	16(26.3)	28(5.6)	5.9 [0.73-46.67]	0.09
≥ 60	131(26.3)	67(14.4)	0.2 [0.83- 0.58]	0.002*

AOR, adjusted odds ratio; 95% CI, 95% confidence interval;* Significant difference.

Table 6-5: Logistic regression model to determine the socio-demographic differences in public awareness of signs and symptoms in Addis Ababa, Ethiopia.

	Level of awareness for cancer signs and symptoms			
Study Variables	**Good n (%)**	**Poor n (%)**	**AOR [95% CI]**	**p-value**
Gender				
Male	209 (41.9)	108 (21.6)	1.00	
Female	193 (38.7)	90(18.0)	1.2 [0.79- 1.81]	0.39
Marital status				
Single	165 (33.2)	83(16.6)	1.00	
Married	197(39.5)	95(19.0)	2.6[0.91-7.39]	0 .07
Divorced	24(4.8)	9(1.8)	0.8 [0.54 - 1.37]	0.52
Education				
Illiterate(can't read and write)	14(2.8)	28(5.6)	1.00	
Primary	39(7.8)	22(4.4)	4.5 [1.72- 11.79],	0.02*
Secondary	88(17.6)	50(10.0)	4.6 [1.86- 11.43]	0.001*
Tertiary	231(46.3)	82(16.4)	7.5 [3.04- 18.56]	< 0.01*
Employment				
Unemployed	57(11.4)	30(6.0)	1.00	
Governmental organization	85(17.0)	34(6.8)	0.4 [0.14- 1.49]	0.19
Non-governmental organization/private	206(41.3)	102(20.4)	0.4 [0.14- 1.20]	0.10
Retired	16(3.2)	9(1.8)	0.7 [0.24-2.28]	0.59
Age in years				
18-29	148(29.7)	77(15.4)	1.00	
30-39	129(25.8)	48(9.6)	0.5 [0.87- 2.48]	0.15
40-49	70(14.0)	27(5.4)	0.2 [0.78-3.05]	0.21
50-59	37(7.4)	16(3.2)	1.3 [0.62-2.88]	0.46
≥ 60	18(3.6)	30(6.0)	0.3 [0.12- 0.65]	0.003*

OR, odds ratio; 95% CI, 95% confidence interval;* Significant difference.

6.3.5 Awareness of hepatocellular carcinoma signs and symptoms

The study participants' responses to open-ended (recall) and closed (recognize) questions about HCC signs and symptoms are presented in Table 6- 6. When asked an open question, the majority of survey respondents (25.8%) recalled jaundice as HCC signs and/or symptoms. The second most frequently recalled sign was swelling (9.7%). A loss of appetite was reported by 4.6 % as a sign and/or symptom of HCC, while nausea or vomiting was recalled by 4.3 %. When closed questions are used, the highest and lowest signs and symptoms of HCC recognized were jaundice (78.1%) and abdominal pain (74.9%), respectively.

Table 6- 6: Percentage of participants who recalled /recognized warning signs and symptoms of hepatocellular carcinoma (N = 595)

	Unprompted awareness	**Prompted awareness**
Warning signs and symptoms of HCC	**Number of participants (%) who recalled HCC signs and symptoms**	**Number of participants (%) who recognized HCC signs and symptoms**
Loss of appetite	27 (4.6)	409 (68.66)
Feeling very full after a small meal	15 (2.50)	410(68.9)
Nausea or vomiting	26 (4.3)	321(54.0)
Pain in the abdomen (belly) or near the right shoulder blade	18(3.0)	253(42.4)
Swelling or fluid build-up in the abdomen (belly)	58(9.7)	445(74.9)
Yellowing of the skin and eyes (jaundice)	154(25.8)	465 (78.1)

HCC, hepatocellular carcinoma.

6.3.6 Awareness of hepatocellular carcinoma risk factors

Table 6-7 describes the participants' awareness of HCC risk factors as measured by unprompted (open-ended) and prompted (closed) questions. When asked open questions, alcohol consumption was recalled by the majority (81.7%) of respondents as a risk factor for HCC. Almost three-quarters (70.4%) of those surveyed recalled 'aflatoxin B1 exposure,' and 67.4% recalled 'type II diabetes.' Only 35.6% and 45.9% of respondents recognized 'Hepatitis B virus' and 'Hepatitis C virus,' respectively. When open-ended questions were used, 19.7% and 16.5% of respondents

remembered 'smoking' and 'alcohol consumption,' respectively. While type II diabetes, obesity, and overweight were all mentioned by 2% of participants, the remaining risk factors were recalled by less than 2% of those surveyed.

Table 6-7: Percentage of participants who recalled and recognized risk factors of hepatocellular carcinoma (N = 595)

	Unprompted awareness	**Prompted awareness**
HCC Risk factors	**Number of participants (%) who recalled HCC risk factors**	**Number of participants (%) who recalled HCC risk factors**
Smoking	117(19.7)	384(64.5)
Type II diabetes	12(2.0)	401(67.4)
Alcohol consumption	98(16.5)	486(81.7)
Overweight	12(2.0)	288(48.4)
Obesity	12(2.0)	297(49.9)
Aflatoxin exposure	11(1.8)	419(70.4)
Hepatitis B virus	11(1.8)	212(35.6)
Hepatitis C virus	10(1.7)	273(45.9)

Obesity; BMI= 30.0 and above, overweight; BMI= 25.0 - 29.9; HCC, hepatocellular carcinoma.

6.3.7 Hepatocellular carcinoma awareness signs, symptoms, and risk factors

The odds of being aware of HCC signs, symptoms, and risk factors by socioeconomic status as measured by closed questions are shown in Tables 6-8 and 6-9. Though not statistically significant, the odds of awareness about HCC risk factors was 0.70 (95% CI, 0.29-1.71; p=0.44) times lower among individuals aged 60 and older than those aged 18 to 29. Moreover, respondents aged 40-49 and 50-59, respectively, were 2.09 (95% CI, 1.17-3.73; p= 0.01) and 2.63 (95% CI, 1.04-6.56; p= 0.03) times more likely to be aware of HCC signs and symptoms than those aged 18 to 29.

Table 6-8: Socio-demographic correlates of public awareness of HCC signs and symptoms in Addis Ababa, Ethiopia.

	Level of Awareness for HCC signs and symptoms			
Study Variables	**Good n (%)**	**Poor n (%)**	**AOR [95% CI],**	**p value**
Gender				
Male	199(40.9)	56 (11.5)	1.00 (reference)	0.87
Female	179(36.8)	52(10.7)	1.0[0.66- 1.63]	
Marital Status				
Single	198(40.7)	42(8.6)	1.00	
Married	147(30.3)	59(12.1)	1.3[0.51- 3.42]	0.56
Divorced	33(6.8)	7(1.4)	1.5 [0.89 - 2.51]	0.12
Education				
Illiterate (can't read and write)	31(6.4)	5(1.0)	1.00 (reference)	
Primary	39(8.0)	17(3.5)	0.5, [0.16- 1.67]	0.27
Secondary	85(17.5)	31(6.4)	0.8, [0.25- 2.36]	0.64
Tertiary	223(45.9)	55(11.3)	1.2, [0.37- 3.55]	0.81
Employment				
Unemployed	56(11.5)	18(3.7)	1.00 (reference)	
Governmental organization	93(19.1)	21(4.3)	0.6, [0.10- 3.04]	0.49
Non-governmental organization/private	213(43.8)	67(13.8)	0.5, [0.09-2.52]	0.39
Retired	16(3.3)	2(0.4)	0.5, [0.092.45]	0.36
Age in years				
18-29	116(23.9)	22(4.5)	1.00 (reference)	
30-39	58(11.9)	14(2.9)	1.0, [0.66- 1.63]	0.88
40-49	42(8.6)	7(1.4)	2.1, [1.17-3.73]	0.01*
50-59	28(5.8)	3(0.6)	2.6, [1.04-6.56]	0.03*
≥ 60	134(27.6)	62(12.8)	3.8, [0.98- 14.45]	0.06*

AOR, adjusted odds ratio; 95% CI, 95% confidence interval;* Significant difference.

Table 6-9: Logistic regression model to determine the socio-demographic differences in public awareness of HCC risk factors in Addis Ababa, Ethiopia.

	Level of Awareness for HCC risk factors			
Study Variables	**Good n (%)**	**Poor n (%)**	**AOR [95% CI]**	**p-value**
Gender				
Male	146 (30.0)	109 (22.4)	1.00	0.48
Female	121 (24.9)	110 (22.6)	0.9 [0.59-1.27]	
Marital status				
Single	127 (26.1)	113 (23.3)	1.00	
Married	124 (25.5)	82 (16.9)	0.5 [0.24- 1.10],	0.86
Divorced	16 (3.3)	24(4.9)	0.8 [0.53- 1.26]	0.35
Education				
Illiterate (can't read and write)	16(3.3)	20(4.1)	1.00	
Primary	31(6.4)	25(5.1)	0.5 [0.16- 1.67]	0.27
Secondary	53(10.9)	63(12.9)	0.8 [0.25- 2.36]	0.64
Tertiary	167(34.4)	111(22.8)	1.2 [0.37- 3.55]	0.81
Employment				
Unemployed	38(7.8)	36(7.4)	1.00	
Governmental organization	76(15.6)	38(7.8)	1.8 [0.54- 3.27]	0.53
Non-governmental organization/private	114(23.5)	136(27.9)	0.9 [.38- 2.05]	0.77
Retired	9(1.9)	9(1.9)	1.3 [0.56- 2.96]	0.56
Age in years				
18-29	84(17.3)	54(11.1)	1.00	
30-39	34(7.0)	88(18.1)	1.2 [0.75- 1.94]	0.44
40-49	26(5.4)	23(4.7)	0.8 [0.44-1.48]	0.49
50-59	13(2.7)	18(3.7)	0.9 [0.48-1.91]	0.91
≥ 60	110(22.6)	86(17.7)	0.7 [0.29- 1.71]	0.44

AOR, adjusted odds ratio; 95% CI, 95% confidence interval;* Significant difference.

6.4 Discussion

This study assessed public awareness of both general cancer and hepatocellular carcinoma (HCC) risk factors and signs among individuals aged 18 and older in Addis Ababa, Ethiopia, and found that the identification of cancer and HCC signs and risk factors was lower with open-ended questions than with closed questions. The odds of awareness about cancer risk factors was 0.2 (95% CI 0.83–0.58; $p = 0.002$) times lower among individuals aged 60 and older than those aged 18 to 29. Respondents with primary, secondary, and tertiary education were also found to be more aware of cancer signs and symptoms than those who were illiterate. A higher proportion of participants were aware of cancer in general rather than HCC. Moreover, when compared to the other risk factors for HCC, HBV, and HCV were recognized by a low proportion of study participants.

The finding that the identification of cancer and specifically HCC signs and risk factors was lower with open-ended questions than with closed questions was consistent with the findings Su et al (449) from Malesia and Rob et al (657) from the United Kingdom (657), in which recall of cancer signs and/or risk factors was lower with open-ended questions than with closed questions. However, determining whether a score from an open-ended or closed-ended question better reflects cancer awareness is difficult. Since recall is limited by memory when open questions are asked, it understates awareness, and respondents may find it easy to guess when asked closed questions, resulting in an overestimation of awareness (657). It has been suggested, however, that the accessibility of beliefs is important in predicting behaviour, intentions, and attitudes, and that the most accessible beliefs are those that can be readily recalled or brought to mind: ‘people’s attitudes follow spontaneously and consistently from beliefs accessible in memory and then guide corresponding behaviour (657). When applied to our case, this concept suggests that recognizing signs and risk factors in response to closed-ended questions is less likely to relate to help-seeking than recalling signs and risk factors in response to open-ended questions. Another study, similar to this study, suggests that symptoms recalled in response to open-ended questions are more likely to lead to help seeking than those simply recognized (657).

The demonstration that individuals aged 60 and older have low recognition of cancer signs and risk factors is in agreement with the report of Robb et al (657) from the UK. In other studies, however, young age groups (15-34 years) were found to have lower cancer symptom awareness (657, 658). Moreover, although not statistically significant, this study found that individuals aged 60 and over were less aware of HCC risk factors. The Ethiopian government launched its first national cancer control plan in 2015, with one of its goals being to raise public awareness of cancer. The awareness program, however, gives little attention to the elderly (172). This could explain why, in this study, older people were the least aware of cancer symptoms and risk factors, in contrast to previous studies.

Ethiopia's national cancer control plan also called for cancer awareness programs to be integrated into the daily routines of health education provided at all public healthcare facilities (172). Medication and transportation to the country's public healthcare facilities, on the other hand, are too expensive, which may have discouraged the elderly from seeking medical help or visiting the healthcare facilities and benefiting from the awareness program provided there (138, 575, 576). This is primarily because the majority of Ethiopia's elderly do not have a steady source of income or adequate pensions (581, 582). Moreover, poverty-related illnesses are becoming more prevalent in the country, leaving many children orphaned or abandoned (576, 587, 588). Many elderly people are compelled to care for these children because they are almost always their grandchildren, exacerbating the older respondents' financial difficulties (576). Thus, these factors may have reduced the older participants' healthcare-seeking behaviour and made them less likely to benefit from the awareness program provided by the country's public health institutes.

The Ethiopian government's free medical service system for the poor is also not functioning as intended for a variety of reasons (577, 578). For instance, patients who visit public healthcare facilities; where free medical services for the poor are available, are frequently requested to purchase medications from private drugstores or be referred to private laboratories, which are more expensive than comparable public healthcare facilities (576). The financial hardships of older adults in Ethiopia may also have discouraged them from seeking medical help or visiting public healthcare facilities and benefiting from cancer awareness education provided there.

In the present study, respondents with primary, secondary, and tertiary education were more aware of cancer signs and symptoms than those who were illiterate. This was consistent with the study in the UK (657), where a high level of education was associated with higher cancer sign awareness. Similar findings have been reported in Denmark, where higher education is associated with a higher level of cancer risk factor awareness (659). Another study in Malesia found individuals with postsecondary education were more aware of colorectal cancer signs and risk factors (449). In Ethiopia, particularly in Addis Ababa, government institutions and schools are adopting cancer awareness programs to teach students and staff how to lower their risk of developing cancer and recognize its early signs and symptoms (660, 661). Moreover, educated people in Ethiopia use social media platforms more than illiterate individuals (662-664), which provides them with more cancer information and raises their awareness of cancer symptoms and risk factors (665). Thus, raising cancer awareness in illiterate people may be aided by using other methods of awareness creation, such as public cancer awareness creation via national television and radio, which are accessible to almost everyone.

Low socioeconomic status (SES) has also been associated with a lower level of cancer awareness (658). In various regions of the world, it has been found that education—one of many indicators of socioeconomic status—is inversely correlated with cancer awareness (666, 667). Uneducated people frequently face complex socio-cultural challenges, such as a perceived social distance between themselves and their doctors as a result of income and social status differences (668). Moreover, people with lower socioeconomic status reported greater anxiety and embarrassment about what the doctor might find (669). Thus, these factors may have reduced study participants' healthcare-seeking and made them less aware of cancer in the context of lower education.

In this study, a lower proportion of respondents identified HBV and HCV as risk factors for HCC. The cause of low public awareness of the association between HBV and HCV and the risk of HCC is difficult to explain. However, this could be due to a lack of emphasis in Ethiopia on raising awareness about the link between viruses and the risk of HCC, as opposed to raising efforts that

have been paid to raise awareness about the link between other risk factors such as smoking and alcohol use and the risk of HCC (117). However, it has been reported that HBV and HCV cause the vast majority of HCC cases worldwide. While HCV is reported to be responsible for more than half of HCC cases worldwide, HBV causes 10-25% of cancer cases worldwide (54, 71-73). Few studies have also suggested that HBV and HCV are also important risk factors for HCC in Ethiopia (137). Moreover, the burden of HBV and HCV on Ethiopians is increasing, expected to rise the burden of HCC in the country (160-162). Given the potential role of HBV and HCV in increasing the risk of HCC in Ethiopia, it is necessary to devise a strategy to mitigate their potential impact on HCC risk, which includes increasing public awareness of the link between the viruses and the disease.

This study also found higher proportion of participants were more likely to be aware of cancer signs and risk factors in general than specific to HCC. Ethiopia's government launched a national cancer control plan in 2015, with one of the strategies being increased public awareness of cancer. The awareness campaign, on the other hand, focused on raising public awareness of cancer in general, as well as a few specific types of cancer, such as breast and cervical cancer (117). Several types of cancer with public health implications, including HCC, have received little attention in the country (117). This could therefore be one of the reasons for the low awareness of HCC among the participants. Thus, there should be a focus on raising public awareness of HCC and other risk factors in Ethiopia, particularly in Addis Ababa.

This study has strengths and limitations. It is the first study to assess cancer signs, symptoms, and risk factors awareness in Addis Ababa, Ethiopia, using a population-based sample. It also reduced interviewer bias by training surveyors to appear neutral during the interview. The use of the CAM questionnaire, a validated measure of cancer awareness, is also the study's strength. Another strength of the study is its use of both open and closed questions to assess awareness of cancer signs and risk factors. One of the study's weaknesses is that the awareness scores for recognizing signs and risk factors in closed (recognize) questions may have been exaggerated because some participants may have guessed the correct answer. Moreover, awareness scores to open-ended (recall) questions may be underestimated because recall is limited by memory (657).

6.5 Conclusions and recommendations

In conclusion, participants who couldn't read or write, as well as those who were older, had lower awareness of cancer signs. Therefore, to promote prompt help-seeking and enhance HCC outcomes, future cancer control efforts in Addis Ababa, including public awareness campaigns, should target population groups including lower education and literacy levels, and individuals 60 and older.

The finding that cancer sign awareness is lower among people who can't read and write suggests that there is a need to raise awareness in this group in the country. The finding that the elderly had poorer cancer awareness in this study suggests that extra efforts should be made to raise their awareness. This can be accomplished by directing awareness campaigns toward these groups. It is also suggested that cancer awareness education provided in public health facilities in the country be appropriate for and accessible to the elderly.

Cancer awareness is provided in Ethiopian public healthcare facilities, but the elderly's economic challenges prevent them from visiting the facilities and benefiting from the awareness programs there (581, 582). Thus, alternative cancer awareness mechanisms are required for the elderly. This could include printing cancer information on cans and bottles of alcoholic beverages, as well as packets of cigarettes and other goods. Cancer awareness campaigns in Addis Ababa's villages and sub-cities may also help to raise the awareness of the elderly, who are unable to access cancer awareness programs in the country's public healthcare facilities due to financial constraints.

More research is needed to establish the reason for the observed socioeconomic disparities in cancer awareness in this study. Future research should investigate if cancer incidence and survival are related to cancer awareness in Ethiopia, as well as the mechanism underlying the link. Furthermore, to establish a more effective national control strategy, it is required to explore public awareness of cancer indications and risk factors in various regions of Ethiopia.

CHAPTER SEVEN: CURRENT INFRASTRUCTURE, EDUCATION, AND FINANCE NEED TO CONTROL HEPATOCELLULAR CARCINOMA IN ETHIOPIA

Aim Six: To explore liver cancer clinicians' perceptions of the current educational, infrastructure, and financial needs to control HCC in Ethiopia.

7.1 Background

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death, with less than a 20% five-year survival rate (670, 671). Survival, on the other hand, is influenced by the stage of the tumour at the time of diagnosis, as well as comorbidities (672). Those who are diagnosed with small and isolated HCCs at an early stage have a higher rate of survival and are more likely to benefit from curative therapies (673-675). However, HCC is frequently detected in advanced stages, when there are few treatment options (676).

Clinical guidelines for the management of HCC have been developed (392-394) by the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), the Japanese Society of Hepatology, and the Asian Pacific Association for the Study of the Liver (APASL) (392-394). These guidelines recommended curative treatment for early-stage HCC, such as liver transplantation, percutaneous ablation, and surgical resection. There are, however, few effective options for those with advanced disease (392-394). The guidelines developed thus far differ from one another, and best practice guidelines for optimal HCC management are required (395).

Guidelines are essential in the management of diseases that are of public health importance (396). It has also been reported that there is a need for a broader strategy to address diseases of public health importance, including cancer (397). HCC has been identified as a significant public health problem by policymakers (11, 528, 529). However, unlike clinical guidelines, there is no broader strategy or plan such as a national HCC control plan, from disease prevention to early detection and treatment, in many countries around the world (13). There is also little attention paid to understanding public policy needs to control HCC in many countries around the world which could help develop broader cancer control strategies or plans (13).

In recent years, few qualitative studies have been conducted to understand public policy needs to control HCC. A study conducted in the United States assessed the needs for HCC control and care and educational needs of those involved in HCC care (677). Another study identified improving access to liver cancer treatment, raising public awareness of liver cancer, and developing infrastructure as among the many other needs to be addressed for effective HCC control in Asia (678). Another study looked into leading liver cancer clinicians' perceptions of public policy needs to control liver cancer on a global scale (13). This study identified, among other things, the need for early risk assessment by primarily focusing on raising awareness, specifically public, political, and medical community awareness, and improving funding for liver cancer screening and treatment to better control the disease (13). However, because each country's readiness and need to combat liver cancer varies, an effort should be made to assess each country's readiness or need to control the disease (13).

In Ethiopia, little attention has been paid to identifying the need to develop cancer control policies, and no study has assessed the country's need to control HCC (172, 679). However, it has been reported that effective public policy for cancer control entails several factors (16), including assessing the current state of the cancer problem, age and gender differences in disease burden. It also includes identifying gaps in physical (e.g., infrastructure), human resources (e.g., health-care personnel), and financial resources in cancer control (16). In Ethiopia, no study assessed the burden of HCC and associated risk factors at the population level and how the incidence affects the population over time. Moreover, no study evaluated the infrastructure, education, and financial needs to control the disease in the country. Thus, this study was designed to assess clinician perspectives on the need for HCC control in Ethiopia. In this chapter, in-depth interviews were conducted with liver cancer clinicians to learn about their perceptions of infrastructure, education, and financial needs to control HCC in Ethiopia. This was done to uncover perceived infrastructural, educational, and financial gaps in HCC control in the country, which could help design a careful HCC control plan in the country.

7.2 Method Summary

An in-depth interview was used to investigate liver cancer clinicians' perceptions of Ethiopia's current infrastructure, finance, and educational needs to control HCC. Purposive sampling was used to identify participants with diverse perspectives and firsthand knowledge of the research topic. The study's target population was Addis Ababa-based liver cancer clinicians involved in policy and the prevention, diagnosis and management of liver cancer.

During the recruitment process, potential key participants that meet the following criteria were identified and compiled:

I) actively working in Ethiopia on liver cancer or HCC in Ethiopia;

II) involvement in liver cancer (HCC) clinical practice, policy, or research;

III) membership in a national or international association for liver cancer or HCC, or publication in a peer-reviewed journal on liver cancer;

IV) having the ability to communicate in Amharic;

V) willingness to provide demographic information, and

VI) willingness to provide consent.

Two different methods of recruitment were used. The first method was to distribute promotional texts about the study to cancer care centres in Addis Ababa. Among other things, the promotional text contains information about the eligibility criteria and the researchers' addresses. Participants who confirmed their willingness to participate in the study by responding to the letter's contact information were scheduled for an interview. The second method entailed approaching the heads of oncology departments at cancer care institutes in Addis Ababa and requesting that promotional materials for the study be distributed during staff meetings. The promotional text included information about the study as well as the investigator's contact information. Those who were interested used the information provided to contact the researcher.

Before the interview, the investigator introduced himself to the study participants. Following that, the participants were given an information sheet outlining the study. They were then made aware of any possible risks associated with the study. Following that, they were thanked for agreeing to

participate in the study, invited to ask clarifying questions about the study, and asked to sign a consent form before the interview began.

Briefly, in-depth interviews were audio-recorded, and a verbatim transcription of the interview was created in English. Data familiarization followed the transcription process. The data were examined using conventional content analysis, which doesn't require any software, as described elsewhere (465, 472). The transcribed interview data were then divided into smaller portions known as meaning units. Condensed meaning units were then created by condensing meaning units. Following the condensing of the 'meaning units,' codes for each 'condensed meaning unit' were developed. The codes that appeared to be dealing with the same issue were sorted. After categorizing the codes, an analysis was performed, and themes were formed by grouping two or more categories. The detailed method used in this section is described in detail in Chapter 3 of the thesis.

7.3 Results

Table 7-1 shows the general characteristics of the study participants. The study included a total of 13 liver cancer clinicians working in cancer care institutes in Ethiopia. Four of the study's participants were female, whereas nine were male. . The educational qualifications of the participants comprised 38.5% physicians (general practitioners or oncologists), 23.1% public health officers, 23.1% masters of public health (medical doctors or health officers with an MPH degree), and 15.4% oncology nurses. The participants' median work experience in healthcare was 8 years, with a range of 5 to 34. While 23.1% of the participants were unmarried, 76.9% were married. Participants in the study work at five cancer care institutes in Addis Ababa. The interview elicited a wide range of perceptions about Ethiopia's current infrastructure, education, and financial needs for HCC control. Three major themes have emerged: HCC prevention, raising HCC awareness, and improving HCC funding. Table 7-2 provides an overview of these major themes and the sample narratives that each theme encompasses.

Table 7-1: Socio-demographic characteristics of the study participants.

Variables	Study participants (N=13)
Sex	
Male	9(69.2%)
Female	4(30.8%)
Age median (range (minimum-maximum))	38 (29-54)
Marital status	
Single	3(23.1%)
Married	10(76.9%)
Education/educational background	
Medical doctor	5(38.5%)
Public Health officer	3(23.1%)
Master of Public health	3(23.1%)
Oncology nurse	2(15.4%)
Median (range) work experience in years	8 (5-34)

Table 7-2: Overview of the major themes and the sample narratives**.**

Theme	Dimension	Sample narratives
Promoting HCC prevention	Screening	*I believe that one of the country's problems with HCC is a lack of screening programs and accurate case identification.*
	Hepatitis B and C infections	*HBV and HCV screening is frequently done only on pregnant women who visited cancer care facilities in the country, making prevention and control of HCC in the country difficult.*
	Comorbidities	*I think that if people with comorbidities are screened for HCC, it is possible to prevent and control the disease.*
Raising HCC awareness	Public awareness	*I believe that little has been done to raise public awareness of HCC and that people believe cancer is a curse from God, which is one of the barriers to the prevention and control of the disease.*
	Health professionals	*As far as I'm aware, a few of the major hospitals in the nation provide training on advanced cancer diagnosis techniques to a few medical professionals. There is also occasional training on cancer therapy for medical doctors, but no specifics on HCC.*
Improve funding	HCC treatment	*Due to a shortage of financing, it is difficult to develop institutes with the necessary infrastructure for the detection and treatment of HCC and train healthcare professionals in cancer therapy.*
	HCC diagnosis	*I believe the country is underfunding cancer diagnosis. Imaging and CT scans, for example, are only available in a few hospitals across the country. As a result of such scarcity, cancer staging and advanced diagnostic techniques are limited to a few hospitals, and doctors rarely refer patients.*
	HCC Screening	*I believe that the main reason for the country's lack of screening and other prevention activities is a lack of funding. Although some health institutes in the country have received financial support for prevention and control activities, I believe the fund they receive is insufficient.*

Theme 1: HCC prevention

7.3.1.1 Early detection or screening

The study participants emphasized the importance of public screening for effective HCC prevention and control in the country. They described that the majority of HCC patients in the country presented to cancer care facilities at an advanced stage, making disease prevention and control difficult. They also emphasize the importance of detecting cases of HCC early to reduce the disease burden and improve outcomes. One of the study participant's responses summarizes this as follows:

"One of the problems with HCC prevention and control in the country, in my opinion, is a lack of screening. The majority of our patients are diagnosed at an advanced stage. This makes disease prevention and controls difficult. It also makes treatment difficult, resulting in a poor disease outcome."

The importance of early detection of HCC in high-risk individuals was also emphasized by participants. They emphasized the significance of HCC testing in patients with HCC risk factors and other comorbidities. One of the respondents described that:

"*People who are with HCC risk factors and other comorbidities, in my opinion, should be tested for HCC. This, I believe, will assist the prevention and control of the disease in the country.* "

The study participants also mentioned that the lack of accurate diagnosis of HCC in many health facilities in the country is becoming a challenge for the prevention and control of the disease. They described that HCC cases in the country are often diagnosed clinically i.e. using signs and symptoms.

"*There are problems with accurate diagnosis or identification of HCC in many cancer care facilities across the country. Cases of HCC in the country are frequently diagnosed clinically rather than using advanced diagnostic techniques.* "

7.3.1.2 Hepatitis B and C virus

Preventing hepatitis B and C infections, according to respondents, is an important step for the prevention and control of HCC. Respondents also mentioned that Ethiopia has launched a hepatitis B vaccination program though it was only recently introduced in the country. They also said that the majority of hepatitis B and C patients do not receive the necessary care until the virus progresses or causes other diseases such as HCC or complications. This is summarized in one of the respondent's quotes:

"HCC is one of the diseases that has received little attention in Ethiopia at the moment. I believe the country lacks a system in place to manage the disease and its risk factors. The majority of hepatitis patients do not receive the attention they deserve on time; most of the time, they receive medical attention after the disease has progressed and caused other diseases such as cancer, including HCC, or other complications. Hepatitis vaccination has also recently begun in the country. "

Respondents also described that hepatitis B and C screening is only done on pregnant women visiting health institutes in the country and not on other groups of people. Poor public awareness of the link between hepatitis and the risk of HCC has also hampered the country's efforts to prevent and control the disease. One of the study's participants said:

"Only pregnant women are routinely screened for hepatitis in cancer care institutes in the country, and other population groups are excluded from hospital screening programs. This is exacerbated by a lack of public awareness about the association between the hepatitis B and C virus infections and HCC. "

7.3.2 Theme 2: Raising Awareness

Another theme that emerged was the need to raise public and healthcare professional knowledge and awareness of HCC. The majority of the respondents reported that there is low awareness and knowledge about the disease and its risk factors among the general public and some health

professionals. Awareness is discussed in more detail in terms of public and health professional awareness.

7.3.2.1 Public awareness

The study participants perceived that there is poor public awareness of HCC in Ethiopia. They stated that the general public in Ethiopia views cancer as a curse from God, owing to their lack of knowledge about the disease. Some respondents also described that there is little focus in the country on raising public awareness about HCC risk factors such as hepatitis B and C infections. This is summarized in one of the respondents' responses:

'' The lack of public awareness of HCC, I believe, has an impact on efforts to reduce the disease's burden or prevent it in the country. Cancer is viewed as a curse from God rather than a disease like any other. There has been little effort in the country to raise public awareness of HCC. Instead, a lot of work has been done on infectious diseases. Although hepatitis B and C infections are transmitted diseases, the most widely known transmitted disease in the population is HIV, and much work has been done to raise public awareness about HIV than hepatitis B and C. ''

The study participants also mentioned a lack of public awareness about other risk factors for HCC. They described people's lack of awareness about the association between certain risk factors for HCC, such as alcohol, and the disease. This is summarized by the response of one of the respondents:

''The public, in my opinion, should be made aware of the association between alcohol, aflatoxin, and other HCC risk factors and HCC. This, I believe, will help to reduce disease burden or facilitate disease prevention. ''

7.3.2.2 Health professionals' awareness

According to the participants, an effort is underway to improve knowledge of advanced cancer detection methods among medical doctors working on cancer in a few large cancer care facilities

across the country. However, they said the training was occasional and on cancer therapies in general, but not specifically on HCC.

"In a few large hospitals in the country, there is training on advanced cancer diagnosis methods. Cancer therapies are also given as a course in our medical education. Raising health professionals' knowledge and awareness of cancer and cancer therapy is also occasionally provided by a few institutions such as Ethiopian medical associations. However, there is no provision in the country for increasing health professionals' knowledge and awareness of HCC."

Participants in the study also indicated that little attention is paid to increasing cancer and HCC knowledge and awareness through continuous training for health professionals who are not medical doctors. They described the presence of occasional cancer training for medical doctors but not for other health professionals. This is summarized by one of the respondents:

" There is occasional and insufficient training for health professionals on cancer or HCC. Those who are not medical doctors, such as nurses and health officers, receive almost no training on cancer or HCC. Even doctors who receive cancer training, I think, are very few. There is also no training or awareness about cancer in the country, as there is for other chronic diseases. "

7.3.3 Theme 3: Improve funding

The other theme that emerged was related to increasing funding for activities such as HCC screening, diagnosis, and treatment.

7.3.3.1 Screening and diagnosis

The study participants mentioned that there is a need for HCC screening in the country. They described that screening for HCC among individuals with risk factors for the disease, such as hepatitis B and C infections, has received little attention in the country. They stated that a lack of funding is the primary reason for the country's lack of focus on screening. One of the study participants summarized this as follows:

"I believe there is a problem with cancer funding in general in the country. Inadequate funding, I believe, is the main cause of the country's scarcity of HCC screening and other related issues. A few cancer care institutes in the country are collaborating with an international organization to improve funding for diagnostic infrastructure, cancer screening, and other programs. However, I believe that international organizations' funding is insufficient to allow cancer care institutes to fully implement their screening and other programs. I believe that if the country's cancer care institutes received more such support, they would do better. "

The lack of funding for infrastructure for HCC and its risk factor diagnosis was also mentioned by study participants. They pointed out that there isn't much diagnostic infrastructure for determining hepatitis viruses' viral loads. Only a few cancer care institutes in Addis Ababa have access to such diagnostic infrastructure.

"I believe the country is underfunding cancer diagnosis. Imaging and CT scans, for example, are only available in a few hospitals across the country. As a result of such scarcity, cancer staging and advanced diagnostic techniques are limited to a few hospitals, and doctors also rarely refer patients for such advanced diagnosis."

7.3.3.2 Treatment

The respondents described that access to cancer treatment in the country is limited. They also mentioned a lack of funding for training health professionals in cancer therapy. Some respondents described that there are areas in the country where people do not receive adequate care therapy. Respondents pointed out that the likely high cost of new therapies also limited patient access.

"A budget is required to do anything related to cancer treatment, prevention, and control. Cancer funding is generally insufficient in almost every developing country. Cancer funding for treatment, prevention, and control, I believe, is limited in Ethiopia, as it is in other developing countries. Due to a lack of funding, there is a problem with training health professionals in cancer and establishing institutes with adequate infrastructure for HCC diagnosis and treatment."

7.4 Discussion

This qualitative study examined liver cancer clinicians' perceptions of the current need to prevent and control HCC in Ethiopia. It identified the following needs: improving disease prevention and control through screening for HCC in the general population, at-risk individuals, and those with comorbidities; raising public awareness of the disease and its risk factors, as well as health professionals' knowledge of HCC through continuous training; and increasing funding for HCC diagnosis, treatment, and screening.

This study's finding that HCC screening is one of the needs in HCC control in Ethiopia is consistent with the finding of Bridges et al (13), who reported the importance of early HCC screening in the control of the disease. Screening the general population or those at high risk of cancer aids in the early detection of cancer (680). Early detection of cancer improves disease control by making treatment easier or improving outcomes (643). By the time signs and symptoms appear, the tumour has grown in size, making treatment difficult (643, 680-682).

Cancer screening received little attention in Ethiopia until 2015, but since then, the country's Ministry of Health has developed a national cancer control program that focused on cervical and a few other cancer types while ignoring several others, including HCC (117). Recent reports, however, indicate that cervical cancer screening coverage in Ethiopia is also low; for instance, only one out of every seven women in the country received cervical cancer screening (683, 684). The reason for Ethiopia's low cancer screening attention and coverage is unclear (117). Several factors, however, have been reported to impede cancer screening, including state and local budget constraints, clinicians' lack of knowledge on how to promote or perform screening tests, and public awareness of the importance of cancer screening (685). Therefore, the reasons for low attention to screening for various cancer types, including HCC, as well as low screening coverage for the cancer types targeted by the national cancer control program of Ethiopia, need to be investigated and a more comprehensive screening program implemented in the country.

Raising public awareness of HCC and its risk factors is also identified by study participants as one of the needs for disease prevention and control in Ethiopia. The interviewed clinicians also

identified the need to improve health professionals' overall knowledge of HCC, as well as advanced HCC diagnosis and treatment methods. In agreement with this study, another study in Asia (678) identified public awareness of HCC as one of the critical strategies for effective disease control in the region. Similarly, another study found that raising public awareness of HCC and its risk factors is one of the needs for effective disease control (13).

In recent years, only a few studies have been conducted in Ethiopia to assess public awareness of a few types of cancer, such as cervical and breast cancer and these studies have found low public awareness (166, 168-170). Little attention has been paid in the country to determining public awareness of various cancer types, including HCC (117). However, it has been reported that the general public should be informed about cancer and its risk factors, available screening procedures that can help lower cancer risks, as well as recommendations for how frequently and when they should be screened (685). Without this awareness and knowledge, people are unlikely to consider screening or make behavioural changes that are critical for cancer prevention and control (685). Thus, as suggested by the study participants there should be efforts to raise public awareness of HCC and its risk factors in Ethiopia for effective disease prevention and control in the country.

Improved funding for HCC screening, diagnostic and treatment infrastructure is another need identified by study participants for HCC control. The study's findings are consistent with a previous study, which found that increased funding for HCC screening and treatment infrastructure is a need for controlling the disease (4). Another study identified HCC transplantation infrastructure and access to treatment as the highest and lowest priorities for the control of the disease, respectively (678).

In Ethiopia, cancer was not a priority until the government launched a national cancer control policy in 2015 (117). In 1997, for instance, the country launched a 20-year National Health Sector Development Program (HSDP) (158, 159). The program was completed in 2015, with disease prevention, decentralization of healthcare delivery, and increased national health spending among its priorities (158, 159). However, cancer and other non-communicable diseases were not given

the attention they deserved during the HSDP era because communicable diseases were competing priorities (158, 159). As a result, adequate government funding for cancer infrastructure, education, and research has not been made available on a timely basis (105). According to the Ethiopian Ministry of Health, this has contributed to the country's low preparedness to tackle the cancer burden and the salient increase in non-communicable diseases, including cancer, in the country (117). Thus, this, as well as the responses of study participants, point to the need for HCC funding to aid in the prevention and control of the disease in the country.

7.5 Conclusions and recommendations

The study identified three major needs for cancer control in Ethiopia. This study identified the need for disease prevention by screening the general public and those with HCC risk factors or other comorbidities. The study also identified raising public and health professional awareness of cancer as a need for disease control, as well as increasing funding for cancer diagnosis, treatment, and screening. The needs identified in this study refer to gaps in HCC screening, diagnosis, treatment, and other areas needed to develop an effective HCC control strategy/plan in the country.

The findings of this study suggested that HCC screening is needed in Ethiopia to prevent and control the disease. However, some factors must be considered when implementing an HCC screening program in the country. First, clinicians working on HCC in the country should be aware that screening is recommended and appropriate, as simply providing regulation or disseminating guidelines has been shown to not change practice behaviour (686, 687). Low screening performance of clinicians has also been reported, owing to their assumptions that, while screening is appropriate for patients, it is not their responsibility (688). Thus, in addition to the implementation of screening programs in Ethiopia, rules and regulations should be put in place to advise clinicians that it is their responsibility to do HCC screening.

The study's findings also point to the importance of raising public awareness about HCC and its risk factors. Awareness includes simply being aware of the disease's existence and risk factors, the disease's signs and symptoms, the fact that they are at risk of developing HCC, and the

importance of screening or early detection. Awareness of the disease and its risk factors, as well as its signs and risk factors, is essential for disease prevention and control, as it is essential for early diagnosis and better health-seeking behaviour (647). Cancer screening has also been reported to be underutilized if public awareness of the importance of screening is lacking (685).

In Ethiopia, funding should also be provided for HCC diagnosis, treatment, and screening to improve disease prevention and control. The development of infrastructure for cancer diagnosis and staging should be funded. The country should fund access to appropriate cancer treatment. Financial and access barriers to treatment and screening should be eliminated as well, for example, through the use of health insurance coverage and the availability of free screening and treatment at public and private cancer care institutes.

In general, it is recommended that the Ethiopian government address the needs identified by study participants and develop comprehensive cancer control strategies for the country. There is also a need to establish mechanisms to assess the performance of comprehensive strategies that will be implemented. Future similar research should be conducted in other regions of Ethiopia to determine how the need for HCC control varies by region.

CHAPTER EIGHT: GENERAL DISCUSSION

Chapter overview

In Ethiopia, little attention has been paid to assessing the current state of various cancer types and identifying gaps in current cancer control efforts, which could have aided in careful cancer control planning (117). For instance, little attention has been paid in the country to assessing: 1) the incidence and trends of HCC; 2) the burden of HCC risk factors among HCC patients; 3) general public awareness of cancer, including HCC; and 4) perceived infrastructure, funding, and financial needs in HCC control from the clinician perspective. Addressing these gaps could aid in the development of a thorough HCC or cancer control plan in the country. After this thesis identified the above-mentioned gaps by conducting systematic reviews, to address the gaps, I conducted a four-stage project that comprised three quantitative studies (two retrospective studies and a cross-sectional survey) and a qualitative study in the form of an in-depth interview in Addis Ababa, Ethiopia. This chapter synthesises findings from the thesis's four projects mentioned above.

8.1 Incidence and trends of hepatocellular carcinoma

Assessing the incidence and trend of cancer in a population using reliable data has been reported to be useful for cancer control planning (16). However, accurately determining the incidence and trends of HCC in several SSA countries has received little attention due to several factors, including a lack of cancer registries and poor data recording in cancer care institutes in the region (689). For instance, in Ethiopia, a SSA country, no study has been conducted to assess the incidence and trend of HCC in the general population, owing to a lack of reliable data sources such as cancer registries (172). The Ethiopian government established the first and only cancer registry in the capital city in 2011, but no study assessed the incidence and trend of HCC using data from such a reliable source (172). However, given the rising incidence of HCC risk factors in Ethiopia as well as the country's inadequate health care system, the disease is expected to cause significant harm to the country's health and economy (172). Thus, Project One of this thesis assessed for the first time the incidence and trend of HCC in Addis Ababa, Ethiopia. The project found: 1) a higher HCC incidence in men than in women throughout the study period (2012-2019),

with an increase in incidence for men between 2012 and 2019; and 2) a significant increase in the incidence of HCC in individuals aged 55 and older than those aged 35-54 and under 35 in 2019.

The higher HCC incidence in men compared to women in this study is consistent with the findings of other African studies (15, 554-556). It has been reported that men have a higher HCC incidence for a variety of reasons, including gender differences in risk factor exposure (690, 691). Men, for instance, are said to be more likely than women to have NAFLD, and type II diabetes is said to be more common in men than in women (690, 691). Moreover, HBV and HCV; the two major risk factors for HCC (692), were found to be more common in men than in women in Ethiopia and Addis Ababa (31, 558). Project Two of this thesis also found that HBV and HCV infections were more common in men than women HCC patients in Addis Ababa. Moreover, men are reported to have a lower risk perception than women, and men were reported to be more likely than women in SSA to have chronic HBV infection (roughly twice that of females) (557, 693). The aforementioned factors may thus explain the high incidence of HCC in men in this project.

It was also found that the incidence of HCC is higher in adults over the age of 54, which contradicted data from SSA studies (570, 571). The incidence was highest in people aged 35 to 45 in Uganda and between 30 and 50 in another study in Uganda (570, 571). In a Kenyan study, the incidence was highest in those 35 to 45 years of age (572), while in a second study, it was highest in people 30 to 40 years of age (573). The findings of Project Three of this thesis, which assessed public awareness of cancer and HCC in Addis Ababa, as well as the findings of other studies, may explain the increase in HCC incidence in older people in this study compared to previous studies. Project Three of this thesis found lower awareness among the elderly than among those who were young in Addis Ababa. However, awareness and knowledge about cancer have been reported to improve healthcare seeking (647). Moreover, elders in Ethiopia have previously been reported to be economically disadvantaged, making them less likely to seek early health care (581, 582). As a result of their low healthcare-seeking behaviour, they may be less likely to visit public health institutes in the country and benefit from cancer education provided there, which could help them take preventive measures.

Cancer can affect people of all ages, but it primarily affects the elderly, with the elderly accounting for approximately 60% of cancer cases (694, 695). One possible explanation is that as people get older, they are more likely to be exposed to cancer risk factors and develop unhealthy habits that put them at risk for the disease (696). Increased cancer risk with age has also been linked to immune response (245). The immune system is strong at a young age, capable of identifying and killing precancerous cells (245). However, as we age, our immune systems weaken and fail to target these precancerous cells (245, 247, 579). The failure of tumour-suppressing genes has also been linked to an increase in cancer incidence. For instance, DNA methylation, which prevents tumour suppression, increases with age, increasing the risk of cancer development (697, 698). The factors mentioned above may also have contributed to the higher incidence of the elderly in this study.

Moreover, according to Project Four of this thesis, which focuses on the perceptions of liver cancer clinicians, HBV screening is frequently done only on pregnant women who visited cancer care facilities in Ethiopia. Other studies conducted in Ethiopia, however, found that frequent screening of pregnant women for hepatitis B is not compulsory in the country, restricting its full implementation throughout the country. The implementation of such screening is likely to reduce their risk of developing HCC. HBV screening in the healthcare institute in Ethiopia for only pregnant women may have also contributed to the decrease in HCC in women between 2017 and 2019.

8.2 Hepatitis B and C infections in hepatocellular carcinoma patients and stage at hepatocellular carcinoma diagnosis

HBV and HCV are major risk factors for HCC (699). They are responsible for more than half of all HCC cases globally (699, 700). Many countries around the world, however, pay little attention to assessing their association with HCC development (56). Such data, on the other hand, can be used to develop careful HCC control plans (16). According to the WHO, hepatitis is endemic in Ethiopia (160-162). However, little attention has been paid to determining the prevalence of hepatitis B and C infections in HCC patients in the country (137, 172). Thus, Project Two of this

thesis, therefore, conducted a retrospective study to determine HBV and/or HCV infection among HCC patients diagnosed at Tikur Anbessa Specialized Hospital in Addis Ababa and stage at HCC diagnosis in Addis Ababa, and found: 1) the majority of HCC cases diagnosed between 2012 and 2020 at Tikur Anbessa Specialized Hospital were with HBV (32.8%), HCV (17.7%) and HBV and HCV coinfection (10.6%); and 2) the majority of HCC cases (54%) diagnosed at Tikur Anbessa Specialized Hospital between 2012 and 2020 were in stages III and IV, with only a few cases (20.2%) in stage I.

A higher proportion of HBV and HCV co-infections in HCC patients in this study could be attributed to a variety of factors. Ethiopia is classified as a country with endemic viral hepatitis (541), with a recent HBV prevalence of 7.4% and an HCV prevalence of 3.1% (625-627). The prevalence of injectable drug use is also increasing in Ethiopia, and drug users in Ethiopia's capital city, Addis Ababa, have been reported to share needles and other injecting equipment, which accelerates the spread of HCV and HBV in the city (536). Chronic hepatitis C and B infections account for more than 60% of chronic liver diseases in the country (161). Moreover, body alteration, such as piercing and tattooing, is becoming more common in Ethiopia, and this trend is linked to an increase in the prevalence of HBV and HCV in the country (537, 625, 628).

As found in Project Four of this thesis, little attention has been paid in the country to screening the general public for HCC and other cancer risk factors such as HBV and HCV. Participants in Project Four of this thesis also reported that there has been less funding for HCV and HBV diagnosis and viral load determination in the country, resulting in a lack of advanced diagnostic techniques in the majority of the country's health institutes. Moreover, participants in the qualitative study stated that there has been no awareness creation program in Ethiopia on the link between HCC and its risk factors, such as HBV and HCV. This is supported by the federal ministry of health of Ethiopia's report, which states that there has been no screening for HBV and HCV or awareness of HCC risk factors in the country (172). The above-mentioned factors may explain the high proportion of HBV and HCV in this study.

The majority of the HCC cases diagnosed at Tikur Anbessa Specialized Hospital in Addis Ababa between 2012 and 2020 were in stages III and IV. It has also been reported by the Ethiopian Ministry of Health that the majority (85%) of cancer patients in Ethiopia are diagnosed at an advanced stage with few treatment options (172). A rigorous discussion, however, could not be held due to a lack of comparable studies. Several factors may contribute to the majority of patients being diagnosed at advanced stages (stages III and IV). The factors can be three-pronged, which encompass patient, clinician, and health system-related reasons.

Patients may be unable to recognize cancer symptoms in themselves, resulting in an earlier-stage diagnosis (630). Project Four of this thesis also found that there has been little effort to raise public awareness of the symptoms and signs of HCC in Ethiopia. The primary care physician may fail to recognize and treat patients with suspicious HCC symptoms, particularly in children (172). The finding in Project Four of this thesis that the Ethiopian government has paid little attention to providing continuous training to health professionals working on HCC in this thesis's qualitative study strengthens this argument.

Project Four of this thesis also found that the government invests less in cancer diagnosis and treatment infrastructure in Ethiopia. It was also found in Project Four that advanced diagnosis and treatment infrastructure are only available in a few cancer care institutes, and there is a poor referral system. These factors may have also contributed to the late-stage diagnosis observed in Project Two of the thesis.

A poor health system, including the absence of a screening program, can also contribute to a late cancer diagnosis (631). According to participants in Project Four of this thesis, Ethiopia does not have a screening program for HCC in people who are at risk of the disease, such as HBV and HCV patients. There is also no funding for designing and implementing screening programs in the country. The factors mentioned above may have contributed to the high proportion of advanced HCC cases observed in Addis Ababa in Project Two of this thesis.

8.3 Hepatocellular carcinoma and General Cancer Awareness

A further barrier to effective cancer/ HCC control planning in Ethiopia is the lack of information on general public awareness of cancer/HCC signs, symptoms, and risk factors (110, 166, 167).

According to Ethiopia's Federal Ministry of Health, 80% of cancer cases in the country are discovered at advanced stages, which is suggested to be due to the general public's poor awareness of cancer (105). However, there have only been a few studies on the public's awareness of cancer in Ethiopia in recent years, and these studies have mainly focused on a few cancer types like colorectal, breast, and cervical cancer (166, 168-170). Because these studies focused on cancer types other than HCC and were carried out in various contexts, circumstances, periods, and populations, it is challenging to generalize their findings to HCC. Moreover, no previous research has looked into the public's awareness of HCC symptoms and risk factors in Ethiopia.

Thus, Project Three used a cross-sectional survey to assess public awareness of cancer and HCC signs, symptoms, and risk factors and found: 1) lower awareness of cancer and HCC signs and risk factors when open questions were used as opposed to closed questions; 2) lower cancer awareness among those aged 60 and older compared to those aged 18 to 29; 3) higher awareness of cancer signs and symptoms among those with primary, secondary, and tertiary education compared to those with no formal education, which are discussed below.

The demonstration in Project Three of this thesis that individuals aged 60 and older have low recognition of cancer signs and risk factors is consistent with the report of Robb et al (657) from the UK. However, younger age groups (15-34 years) were found to have lower cancer symptom awareness in other studies (657, 658). In 2015, the Ethiopian government launched its first national cancer control plan, with one of its goals being to raise cancer awareness among the general public. The elderly, on the other hand, receive little attention in the awareness program (172). This could explain why, in contrast to previous studies, older people were the least aware of cancer in this study.

Until recently, the Ethiopian government placed a high priority on infectious disease control, while cancer prevention and control received little attention (172). The qualitative section of this thesis also found that cancer in general, and HCC in particular, has received less public recognition and that less effort has been made to raise public awareness of the disease in Ethiopia. Moreover,

there was no internet access in Ethiopia until recently, and internet access coverage in the country is also very low. This appears to imply that older people had no option of using the internet and learning about cancer from various sources. As a result of the aforementioned factors, older people in this study may have a low awareness of cancer.

Low socioeconomic status (SES), such as low income, has also been linked to decreased cancer awareness (655). The elderly in Ethiopia face economic challenges and inadequate income. However, the cost of medical care and transportation to public health facilities in the country is prohibitively expensive, discouraging them from seeking medical attention and visiting public health facilities (138, 575, 576). Although the Ethiopian government established a system called health care for the poor, it has been reported that it is not functioning as intended, which discourages the elderly from seeking health care or visiting public health care institutes in the country (577, 578). The elderly may have been less likely to benefit from the cancer education program because of their poor public health care seeking and visiting health care institutes.

In Project Three of this thesis, respondents with primary, secondary, and tertiary education were more aware of cancer signs and symptoms than those who were illiterate. This was consistent with findings from studies in the United Kingdom (657) and Malesia (449), in which a higher level of education was associated with greater cancer sign awareness. In Denmark, respondents with a high level of education were also more aware of cancer risk factors (659). Government institutions and schools in Ethiopia, particularly in Addis Ababa, are implementing cancer awareness programs to teach students and staff how to reduce their risk of developing cancer and recognize its early signs and symptoms (660, 661). Moreover, educated Ethiopians use social media platforms more than illiterates (701), providing them with more cancer information and raising their awareness of cancer symptoms and risk factors (665). Raising cancer awareness in illiterate people may thus be aided by other methods of awareness creation, such as public cancer awareness creation through national television and radio, which are accessible to almost everyone.

In Project Three, a lower proportion of respondents identified HBV and HCV as risk factors for HCC. The cause of low public awareness of the link between HBV and HCV and the risk of HCC is difficult to pinpoint. However, this could be due to a lack of emphasis in Ethiopia on raising awareness about the link between viruses and the risk of HCC, as opposed to efforts to raise awareness about the link between other risk factors such as smoking and alcohol use and the risk of HCC (105). It has been reported that the vast majority of HCC cases worldwide are caused by HBV and HCV (54, 702). While HCV is thought to be responsible for more than half of all HCC cases worldwide, HBV is responsible for 10-25% of all cancer cases worldwide (73). A few studies have suggested that HBV and HCV are important risk factors for HCC in Ethiopia (93, 109-113, 532). Moreover, the burden of HBV and HCV on Ethiopians is said to be increasing. Project Two of this thesis found that the majority of HCC patients in Addis Ababa had HBV and/or HCV infections, which is expected to increase the country's HCC burden. Given the potential role of HBV and HCV in increasing the risk of HCC in Ethiopia, a strategy to mitigate their potential impact on HCC risk is required, which includes raising public awareness of the virus-disease link.

8.4 Current needs to control hepatocellular carcinoma

According to the WHO, evaluating the existing cancer control plan and ongoing activities is one of the needs for cancer control planning (16). Identifying gaps in physical (e.g., infrastructure), human (e.g., health-care personnel), and financial resources in cancer control is an important part of evaluating the current cancer control plan and ongoing activities (16). However, no study in Ethiopia examined the aforementioned gaps in HCC or cancer control.

Thus, Project Four of this thesis investigated the perceptions of liver cancer clinicians in Ethiopia about the infrastructure, education, and funding needed to control HCC. The project identified the need to promote HCC prevention through screening for the disease and its risk factors. Those at high risk of HCC, such as those with HBV and HCV, as well as those with comorbidities, should be screened for better disease control. The findings of this study, which indicate that HCC screening is one of the needs for HCC control in Ethiopia, are in line with those of Bridges et al. (13), who reported the significance of early HCC screening in the control of the disease.

Project Four also identified raising HCC awareness as a need for disease control in the country. It found a need to increase general public awareness of HCC and the link between the disease and its risk factors. The project also identified the need for continuous training to improve health professionals' knowledge and awareness of HCC. Similar to this study, another Asian study (678) identified raising public awareness of HCC as one of the needs for efficient disease management in the region. Similarly to this, a different study discovered that one need for efficient HCC control is increasing public awareness of the disease and its risk factors (13).

Another need identified in Project Four of this thesis is funding. It revealed that increased funding for HCC treatment is needed for the country to control the disease. It has also been identified that there is a problem with treatment access in the country. Increased funding for HCC diagnosis is also needed, according to Project Four, particularly for the introduction of advanced HCC, HBV, and HCV diagnostic infrastructure. Project Four has also determined that increased funding for the implementation of HCC screening programs is required to control the disease in the country.

A previous study discovered that increased funding for HCC screening and treatment infrastructure is also required for disease control (13). Another study identified HCC transplantation infrastructure and treatment access as the highest and lowest priorities for disease control, respectively (678).

8.5 Conclusions, recommendations, and implications

In Ethiopia; a SSA country, little attention has been paid to determining the burden of HCC and identifying gaps in controlling the disease, as has been the case for several cancer types in the country (172). The scarcity of epidemiological data on HCC makes developing a prevention and control plan/strategy difficult (16). This is because, according to WHO, cancer control planning entails, among other things, understanding the disease burden and gaps in the country's current cancer control plan or strategy (16). Thus, in Addis Ababa, this thesis assessed: 1) the incidence and trend of HCC using population-based cancer registry data; 2) public awareness of HCC and cancer signs, symptoms, and risk factors; 3) infrastructure, educational, and funding needs to control HCC; and 4) HBV and HCV infections in Addis Ababa HCC patients.

This thesis found a higher HCC incidence in men and the elderly between 2012 and 2019. It was also found in this thesis that the majority of HCC cases in Addis Ababa had HBV (32.8%), HCV (17.7%), or HBV and HCV coinfection (10.6%). The majority of HCC cases (54%) in Addis Ababa were also in stages III and IV, with only a few cases (20.2%) in stage I. Moreover, awareness of cancer signs and symptoms was found to be lower in those aged 60 and older than in those aged 18 to 29. The research also found that those with primary, secondary, and tertiary education were more aware of cancer signs and symptoms than those with no formal education. The research participants in the qualitative section of this thesis also identified the following needs for HCC control: increasing public awareness of HCC; improving the knowledge of health professionals regarding HCC through ongoing training; and increasing the budget for HCC diagnosis, treatment, and screening.

The findings in Project One of this thesis, that there is an increasing incidence of HCC in men and the elderly, point to the need for an appropriate HCC prevention and control strategy or plan that emphasizes these groups. The plan or strategy may employ a variety of techniques, including the following:

I. Screening for HCC in the general public if resources allow, and if not, on those at high risk of the disease, such as men and the elderly.
II. Raising public awareness, especially among men and the elderly, about HCC, its risk factors, and the importance of early detection and screening for HCC.
III. HCC advocacy to improve the lives of patients and encourage policymakers to pay attention to the disease and take appropriate action.
IV. Addressing the elderly's economic challenges may improve their health-care-seeking behaviours or encourage them to visit healthcare institutions in the country despite the high treatment costs.

The demonstration in Project Two of this thesis that the majority of HCC patients in Addis Ababa were infected with HBV and/or HCV emphasizes the importance of reducing HBV and HCV

infections in the country. This can be done through a variety of methods, including those listed below:

i. Raising public awareness of HBV and HCV, as well as their role in increasing the risk of HCC.
ii. If resources allow, screen the general public for HBV and HCV; otherwise, screen those at risk of HBV and HCV, such as injecting drug users.
iii. Increasing funding for HBV and HCV diagnostic infrastructure and access to standard treatment.
iv. Expansion of HBV vaccination, as well as early detection and treatment of HCV cases.
v. Regulating the body modification (tattooing and body piercing) industries, establishing safety standards for body modification practices in the country, and training body modification practitioners in aseptic techniques.

The finding in Project Three of this thesis that there is low awareness of cancer and/or HCC in the elderly and illiterate suggests that there is a need to raise awareness in these groups as well as address impediments that prevent them from being aware of the disease. The following may help raise their awareness:

i. Improving the health-care-seeking behaviour of the elderly. Encouraging the elderly to visit public health facilities in the country and take advantage of cancer awareness programs provided there. This can be accomplished by strengthening social associations in the country that provide financial assistance and improving their economy by directing income-generating activities.
ii. Raising cancer and HCC awareness in illiterate and elderly people through methods that are easily accessible to them, such as television and radio, as well as other means.
iii. Incorporating HCC awareness into the daily cancer education program in the country's public hospitals, with a focus on the elderly and illiterates.
iv. Labelling alcohol bottles and tobacco packs with cancer/HCC warning signs or information on cancer/HCC risk associated with tobacco and alcohol use, as this type of

awareness method is likely to be accessible to nearly all population subgroups, including the elderly and illiterate.

8.6 Strengths and limitations of the thesis

8.6.1 Strengths of the thesis

The thesis's strengths have been indicated in relevant chapters of the thesis, and this section describes the main strengths. This is the first study that uses data from a population-based cancer registry (AACCR) to assess the incidence and trends of HCC in Addis Ababa. This aided in determining the disease burden in the general population using a representative sample for the first time in the country. The AACCR collects data from all cancer care facilities in Addis Ababa, making the data used in this study representative of the population under investigation.

Another strength of this thesis is that it is the first to conduct a population-based survey in Addis Ababa to assess public awareness of HCC signs, symptoms, and risk factors. The use of a validated cancer awareness measure, as well as open and closed questions, is also a strength of the thesis. Moreover, this is the first study to look at how liver cancer clinicians perceive infrastructure, education, and funding gaps in HCC control in Addis Ababa.

8.6.2 Limitations of the thesis

The limitations of studies in the thesis are described in the respective chapters, and this chapter presents the pertinent limitations. Due to a lack of data on HCC risk factors in the AACCR, this thesis was unable to extract risk factor data for each HCC case extracted from the registry which could have helped to better explain the possible causes of the incidence and trend of HCC observed in this study.

The data for determining HCC incidence and trends in Addis Ababa was extracted from the ACCR which collects data from all cancer diagnosis and treatment facilities in the city. However, due to a variety of factors, including financial hardship, some groups of the population, such as the elderly, may not get HCC diagnosis and treatment access in the city and may be missed by the cancer registry. HCC cases may be missed by the cancer registry due to the lack of a health system that allows screening of patients at risk of HCC, such as those with HBV and HCV. The findings of this

study may not be representative of Ethiopia as a whole because data for this study were only collected from Addis Ababa.

In this thesis's cross-sectional survey study, a validated questionnaire containing closed-ended and open-ended items was used. The awareness score from the closed-ended question in this thesis's cross-sectional survey study may be exaggerated because participants may have found it easy to guess the correct answer. Because recall is dependent on memory, the awareness score from open-ended questions may also be underestimated.

In this thesis, data on HBV and HCV incidence among HCC patients were obtained from the Tikur Anbessa Specialized Hospital in Addis Ababa. It would have been preferable if the data had been collected from all of the cancer care institutes in the city. However, as explained in the relevant chapter of the thesis, the poor data archive system of the cancer care institute in the city prevented us from accessing data from all of the institutes.

Although data on patients' positivity for HBV and HCV were extracted, the precise diagnostic method used to diagnose each HBV and HCV case was not extracted, limiting this study from examining differences in HBV and HCV infections among HCC patients based on the method of diagnosis. This could have helped explain the differences in HBV and HCV infections in HCC patients by socioeconomic status.

8.7 Future studies

The incidence and trend of HCC are examined in this study using only data from Addis Ababa residents. Understanding the incidence and trend of HCC in other parts of Ethiopia has received little attention. It has been reported, however, that determining the incidence and trend of HCC is important for developing a thorough national HCC control plan in the country (16). Thus, future research should look at the incidence and trends of HCC in other Ethiopian regions to further understand the national HCC burden and design a better national HCC control plan for the country. However, because the cancer registry is only available in Addis Ababa, cancer registries in other regions of the country are needed. As a result, future research should look at the feasibility and cost-effectiveness of establishing similar registries in other regions of the country.

This study only determined HBV and HCV burden in HCC patients due to a lack of data on other HCC risk factors. However, it has been reported that various risk factors for HCC, such as alcohol intake and tobacco smoking, are prevalent in the Ethiopian general population (119, 560, 703, 704). Assessing the role of these factors in HCC development in the country aids in the development of a careful HCC control plan (16). Thus, future studies should assess the impacts of HBV, HCV, and other risk factors on HCC development to better understand the role of risk factors in increasing the risk of HCC in the country and develop a careful HCC control plan.

This study does not consider public awareness of some components of cancer control, such as public awareness of cancer or HCC, because its goal is to determine socio-demographic differences in public awareness of cancer and HCC signs, symptoms, and risk factors. Future studies should look into public awareness of the importance of screening and early detection.

Because there was no data linking mechanism in Ethiopia at the time of the study, it was not possible to link each HCC case identified in the cancer registry to risk factor exposure in other databases in the country. Therefore, future studies should use data from the AACCR to determine the incidence and trend of HCC, as well as link HCC cases to risk factor exposure in other existing databases when available in the country.

This study only looked at the country's infrastructure, educational, and research needs to control HCC. Using the data from this study and other similar data collected in the country in the future, other studies must address other needs (e.g., identifying feasible interventions for the gaps identified in the studies, establishing intervention priorities, and determining target groups) in order to design a careful HCC or cancer control plan or for policy formulation.

APPENDICES

Appendix 1: Supplementary materials for the systematic reviews

Appendix 1.1: Literature search terms

#	Search terms used in PubMed for HBV and HCV infections in HCC development
1	hepatocellular carcinoma OR liver malignancy OR malignant hepatoma OR liver neoplasm OR Hepatoma OR liver cancer OR Hepatocarcinoma
2	diabetes OR obesity OR smoking OR alcohol OR hepatitis B virus OR hepatitis C virus OR alcohol-related disorder OR Porphyrias OR Wilson's disease OR Alpha-1 antitrypsin deficiency OR aflatoxin B1 OR non-alcoholic fatty liver disease OR impaired glucose metabolism OR metabolic syndrome OR glycogen storage disease OR chronic obstructive pulmonary disease
3	causal interaction OR biological interaction OR additive interaction OR multiplicative interaction OR mechanistic interaction OR risk factors interaction OR sufficient cause interaction OR synergism
4	1 AND 2 AND 3. Filters: Published Date: 19980101-20201130; Human; English. Field: Title/Abstract
	Search terms used in CINAHL(EBSCO) for HBV and HCV infections in HCC development
5	("hepatocellular carcinoma" OR (MH "Carcinoma, Hepatocellular") OR "liver malignancy" OR (MH "Liver Neoplasms") RO "malignant hepatoma" OR "Hepatoma" OR "liver cancer")
6	((MH "Diabetes Mellitus, Type 2") OR "diabetes" OR "obesity" OR "smoking" OR "alcohol" OR (MH "Alcohol Drinking") OR (MH "Hepatitis B, Chronic") OR (MH "Hepatitis B") OR "hepatitis B virus" OR (MH "Hepatitis C, Chronic") OR (MH "Hepatitis C") OR "hepatitis C virus" OR (MH "Alcohol-Related Disorders") OR "alcohol-related disorder" OR "Porphyrias" OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR (MH "Aflatoxins") OR "aflatoxin B1" OR (MH "Nonalcoholic Fatty Liver Disease") OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism" OR "metabolic syndrome" OR "glycogen storage disease" OR "chronic obstructive pulmonary disease")
7	(''causal interaction*'' OR ''biological interaction*'' OR "additive interaction" OR "multiplicative interaction'' OR "mechanistic interaction" OR "risk factors interaction" OR "sufficient cause interaction'' OR synergism).
8	1 AND 2 AND 3. Filters: Published Date: 19980101-20201130; Human; English.
	Search terms used in Scopus for HBV and HCV infections in HCC development
9	(TITLE-ABS-KEY ("hepatocellular carcinoma" OR "liver malignancy*" OR "malignant hepatoma" OR "liver neoplasm" OR "hepatoma" OR "liver cancer" OR "hepatocarcinoma")

10	TITLE-ABS-KEY (diabetes OR obesity OR smoking OR alcohol OR "hepatitis B virus" OR "hepatitis C virus" OR "alcohol-related disorder*" OR porphyrias OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism" OR "metabolic syndrome" OR "glycogen storage disease" OR "chronic obstructive pulmonary disease")
11	TITLE-ABS-KEY ("causal interaction*" OR "biological interaction*" OR "additive interaction*" OR "multiplicative interaction*" OR "mechanistic interaction*" OR "risk factors interaction*" OR "sufficient cause interaction*" OR synergism))
12	9 AND 10 AND 11. Sorted by: PUBYEAR > 1997 AND PUBYEAR < 2021 AND (LIMIT-TO (LANGUAGE , "English"))
	Search terms used in Medline (Ovid)/Emcare for HBV and HCV infections in HCC development
13	Hepatocellular carcinoma.mp. OR exp Carcinoma, Hepatocellular/ OR exp Liver Neoplasms/ OR liver malignancy.mp. OR malignant hepatoma.mp.OR liver neoplasm.mp. OR exp Liver Neoplasms/ OR hepatoma.mp. OR liver cancer or hepatocarcinoma.mp.
14	Diabetes.mp. OR exp Diabetes Mellitus, Type 2/ OR exp Obesity/ OR obesity.mp. OR exp Obesity, Abdominal/ OR exp Tobacco Smoking/ or smoking.mp. OR alcohol.mp. or exp Alcohols/ OR hepatitis B virus.mp. OR exp Hepatitis B virus/ OR hepatitis C virus.mp. OR exp Hepacivirus/ OR alcohol-related disorder.mp. OR exp Alcohol-Related Disorders/ OR Porphyrias.mp. OR exp Porphyrias/ OR Wilsons disease.mp. OR Alpha-1 antitrypsin deficiency.mp. OR exp alpha 1-Antitrypsin Deficiency/ OR aflatoxin B1.mp. OR exp Aflatoxin B1/ OR non-alcoholic fatty liver disease OR impaired glucose metabolism.mp. OR metabolic syndrome.mp. OR exp Metabolic Syndrome/ OR glycogen storage disease.mp. OR exp Glycogen Storage Disease/ OR chronic obstructive pulmonary disease.mp. OR exp Pulmonary Disease, Chronic Obstructive/
15	Causal interaction.mp OR biological interaction.mp. OR additive interaction.mp. OR multiplicative interaction.mp. OR mechanistic interaction.mp. OR risk factors interaction.mp. OR sufficient cause interaction.mp. OR synergism.mp.
16	13 AND 14 AND 15. Filters: english; humans; yr. ="1998 - 2020".
	Search terms used in PubMed for the burden of HCC in Ethiopia
17	hepatocellular carcinoma OR liver malignancy OR malignant hepatoma OR liver neoplasm OR hepatoma OR liver cancer OR hepatocarcinoma incidence OR prevalence OR epidemiology OR burden OR proportion OR clinical diagnosis OR treatment OR control
18	diabetes OR obesity OR smoking OR alcohol OR hepatitis B virus OR hepatitis C virus OR alcohol-related disorder OR Porphyrias OR Wilson's disease OR Alpha-1 antitrypsin deficiency OR aflatoxin B1 OR non-alcoholic fatty liver disease OR impaired glucose metabolism OR metabolic syndrome OR glycogen storage disease OR chronic obstructive pulmonary disease

19	Ethiopia OR Addis Ababa
20	17 AND 18 AND 19. Filters: Published Date: 19700101-20201130; Human; English. Field: Title/Abstract
	Search terms used in Cochran/Google scholar for the burden of HCC in Ethiopia
21	("hepatocellular carcinoma" OR "liver malignancy*" OR "malignant hepatoma" OR "liver neoplasm" OR "hepatoma" OR "liver cancer" OR "hepatocarcinoma" in Title Abstract Keyword) (incidence OR prevalence OR epidemiology OR burden OR "proportion" OR "clinical diagnosis "OR treatment OR control
22	diabetes OR obesity OR smoking OR alcohol OR "hepatitis B virus" OR "hepatitis C virus" OR "alcohol-related disorder" OR Porphyrias OR "Wilson's disease" OR "Alpha-1 antitrypsin deficiency" OR "non-alcoholic fatty liver disease" OR "impaired glucose metabolism" OR "metabolic syndrome" OR "glycogen storage disease" OR "chronic obstructive pulmonary disease" in Title Abstract Keyword)
23	(Ethiopia OR "Addis Ababa" in Title Abstract Keyword)
24	21 AND 22 AND 23. Sorted by: date Between Jan 1970 and Nov 2020; Human; English.

Appendix 1.2: Newcastle-Ottawa quality assessment (NOS) checklist

I. NOS score for the combined role of HBV and HCV infection in HCC development (Case-control studies)

Author (year)	**Selection**				**Comparability**	**Exposure**			**Total score**
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Ayoola & Gadour (2004)**(492)**	*		*	*	**	*	*		7
Kuper et al. (2000) **(489)**	*		*	*	**	*	*		7
Mak et al., (2018)**(490)**	*	*	*	*	**		*		7
Jeng et al (2014)**(484)**	*		*	*	**	*	*		7
Yun et al. (2010)**(491)**	*	*	*	*	**		*		7
Jeng et al (2009)**(485)**	*	*	*	*	**	*			7
Ohishi et al. (2008) **(488)**	*	*	*	*	**		*		7
Ayoola & Gadour (2004)**(492)**	*		*	*	**	*	*		7
Tsai et al. (2004)**(487)**	*	*	*	*	**	*	*		8
Tsai et al. (2001)**(486)**	*	*	*	*	**	*	*		8

II. NOS score for the burden of HCC in Ethiopia (Cross-sectional studies)

Authors	**Selection/selection bias**				**Comparability**	**Outcome**		**Total**
	Representativeness of the cases	Sample size	Non-Response rate	Ascertainment of the screening/surveillance tool	Confounding factors are controlled	Assessment of the outcome	Statistical test	
Getaneh F and Atnafu A 2020 **(113)**	*		*			**		4
Mekonnen et al., 2015 **(110)**	*		*	*		**		5
Tsega et al.,1995 **(97)**		*	*					2
Tsega et al.,1992 **(96)**	*		*	*		**		5
Fekadu et al.,1989 **(111)**			*			**		3
Tsega et al.,1977 **(92)**			*			**		3

III. NOS score for the burden of HCC in Ethiopia (Cohort studies)

Authors	**Selection/selection bias**				**Comparability**	**Outcome**			**Total**
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Tsega et al.,1977 **(93)**			*			*			2
Pavlica et al.,1970 **(94)**			*			*		*	3

Appendix 2: Basis of diagnosis for cancer

Code	Description	Criteria
0	Death certificate	A death certificate is the only source of information available.
1	Clinical	Diagnosis made before death but without the use of any of the diagnosis methods described in numbers 2 through 7.
2	Clinical investigation	All diagnostic techniques (e.g., Ultrasound Scan, exploratory surgery, X-rays, Endoscopy, imaging, and autopsy) without a tissue diagnosis.
4	Specific tumour markers	Tumour-specific biochemical and/or immunological markers are used to make the diagnosis.
5	Cytology	Tumour examination from primary or secondary sites, including fluids aspirated via endoscopy or needle, as well as microscopic examination of peripheral blood and bone marrow aspirates.
6	Histology of metastasis	Histologic of metastasis tissue examination, including autopsy specimens.
7	Histology of a primary tumour	Histologic examination of primary tumour tissue, however, obtained, includes all cutting techniques and bone marrow biopsies, as well as primary tumour autopsy specimens.
9	Unknown	There is no information on how the diagnosis was made.

Appendix 3: Newcastle - Ottawa quality assessment scale Case-Control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

a) yes, with independent validation *

b) yes, e.g. record linkage or based on self-reports

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases *

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls *

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint) *

b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for _____ (Select the most important factor.) *

b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview where blind to case/control status *

c) interview not blinded to case/control status

d) written self report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes *

b) no

3) Non-Response rate

a) same rate for both groups *

b) non-respondents described

c) rate different and no designation

Appendix 4: Newcastle-Ottawa quality assessment form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative *
   b) Somewhat representative *
   c) Selected group
   d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort *****
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) Secure record (e.g., surgical record) *****
   b) Structured interview *****
   c) Written self-report
   d) No description
   e) Other
4) Demonstration that outcome of interest was not present at start of study
   a) Yes *****
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
   a) The study controls for age, sex and marital status *****
   b) Study controls for other factors (list)_____*****
   c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
   a) Independent blind assessment *****

b) Record linkage *
c) Self- report
d) No description
e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes *
b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for *
b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. *
c) Follow up rate less than 80% and no description of those lost
d) No statement

Appendix 5: Newcastle - Ottawa quality assessment scale for cross sectional studies.

Selection: (Maximum 5 scores)

1) Representativeness of the cases:
   a) Truly representative of the HCC patients (consecutive or random sampling of cases). *
   b) Somewhat representative of the average in the HCC patients (non-random sampling). *
   c) Selected demographic group of users.
   d) No description of the sampling strategy.

2) Sample size:
   a) Justified and satisfactory (≥ 400 HCC included). *
   b) Not justified (<400 HCC patients included).

3) Non-Response rate
   a) The response rate is satisfactory (≥95%). *
   b) The response rate is unsatisfactory (<95%), or no description.

4) Ascertainment of the screening/surveillance tool:
   a) Validated screening/surveillance tool. **
   b) Non-validated screening/surveillance tool, but the tool is available or described. *
   c) No description of the measurement tool.

Comparability: (Maximum 1 stars)

1) The potential confounders were investigated by subgroup analysis or multivariable analysis.
   a) The study investigates potential confounders. *
   b) The study does not investigate potential confounders.

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. **
   b) Record linkage. **
c) Self-report. *
d) No description.

2) Statistical test:

   a) The statistical test used to analyze the data is clearly described and appropriate. *
   b) The statistical test is not appropriate, not described or incomplete.

Appendix 6: AFCRN cancer registry cancer notification form

Local logo	*AFCRN* CANCER REGISTRY CANCER NOTIFICATION FORM	

Cancer registry Number ☐☐☐☐ ☐☐☐☐

1. PATIENT

I.D. Number: _

Given name (First name(s) ....

Surname (Family name)..

Date of birth ☐☐☐☐☐☐☐☐ Age: ☐☐ Sex: ☐ (1=male, 2=female, 9=NK)

Usual residence address: .... ☐☐☐

....

....

Telephone number: ....

Ethnic group: .... ☐☐

2. TUMOUR

Date of incidence: ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

Basis of diagnosis: ☐

0. Death certificate only
1. Clinical only
2. Clinical investigations (X ray etc)
4. Specific tumour markers
5. Cytology / Haematology)
6. Histology of metastasis
7. Histology of primary
9. Unknown

Primary site of the tumour .... C☐☐.☐

Morphology: .... M☐☐☐☐/☐

Stage: .... ☐☐ T: ☐ N: ☐ M: ☐

3. TREATMENT:

Surgery ☐ Radiotherapy ☐ Chemotherapy/ Hormone therapy ☐ Other (specify) ☐ ....

[1=Yes, 2=No, 9=Unknown]

4. SOURCE OF INFORMATION

Institution/ward: ______________________________________ ☐☐☐

Case number ________________

Laboratory ____________________ ☐☐ Lab. Number ______________

5. FOLLOW UP

Date of last contact (dd/mm/yyyy): ______________________ ☐☐☐☐☐☐☐☐

Status at last contact (1=alive, 2=dead, 9=NK) ____________ ☐

Cause of death (1= this cancer, 2= 0ther cause, 9= NK) ☐

Form filled by: _____________________ Date _____________ Signed. __________________

Data entered by: _____________________ Date _____________ Signed. __________________

Appendix 7: Letter of support from Addis Ababa University

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አዲስ አበባ ፡ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር ፲፩ ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለፓባ.ዳ/ፊ3፩፫፬ /2013/20

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ካዲስኮ አጠቃላይ ሆስፒታል
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ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊነደርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተከስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲደግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተከስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊነደርስ ዩኒቨርስቲ የጸደቀበትን ደብዳቤ አያይዘን መላካችንን እንገልጻለን።

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ዳይሬክተር

አዲስ አበባ ዩኒቨርሲቲ
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Aklilu Lemma Institute of Pathobiology
ADDIS ABABA UNIVERSITY

☎ 251-11-276-30-91/213-57-25 Fax: 251-11-2755296 e-mail: aklilu.lemma@aau.edu.et
✉ 1176

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አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፣ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 14 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለፓባ/ዳሬክተር/2013/20

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ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

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ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

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አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፣ ኢትዮጵያ

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Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 14 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለፓባ.ዳሬ/ዐ364 /2013/20

ለ፡ ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስፒታል
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ላጋር ሆስፒታል
ቤቴል ሆስፒታል
ቅዱስ ገብርኤል ሆስፒታል
ካዲስኮ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊነደርስ ዩኒቨርስቲ የPhD ተማሪ የሆነት አቶ ዝናዬ ተክስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲደግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተክስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊነደርስ ዩኒቨርስቲ የጸደቀበትን ደብዳቤ አያይዘን መላካችንን እንገልጻለን።

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

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አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፣ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 17 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለፓባ.ዳሬ/ዐ364/2013/20

ለ፡ ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስፒታል
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ላጋር ሆስፒታል
ቤቴል ሆስፒታል
ቅዱስ ገብርኤል ሆስፒታል
ካዲስኮ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊነይርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተክስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲደግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተክስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊነይርስ ዩኒቨርስቲ የጸደቀበትን ደብዳቤ እያይዘን መላካችንን እንገልጻለን::

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ የፓቶባዮሎጂ ኢንስቲትዩት
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አዲስ አበባ ዩኒቨርሲቲ
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አዲስ አበባ ፣ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 14 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለ.ፓ/ባ.ዳ/ሰ3ደ4 /2013/20

ለ፡ ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስፒታል
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ላጋር ሆስፒታል
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ቅዱስ ገብርኤል ሆስፒታል
ካዲስኮ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊንደርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተከስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲያግላቸው እየጠየቅን ከዚህ ይብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተከስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊንደርስ ዩኒቨርስቲ የጻደቀበትን ይብዳቤ አያይዘን መላካቸንን እንገልጻለን፡፡

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

አክሊሉ ለማ የፓቶባዮሎጂ ኢንስቲትዩት Aklilu Lemma Institute of Pathobiology ADDIS ABABA UNIVERSITY

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አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፡ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር ፮/ ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለ.ፓባ.ጻፊ/፭፮፫፫/ /2013/20

ለ፡ ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስፒታል
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ሊጋር ሆስፒታል
ቤቴል ሆስፒታል
ቅዱስ ገብርኤል ሆስፒታል
ካዲስኪ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊነደርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተከስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲደግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተከስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊነደርስ ዩኒቨርስቲ የጻደቀበትን ደብዳቤ እያይዘን መላካችንን እንገልጻለን።

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

☎ 251-11-276-30-91/213-57-25 Fax: 251-11-2755296 e-mail: aklilu.lemma@aau.edu.et
✉ 1176

አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፡ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 14 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለ.ፓባ.ዳሬ/3649 /2013/20

ለ፡ ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስፒታል
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ላጋር ሆስፒታል
ቤቱል ሆስፒታል
ቅዱስ ገብርኤል ሆስፒታል
ካዲስኮ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊነደርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተክስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲያግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተክስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊነደርስ ዩኒቨርስቲ የጸደቀበትን ደብዳቤ አያይዘን መላካችንን እንገልጻለን፡፡

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

☎ 251-11-276-30-91/213-57-25 Fax: 251-11-2755296 e-mail: aklilu.lemma@aau.edu.et
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አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
አዲስ አበባ ፡ ኢትዮጵያ

ADDIS ABABA UNIVERSITY
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Addis Ababa, ETHIOPIA

ቀን(Date): ጥር 14 ቀን 2013ዓ.ም
ቁጥር(Ref.No):አለፓባ.ዳሬ6364/2013/20

ለ: ሃሌሉያ ሆስፒታል
ቤተ ዛታ ሆስስፒታ
ኮሪያ ሆስፒታል
ላንድ ማርክ ሆስፒታል
ላጋር ሆስፒታል
ቤቴል ሆስፒታል
ቅዱስ ገብርኤል ሆስፒታል
ካዲስኮ አጠቃላይ ሆስፒታል
አዲስ አበባ

ጉዳዩ:- ትብብር እንዲደረግላቸው ስለመጠየቅ።

በአዲስ አበባ ዩኒቨርስቲ የአክሊሉ ለማ ፓቶ ባይሎጂ መካነ ጥናት ባልደረባ የሆኑት እና በአውስትሊያ ፊሊንደርስ ዩኒቨርስቲ የPhD ተማሪ የሆኑት አቶ ዝናዬ ተከስተ ''Determine the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa''በሚል ርዕስ ስር ጥናትና ምርምር ለማካሄ የሚያስፈልገውን መረጃ በመስጠት የተለመደውን ትብብር እንዲደግላቸው እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተከስተ የጥናት ፕሮፖዛል እንዲሁም ጥናት ከአዲስ አበባ ዩኒቨርስቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት እና ከአውስትራሊያ ፊሊንደርስ ዩኒቨርስቲ የጸደቀበትን ደብዳቤ አያይዘን መላካችንን እንገልጻለን።

ከሠላምታ ጋር

መንግስቱ ለገሰ (ዶ/ር)
ዳይሬክተር

☎ 251-11-276-30-91/213-57-25 Fax: 251-11-2755296 e-mail: aklilu.lemma@aau.edu.et
✉ 1176

አዲስ አበባ ዩኒቨርሲቲ
አክሊሉ ለማ ፓቶባዮሎጂ መካነ ጥናት
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⊠ 1176
(Fax): 251-11-2755296/251-11-1239729

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology
Addis Ababa, ETHIOPIA
☎ 251-11-276-30-91/213-57-25
e-mail: aau-ipb@ethionet.et

ቀን (date) 07 ሕዳር 2013 ዓ.ም
ቁጥር(Ref. No.) : ALIPB/0197/2013/20

ለ ቅዱስ ጳውሎስ ሆስፒታል
አዲስ አበባ

ጉዳዩ፡ ትብብር እንዲደረግላቸዉ ስለመጠየቅ፡፡

በአዲስ አበባ ዩኒቨርሲቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነጥናት ባልደረባ የሆኑት እና በአዉስትራሊያ ፌሊነደርስ ዩኒቨርሲቲ የ PhD ተማሪ የሆኑት አቶ ዝናዬ ተከስተ Determining the burden of hepatocellular carcinoma and associated risk factors in Addis Ababa, Ethiopia በሚል ርእስ ጥናትና ምርምር ለማካሄድ የሚያስፈልገዉን መረጃ በመስጠት የተለመደዉን ትብብር እንዲደረግላቸዉ እየጠየቅን ከዚህ ደብዳቤ ጋር አባሪ በማድረግ የአቶ ዝናዬ ተከስተ የጥናት ፕሮጀክት ፕሮፖዛል እንዲሁም ጥናቱ ከአዲስ አበባ ዩኒቨርሲቲ አክሊሉ ለማ ፓቶባዮሎጂ መካነጥናት እና ከአዉስትራሊያ ፌሊነደርስ ዩኒቨርሲቲ የጸደቀበትን ደብዳቤ አያይዘን መላካቸንን እንገልጻለን፡፡

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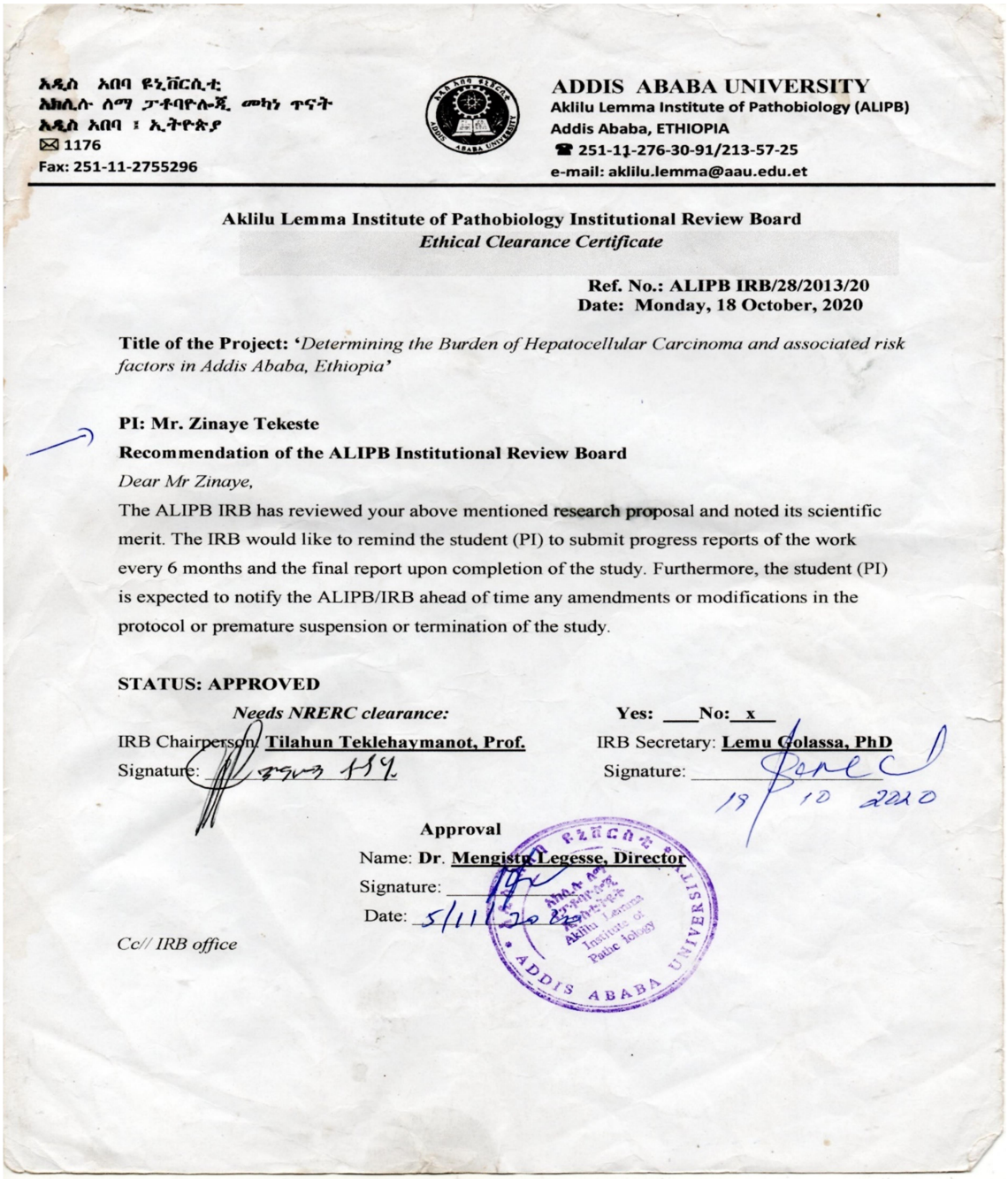
Appendix 8: Ethical approval from the institutional review board (IRB) of Addis Ababa University



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አዲስ አበባ ፣ ኢትዮጵያ
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Fax: 251-11-2755296

ADDIS ABABA UNIVERSITY
Aklilu Lemma Institute of Pathobiology (ALIPB)
Addis Ababa, ETHIOPIA
☎ 251-11-276-30-91/213-57-25
e-mail: aklilu.lemma@aau.edu.et

Aklilu Lemma Institute of Pathobiology Institutional Review Board
Ethical Clearance Certificate

Ref. No.: ALIPB IRB/28/2013/20
Date: Monday, 18 October, 2020

Title of the Project: '*Determining the Burden of Hepatocellular Carcinoma and associated risk factors in Addis Ababa, Ethiopia*'

PI: Mr. Zinaye Tekeste

Recommendation of the ALIPB Institutional Review Board

Dear Mr Zinaye,

The ALIPB IRB has reviewed your above mentioned research proposal and noted its scientific merit. The IRB would like to remind the student (PI) to submit progress reports of the work every 6 months and the final report upon completion of the study. Furthermore, the student (PI) is expected to notify the ALIPB/IRB ahead of time any amendments or modifications in the protocol or premature suspension or termination of the study.

STATUS: APPROVED

Needs NRERC clearance: **Yes: ___No: x**

IRB Chairperson: **Tilahun Teklehaymanot, Prof.**
Signature: _____

IRB Secretary: **Lemu Golassa, PhD**
Signature: _____
19/10/2020

Approval
Name: **Dr. Mengistu Legesse, Director**
Signature: _____
Date: 5/11/2020

Cc// IRB office

Appendix 9: Ethical approval from social and behavioural research ethics committee of the Flinders University

8572 ETHICS approval notice (18 March 2020)

Human Research Ethics <human.researchethics@flinders.edu.au>
Wed 3/18/2020 4:08 AM
To: Zinaye Tekeste Mehari <zinayetekeste.mehari@flinders.edu.au>

1 attachments (3 MB)
8572 conditional approval response (12 March 2020);

Dear Zinaye Tekeste,

Your conditional approval response for project 8572 was reviewed by the Chairperson of the Social and Behavioural Research Ethics Committee (SBREC) and was approved. The ethics approval notice can be found below.

APPROVAL NOTICE

Project No.:	8572
Project Title:	Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia
Principal Researcher:	Mr Zinaye Tekeste Mehari
Email:	meha0006@flinders.edu.au
Approval Date:	18 March 2020
Ethics Approval Expiry Date:	1 March 2021

Appendix 10: Daily household visitation log sheet

INTERVIEWER NAME: _____ TODAY'S DATE: _____

#	Household ID#	Household location	Time visit 1	Time visit 2	Interview complete?	Interview refused?	House vacant/no eligible participant?
					Y/N	Y/N	Y/N

Appendix 11: Cancer awareness measure tool

Survey questions

A. Demographic questions

Thank you for agreeing to take part in the research!

Survey code: _____

Date data collected: _____

Name of data collector: _____

Signature of the data collector: _____

Field coordinator's name: _____

Field coordinator's signature: _____

Code	Questions	
1	What is your age?	_____
		Prefer not to say
2	What is your gender?	Male
		Female
		Prefer not to say
3	What is your marital status?	Single
		Married
		Divorced/ Widowed
		Prefer not to say
4	What is the highest level of education qualification you have obtained?	Elementary student/completed
		High school student/completed
		Diploma /certificate
		Degree or higher

		No formal qualifications/Can't read and write
		Prefer not to say
5	Employment	Government employee
		NGO
		Unemployed
		Self-employed/Private
		Full-time homemaker/Housewife
		Retired
		Prefer not to say
6	Monthly income	

B. Cancer warning signs and symptoms

Code	Questions			
1	There are many warning signs and symptoms of cancer. Please name as many as you can think of:			
2	The following may or may not be warning signs and symptoms of cancer. We are interested in your opinion.			
		Yes	No	I don't know
	Do you think that unexplained weight loss could be a sign or symptom of cancer?			
	Do you think that unexplained lump/swelling could be a sign or symptom of cancer?			
	Do you think that unexplained persistent pain could be a sign or symptom of cancer?			
	Do you think that unexplained bleeding could be a sign or symptom of cancer?			
	Do you think that persistent cough/hoarseness could			

	be a sign or symptom of cancer?
	Do you think that difficulty in swallowing could be a sign or symptom of cancer?
	Do you think that a sore that does not heal could be a sign or symptom of cancer?
	Do you think that coughing up blood could be a sign or symptom of cancer?
	Do you think that shortness of breath could be a sign or symptom of cancer?
	Do you think that tiredness all the time could be a sign or symptom of cancer?

C. Cancer risk factors awareness

1	**What things do you think affect a person's chance of developing cancer?**			
2	These are some of the things that can increase a person's chance of developing cancer. How much do you agree that each of these can increase a person's chance of developing cancer?			
		Agree	Disagree	Not sure
	Smoking			
	Exposure to another person's cigarette smoke (passive smoking)			
	Low intake of fruit/vegetables			
	Alcohol consumption			
	Overweight (BMI= 25.0 - 29.9)			
	Obese (BMI= 30.0 and above)			
	Sunburnt/exposure to the sun			

	Older age
	Eating red or processed meat
	Stress
	Not doing enough exercise/physical activity
	Family history of cancer/having a close relative with cancer

D. HCC warning signs and symptoms

Code	Questions
1	There are many warning signs and symptoms of hepatocellular carcinoma. Please name as many as you can think of:
2	The following may or may not be warning signs and symptoms for hepatocellular carcinoma. We are interested in your opinion.

	Yes	No	I don't know
Do you think that feeling very full after a small meal could be a sign/symptom of hepatocellular carcinoma?			
Do you think that loss of appetite could be a sign/symptom of hepatocellular carcinoma?			
Do you think that pain in the abdomen or near the right shoulder blade could be a sign/symptom of hepatocellular carcinoma?			

	Do you think that ascites (abdominal swelling) could be a sign of hepatocellular carcinoma?
	Do you think that fluid build-up in the abdomen could be a sign/symptom of hepatocellular carcinoma?
	Do you think that Jaundice (yellowing of skin and eyes) could be a sign/symptom of hepatocellular carcinoma?

E. HCC risk factors awareness

1	**What things do you think affect a person's chance of developing HCC?**
2	These are some of the things that can increase a person's chance of developing HCC. How much do you agree that each of these can increase a person's chance of developing HCC?

	Agree	Disagree	Not sure
Smoking			
Type II diabetes			
Alcohol consumption			
Overweight (BMI= 25.0 - 29.9)			
Obesity (BMI= 30.0 and above)			
Aflatoxin exposure			
Hepatitis B virus			
Hepatitis C virus			
Smoking			
Type II diabetes			

Appendix 12: Letter of introduction

Professor Paul Ward

College of Medicine and Public Health

Flinders University

Tel: +61 8 72218415

LETTER OF INTRODUCTION

Dear participants,

This letter is to introduce Mr. Zinaye Tekeste Mehari who is a Ph.D. student at Flinders University, College of Medicine and Public Health, Australia. Mr. Zinaye is undertaking research leading to the production of a thesis or other publications on Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia. He would like to invite you to participate in this study. The study involves an interview, and a maximum of one hour is required to finish the interview. The information that you will provide will remain confidential and no identifying information will be published. You are also free to discontinue your participation at any time or decline to answer any question. Mr. Zinaye will wear a nametag from Flinders University that will help to identify him as a researcher. Mr. Zinaye intends to record the interview on condition that your name or identity is not revealed, and the recording will not be made available to any other person.

Any inquiries you may have concerning this research should be directed to Professor Paul Ward at the following address: Telephone +61 8 72218415 Email paul.ward@flinders.edu.au 27 Thank you for your attention and assistance.

Professor Paul Ward

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number:**8572**). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone at +61 8201 3116, by fax at 8201 2035, or by email human.researchethics@flinders.edu.au

Appendix 13: Information sheet for survey participants

INFORMATION (Survey participants)

Title: Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia

Researcher(s)

Mr. Zinaye Tekeste Mehari

College of Medicine and Public Health

Flinders University

Tel: +61404127843

Supervisor(s)

Professor Paul Ward

College of Medicine and Public Health

Flinders University

Tel: +61 8 72218415

Dr. Emma Miller

College of Medicine and Public Health

Flinders University

Tel: +61 8 7221 8445

Dr. Nega Berhe

Aklilu Lemma Institute of Pathobiology

Addis Ababa University

Tel: +251911408340

Information about the study

We would like to invite you to take part in a study titled “Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia." According to reports, little attention has been paid to determining the burden of hepatocellular carcinoma in Addis Ababa, liver cancer clinicians' perceptions of current infrastructural and educational needs in hepatocellular carcinoma control in Ethiopia, and public awareness of hepatocellular carcinoma and its risk factors in Addis Ababa. Thus, this study will address the aforementioned knowledge gaps. This research project is supported by Flinders University in South Australia. Only the researcher and data collector will have access to the research data obtained from or about you. Moreover, the study's findings will be published so that you can learn about them. However, once the project is completed, the researcher will not provide participants with project feedback.

What will I be asked to do?

We will invite you to participate in a brief interview. Following some age-related questions, we will ask for information about your awareness of hepatocellular carcinoma signs and risk factors in Ethiopia.

What benefit will I gain from being involved in this study?

Although there is no immediate benefit to you, we hope to gain a better understanding of how to help reduce the number of Ethiopians who develop hepatocellular carcinoma as a result of this research. Moreover, you will be provided 1.5 AUD (approximately 30 Ethiopian birr), and also be provided soft drinks or snacks to reimburse participants for their time.

Will I be identifiable by being involved in this study?

While all information obtained in this project will be kept strictly confidential, participation will not be anonymous.

Are there any risks or discomforts if I am involved?

Because you will be asked to participate in an interview, some questions may bring back unpleasant memories. If this happens to you, remember that you are not required to answer any questions that make you uncomfortable, and you are not even required to complete the interview. Please be aware that if you are experiencing emotional distress, the interview will be terminated. Please see the list below for the names and contact information for free counselling services.

Tikur Anbessa Specialized Hospital

+251 11 111 1111

Who is the project leader?

Mr. Zinaye Tekeste is leading this study, and you can reach him at meha0006@flinders.edu.au

How do I agree to participate?

Simply read the acknowledgment comments/consent form below. If you agree, please sign or provide your recorded verbal consent, and we will proceed to the interview.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number: **8572**). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone at +61 8201 3116, by fax at 8201 2035, or by email human.researchethics@flinders.edu.au

Appendix 14: Consent form

Consent form

Interview Consent Form

I, being over the age of 18, hereby consent to participate in the interview as requested for the research project titled "Determining the burden of Hepatocellular Carcinoma (HCC) and associated risk factors in Addis Ababa, Ethiopia."

1. I have read the information above and agree to take part in this research.
2. The project, so far as it affects me, has been fully explained to my satisfaction by the above information. My consent is given freely.
3. Although I understand the purpose of the research project it has also been explained that involvement may not be of any direct benefit to me.
4. I have been informed that, while information gained during the study may be published, I will not be identified and my results will not be divulged.
5. I understand that I am free to withdraw from the project at any time.
6. I am aged 18 years or more, and a resident of Addis Ababa, Ethiopia.
7. I have been informed that participation will have no impact on employment.

I, _____ (name; please print clearly), have read the above information. I freely agree to participate in this study. I understand that I am free to refuse to

answer any question and to withdraw from the study at any time. I understand that my responses will be kept confidential.

Participant Name: _____

Signature _____ __ Date _____

Researcher name: Mr Zinaye Tekeste

Signature _____ Date _____

Any inquiries you may have concerning this research project should be directed to contact the Social and Behavioural Research Ethics Committee (SBREC)**,** Flinders University, emailing to human.researchethics@flinders.edu.au or Institutional Review Board of Addis Ababa University, Aklilu Lemma Institute of Pathobiology.

Thanks for taking the time to read this information sheet and we hope that you will accept our invitation.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number: **8572**) For more information regarding the ethical approval of the project only, the Executive Officer of the Committee can be contacted by telephone at +61 8201 3116, by fax on (08) 8201 2035, or by email to human.researchethics@flinders.edu.au

Appendix 15: Information sheet for health professionals

INFORMATION (Health professionals)

Title: Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia

Researcher(s)

Mr. Zinaye Tekeste Mehari

College of Medicine and Public Health

Flinders University

Tel: +61404127843

Supervisor(s)

Professor Paul Ward

College of Medicine and Public Health

Flinders University

Tel: +61 8 72218415

Dr. Emma Miller

College of Medicine and Public Health

Flinders University

Tel: +61 8 7221 8445

Dr. Nega Berhe

Aklilu Lemma Institute of Pathobiology

Addis Ababa University

Tel: +251911408340

Information about the study

We would like to invite you to take part in a study titled " Determining the Burden of Hepatocellular Carcinoma and Associated Risk Factors in Addis Ababa, Ethiopia." According to reports, little attention has been paid to determining the burden of hepatocellular carcinoma in Addis Ababa, liver cancer clinicians' perceptions of current infrastructural and educational needs in hepatocellular carcinoma control in Ethiopia, and public awareness of hepatocellular carcinoma and its risk factors in Addis Ababa. Thus, this study will address the aforementioned knowledge gaps. This research project is supported by Flinders University in South Australia. Only the researcher and data collector will have access to the research data obtained from or about you. Moreover, the study's findings will be published so that you can learn about them. However, once the project is completed, the researcher will not provide participants with project feedback.

What will I be asked to do?

We will invite you to participate in a brief interview. Following some age-related questions, we will ask your perceptions of current infrastructural and educational needs in hepatocellular carcinoma control in Ethiopia signs and risk factors in Ethiopia.

What benefit will I gain from being involved in this study?

Although there is no immediate benefit to you, we hope to gain a better understanding of how to help reduce the number of Ethiopians who develop hepatocellular carcinoma as a result of this research. Moreover, you will be provided 1.5 AUD (approximately 30 Ethiopian birrs), and also be provided soft drinks or snacks to reimburse participants for their time.

Will I be identifiable by being involved in this study?

While all information obtained in this project will be kept strictly confidential, participation will not be anonymous.

Are there any risk or discomforts if I am involved?

Because you will be asked to participate in an interview, some questions may bring back unpleasant memories. If this happens to you, remember that you are not required to answer any questions that make you uncomfortable, and you are not even required to complete the interview. Please be aware that if you are experiencing emotional distress, the interview will be terminated. Please see the list below for the names and contact information for free counseling services.

Tikur Anbessa Specialized Hospital

+251 11 111 1111

Who is the project leader?

Mr. Zinaye Tekeste is leading this study, and you can reach him at meha0006@flinders.edu.au

How do I agree to participate?

Simply read the acknowledgment comments/consent form below. If you agree, please sign or provide your recorded verbal consent, and we will proceed to the interview.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number: **8572**). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone at +61 8201 3116, by fax at 8201 2035, or by email human.researchethics@flinders.edu.au

Appendix 16: Qualitative interview guide

1. First, could you tell me a little about Ethiopia's strategies for advancing hepatocellular carcinoma prevention, treatment, and research?
2. What do you think are the most significant gaps in Ethiopia's hepatocellular carcinoma prevention?

Aid Memoire

- Prevention of risk factors
- Public awareness
- Screening

3. Now we'd want to focus on Ethiopia's present infrastructure needs in the areas of hepatocellular carcinoma prevention, treatment, and research.

Aid Memoire

- Research facilities/institutes
- Primary, secondary, and tertiary services

4. We'd like to now focus on Ethiopia's current educational needs in the areas of hepatocellular carcinoma prevention, treatment, and research.

Aid Memoire

- Physician training
- Other health professionals training
- Researcher training

5. Can we now discuss any budget gaps in Ethiopia's hepatocellular carcinoma research, prevention, and control?

Aid memoire

- HCC prevention

- HCC control
- HCC Research

I want to thank you again for taking part in the interview and providing responses, which will be kept strictly confidential.

Appendix 17 : WHO world standard population distribution (%), based on world average population between 2000-2025(420)

Age group	World Average 2000-2025
0-4	8.86
5-9	8.69
10-14	8.60
15-19	8.47
20-24	8.22
25-29	7.93
30-34	7.61
35-39	7.15
40-44	6.59
45-49	6.04
50-54	5.37
55-59	4.55
60-64	3.72
65-69	2.96
70-74	2.21
75-79	1.52
80-84	0.91
85-89	0.44
90-94	0.15
95-99	0.04
100+	0.005
Total	**100**

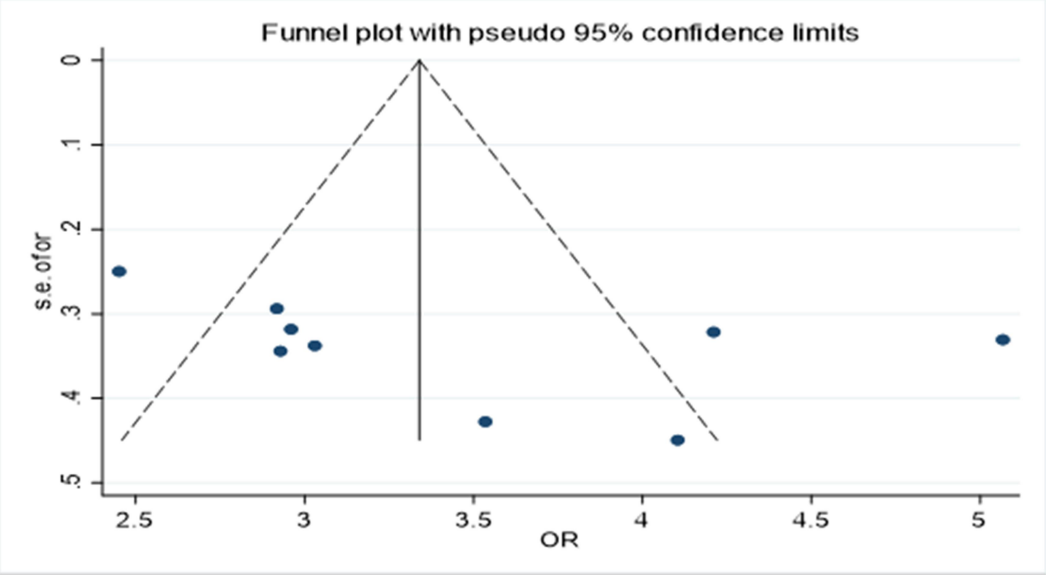
Appendix 18: Projected population size of Addis Ababa by five year age group, sex, urban and rural: medium variant: 1 July 2012 (421)

Age	Total			Urban			Rural		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Ages	3,046,333	1,447,004	1,599,329	3,046,333	1,447,004	1,599,329	-	-	-
0-4	319,560	161,206	158,336	319,560	161,206	158,336	-	-	-
5-9	197,977	98,833	99,135	197,977	98,833	99,135	-	-	-
10-14	215,087	102,692	112,394	215,087	102,692	112,394	-	-	-
15-19	262,584	111,964	150,643	262,584	111,964	150,643	-	-	-
20-24	403,974	158,343	245,690	403,974	158,343	245,690	-	-	-
25-29	416,847	188,717	228,147	416,847	188,717	228,147	-	-	-
30-34	371,564	179,863	191,696	371,564	179,863	191,696	-	-	-
35-39	230,880	124,600	106,253	230,880	124,600	106,253	-	-	-
40-44	185,661	96,119	89,528	185,661	96,119	89,528	-	-	-
45-49	116,581	63,597	52,969	116,581	63,597	52,969	-	-	-
50-54	98,184	48,725	49,456	98,184	48,725	49,456	-	-	-
55-59	76,368	36,491	39,877	76,368	36,491	39,877	-	-	-
60-64	50,970	25,633	25,335	50,970	25,633	25,335	-	-	-
65-69	41,707	20,562	21,143	41,707	20,562	21,143	-	-	-
70-74	28,276	14,182	14,093	28,276	14,182	14,093	-	-	-
75-79	19,093	8,836	10,258	19,093	8,836	10,258	-	-	-
80+	**11,020**	**6,643**	**4,375**	**11,020**	**6,643**	**4,375**	**-**	**-**	**-**

Appendix 19: Projected population size of Addis Ababa by five year age group, sex, urban and rural: medium variant: 1 July 2017(421)

Age	Total			Urban			Rural		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
All Ages	3,435,028	1,625,451	1,809,577	3,435,028	1,625,451	1,809,577	-	-	-
0-4	376,398	189,982	186,383	376,398	189,982	186,383	-	-	-
5-9	318,778	158,640	160,116	318,778	158,640	160,116	-	-	-
10-14	205,936	100,897	105,029	205,936	100,897	105,029	-	-	-
15-19	231,783	107,156	124,635	231,783	107,156	124,635	-	-	-
20-24	289,151	120,369	168,828	289,151	120,369	168,828	-	-	-
25-29	421,412	165,954	255,554	421,412	165,954	255,554	-	-	-
30-34	420,053	190,734	229,342	420,053	190,734	229,342	-	-	-
35-39	368,318	178,060	190,247	368,318	178,060	190,247	-	-	-
40-44	228,016	122,712	105,262	228,016	122,712	105,262	-	-	-
45-49	180,967	93,373	87,573	180,967	93,373	87,573	-	-	-
50-54	112,840	61,223	51,596	112,840	61,223	51,596	-	-	-
55-59	93,671	46,062	47,604	93,671	46,062	47,604	-	-	-
60-64	71,154	33,464	37,690	71,154	33,464	37,690	-	-	-
65-69	45,469	22,425	23,041	45,469	22,425	23,041	-	-	-
70-74	34,526	16,607	17,918	34,526	16,607	17,918	-	-	-
75-79	20,834	10,115	10,719	20,834	10,115	10,719	-	-	-
80+	15,720	7,680	8,040	15,720	7,680	8,040	-	-	-

Appendix 20: Funnel asymmetry for testing publication bias for studies on HBsAg positivity and anti-HCV negativity in HCC development

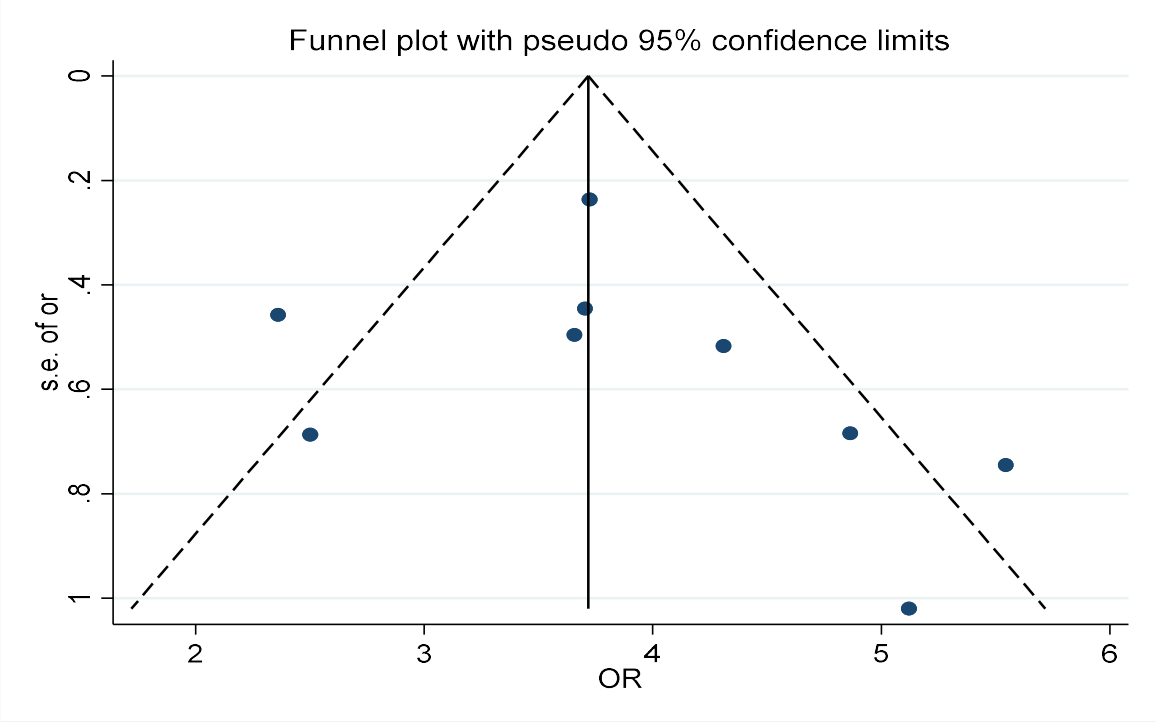


Number of studies = 9 Root MSE = 149.4

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-28.76993	99.59782	-0.29	0.781	-264.2813	206.7415
bias	218.963	304.198	0.72	0.495	-500.3509	938.277

Test of H0: no small-study effects P = 0.495

Appendix 21: Funnel asymmetry for testing publication bias for studies on HBsAg positivity and anti-HCV negativity in HCC development



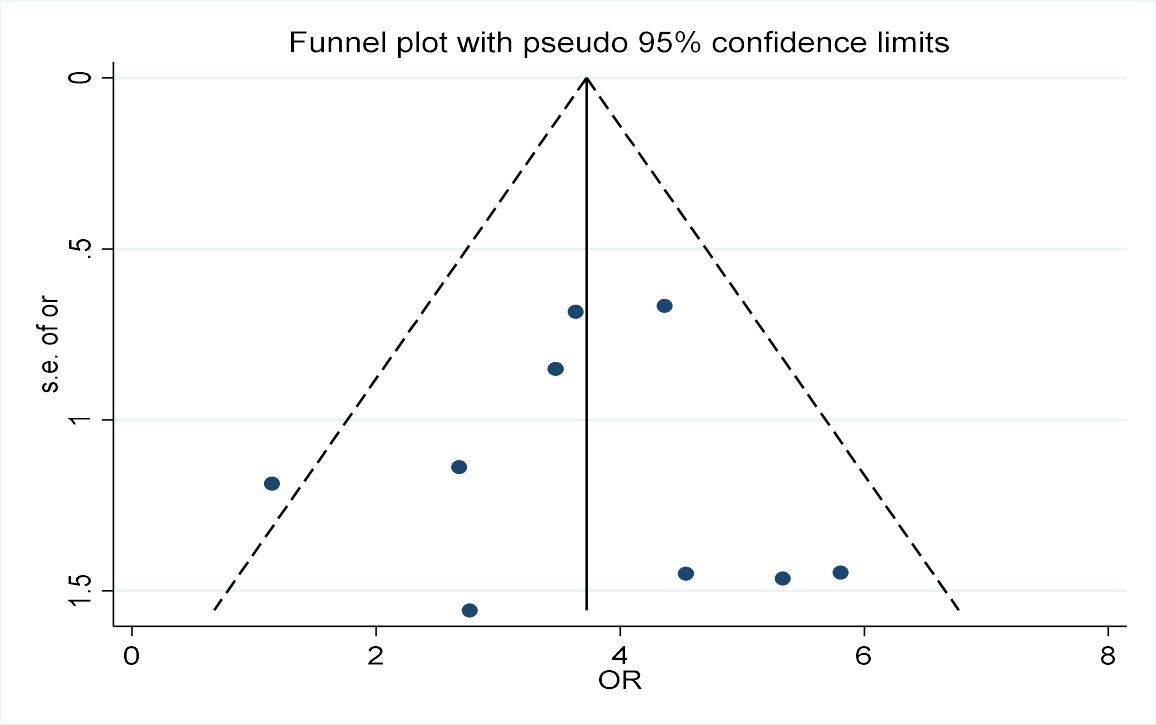
Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = **9** Root MSE = **106.5**

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	**-10.64975**	**39.92183**	**-0.27**	**0.797**	**-105.0499**	**83.75037**
bias	**157.3806**	**86.79664**	**1.81**	**0.113**	**-47.86087**	**362.622**

Test of H0: no small-study effects P = **0.113**

Appendix 22: Funnel asymmetry for testing publication bias for studies on HBsAg positivity and anti-HCV negativity in HCC development



Note: data input format **theta se_theta** assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = **9** Root MSE = **80.15**

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-18.9614	82.9587	-0.23	0.826	-215.1276	177.2048
bias	92.7268	83.36457	1.11	0.303	-104.3991	289.8527

Test of H0: no small-study effects P = **0.303**

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