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Adetunji T. Toriola

Alcohol and Cancer Among Men

Public Health Impact and Perspectives

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If drinking is interfering with your work, you're probably a heavy drinker. If work is interfering with your drinking, you're probably an alcoholic. ~Author Unknown

ABSTRACT: ALCOHOL AND CANCER AMONG MEN: PUBLIC HEALTH IMPACT AND PERSPECTIVES

As many as 2 billion people worldwide consume alcohol. Alcohol consumption has been shown to be associated with a variety of positive and negative health outcomes. According to the World Health Organization (WHO), the short and long term negative health effects of alcohol far outweigh the positive health effects. Cancers, especially cancers of the upper aero digestive tract (UADT) are among the long term negative health consequences of alcohol intake, but recent studies have shown that other cancer sites may also be causally related to alcohol consumption. Since alcohol consumption volume and patterns vary in different parts of the world, alcohol-related morbidity and mortality also follow a similar pattern. The aim of this thesis is to investigate the relationship between alcohol consumption and risk of specific and total cancer among men from Eastern Finland who have been prospectively followed for more than 16 years.

In the first study, we investigated the association between alcohol consumption and colorectal cancer. The mean age of the men at the time of baseline examination was 53 years. Over a follow-up period of 16.7 years, there were 59 cases of colorectal cancer. The cohort was divided into five based on the volume of alcohol consumed. Men within the highest quintile of alcohol consumption (> 115g/week) had a median weekly alcohol intake of 198.8g. Men within the 5th quintile of alcohol consumption had significantly higher risk of colorectal cancer compared to men within the 1st quintile in both the crude (relative risk, RR 4.4, 95%CI 1.6-11.9) and multivariate (RR 3.5, 95%CI 1.2-9.8, p-value 0.02) adjusted analyses and the point estimates were not different in sensitivity analyses excluding the first two years of follow-up.

In the second study, we explored the possible relationship between pattern of drinking and the risk of lung cancer. A total of 621 men (27% of study population) were binge drinkers. There were 65 lung cancer cases, 27 among binge drinkers and 38 among non-

binge drinkers during a follow-up period of 16.7 years. Binge drinking was not associated with an increased risk of lung cancer among non-smokers (RR 1.49, 95%CI 0.88-2.56) but among smokers, binge drinking was associated with a significantly increased risk of lung cancer. The RR associated with binge drinking was 1.70 (95%CI 1.61-4.53) among men who smoked 1-19 cigarettes/day and 2.24 (95%CI 1.29-3.80) among men who smoked ≥30 cigarettes/day. Thus, smoking is likely to confound the relationship between binge drinking and lung cancer, and may totally explain it. An important limitation of this study is the fact that we used a composite measure of binge drinking and not a real measure as determined by response from participants; hence there may be misclassification of binge drinking.

We examined the relationship between alcohol consumption and total cancer in the third study. In the multivariate adjusted model, men within the highest quintile of alcohol consumption (> 115g/day) had a 42% (RR 1.42 95%CI 1.07-1.88) higher risk of cancer compared to men within the lowest quintile. We estimated that about 7% of the cancer cases in this cohort are attributable to alcohol consumption.

In the fourth study, we investigated whether moderate alcohol consumption has any effect on cancer and cancer mortality beyond that observed for smoking. We observed that smoking is an independent risk factor for cancer and cancer mortality. Moderate alcohol consumption had an effect on cancer and cancer mortality beyond the effect of smoking alone. Smokers had a 1.8-fold (95%CI 1.40-2.39) increased risk of having cancer while smokers who consumed moderate alcohol had a 2.3-fold (95% CI 1.86-2.92) increased risk. For cancer mortality, the corresponding relative risks were 2.34 (95%CI 1.58-3.47) and 2.89 (96%CI 2.07-4.04), respectively.

Keywords: Alcohol, cancer, cancer mortality, colorectal cancer, lung cancer, public health, smoking

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Adetunji Toriola

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the publications listed below which are referenced in the text by their roman numerals

I. Toriola AT, Kurl S, Laukkanen JA, Mazengo C, Kauhanen J. Alcohol consumption and the risk of colorectal cancer: the Findrink study. Eur J Epidemiol 2008;23:395-401

II. Toriola AT, Kurl S, Laukkanen JA, Kauhanen J. Does binge drinking increase the risk of lung cancer: results from the Findrink study. Eu J Pub Health 2009;19(4):389-93

III. Toriola AT, Kurl S, Dyba T, Laukkanen JA, Kauhanen J. The impact of alcohol consumption on the risk of cancer among men: a 20-year follow-up study from Finland. Eur J Cancer 2010;46:1488-92

IV. Toriola AT, Kurl S, Laukkanen JA, Kauhanen J. The effects of moderate alcohol consumption and smoking on cancer and cancer mortality. Submitted.

ABRREVIATIONS

ALDH	Acetaldehyde dehydrogenase
ADH	Alcohol dehydrogenase
ASR	Age-standardized incidence rate
BPH	Benign prostatic hypertrophy
BMI	Body mass index
CI	Confidence interval
DNA	Deoxy ribonucleic acid
ECG	Electrocardiogram
EPIC	European Prospective Investigation into Cancer and Nutrition
FCR	Finnish Cancer Registry
GGT	Gamma-glutamyl transpeptidase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIFα	Hypoxia-inducible factor 1α
IARC	International Agency for Research on Cancer
IGF	Insulin growth factor
IGFBP-3	Insulin growth factor binding protein-3
KIHD	Kuopio Ischaemic Heart Disease Risk
MCV	Mean corpuscular volume
MOX	Monooxygenase
NK-κB	Nuclear factor-Kb
PAF	Population attributable fraction
PSA	Prostate specific antigen
RARE	Retinoic acid response elements
RR	Relative risk

SHBG	Sex hormone binding globulin
UADT	Upper aero digestive tract
WHO	World Health Organization

1 INTRODUCTION

Cancer is a very debilitating disease caused by genetic and environmental factors. Even though environmental factors contribute much more to carcinogenesis than the genetic factors, the precise nature and mechanisms of the environmental factors have not been fully elucidated. Acknowledged, however, is the fact that certain lifestyle habits can initiate and promote cancers at different parts of the body with particular predilection for certain organs. An important insight into the role of lifestyle factors in the etiology of cancer is the temporal and geographic variations in the incidence of many cancers. This has enabled epidemiologic and public health studies to determine factors associated with those temporal and geographical variations and risk of cancers

Among the prevalent lifestyle habits believed to be causally related to cancer is alcohol consumption. The relationship between alcohol consumption and cancers in specific sites has been studied but there are still controversies on the presumed association for many sites. Many previous studies have been retrospective case-control studies with the bias inherent in such study design and only recently have results from prospective epidemiological studies less inherent likelihood for bias been published.

The unique cohort of the Kuopio Ischaemic Heart Disease Risk (KIHD) Factor Study with its lengthy and complete follow-up, precise ascertainment of cancers and other confounding factors offer a good opportunity to determine the association between alcohol consumption and cancer risk and to quantify the impact of alcohol consumption on risk of cancer among a well defined population group

2 LITERATURE REVIEW

2.1 GLOBAL BURDEN OF CANCER AND GEOGRAPHICAL VARIATION IN CANCER INCIDENCE AND MORTALITY

Cancer is a significant cause of morbidity and mortality worldwide and its incidence continues to increase over time. In 2002, there were 10.9 million new cancer cases and 6.7 million cancer deaths (Ferlay et al. 2010). By 2008, the annual number of new cancer cases had increased to 12.7 million with a corresponding increase in the number of cancer deaths to 7.6million (Ferlay et al.. 2010). At present, cancer is the 3rd leading cause of death worldwide with wide ranging differences in various parts of the world (American Cancer Society 2007). If present trends are maintained, it has been predicted that there will be 26 million new cancer cases and 17 million cancer deaths annually by the year 2030, when it is expected to be the leading cause of death (WHO 2007, IARC 2008, Thun et al.. 2010).

Among men, the global age-standardized incidence rate (ASR) of cancer is 204.4/100,000 with higher rates encountered in developed regions (301.1/100,000) compared to developing regions (160.3/100,000) (Ferlay et al. 2010). The highest ASR's are found in Australia and New Zealand (356.8/100,000) closely followed by Western Europe (337.4/100,000), Northern America (334/100,000) and Northern Europe (303.5/100,000) (Figure 1). The regions of the world with the lowest ASR's are Middle Africa (88.1/100,000), Western Africa (92.0/100,000) and South-Central Asia (99.7/100,000) (Ferlay et al. 2010). Patterns for mortality rates are less disparate. Globally, the ASR for cancer mortality is 128.8/100,000 (143.9/100,000 in developed regions and 119.3/100,000 in developing regions). However, while Middle Africa still has the lowest ASR for cancer mortality (78.5/100,000), Southern Africa has the highest ASR (172.1/100,000) (Ferlay et al. 2010).

Cancer rates are lower among women. The female: male sex ratio for cancer incidence is 1:1.24 while for cancer mortality, it is 1:1.47 (Ferlay et al. 2010). The female: male sex ratio for cancer mortality is higher because cancers with high fatality (lung, stomach, liver and esophagus) are more common among men compared to women (Parkin et al. 2002, Ferlay et al. 2010, Ferlay et al. 2010). The same pattern with regards to ASR of cancers observed among men is noted among women. The highest ASR for cancer incidence are observed in Australia/New Zealand (276.4/100,000), Northern America (274.4/100,000) and Western (250.9/100,000) and Northern Europe (249.4/100,000) and the lowest are observed in Middle (96.7/100,000) and Northern (98.8/100,000) Africa. While Southern Africa still has the highest ASR for cancer mortality among women, (108.1/100,000), Northern Africa has the lowest (68.2/100,000) (Ferlay et al. 2010)

Among men and women, the five most incident cancer types are cancers of the lung (1.6 million cases, 12.7% of total), breast (1.38 million cases) colorectum (1.2 million cases), stomach (990,000 cases) and prostate (913,000 cases) (Parkin et al. 2002, Ferlay et al. 2010, Jemal 2010) (Figure 2). The sex-specific distribution differs depending on what region of the world it is, reflecting the importance of environmental factors at play in the different regions. In developed regions of the world, the five most incident cancer types among men are prostate, lung, colorectal, bladder and stomach cancers while in the developing regions, the five most incident cancers types are lung, stomach, liver, colorectal and esophageal cancers (Parkin et al. 2002, Ferlay et al. 2010). With regards to mortality, the five cancers that cause the highest number of deaths are lung, liver, stomach, colorectal and esophageal cancers (Parkin et al. 2002, Ferlay et al. 2010) (Figure 3).

Among women, breast cancer is by far the most incident type of cancer both in the developed and developing regions accounting for 1.38 million cases annually (10.9% cancer cases among women) (Ferlay et al. 2010). In developed regions, colorectal, lung,

corpus uteri and stomach cancers make the top five while in the developing regions, cervix uteri, lung, stomach and colorectal cancers complete the top five. Likewise, breast cancer accounts for the highest number of cancer deaths among women worldwide (Ferlay et al. 2010).

Figure 1 Global estimated age-standardized incidence rate of cancers/100,000 in year 2010

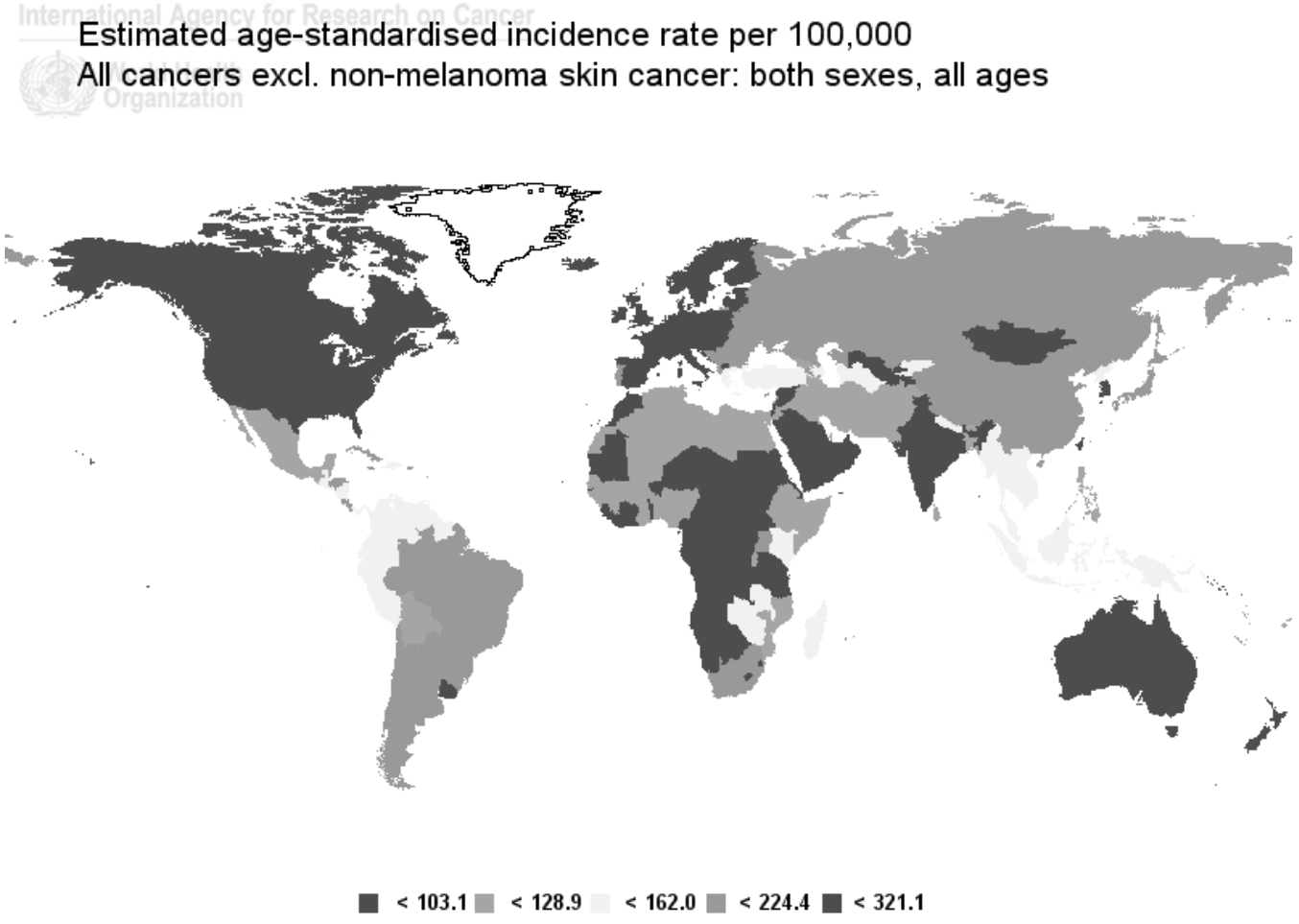
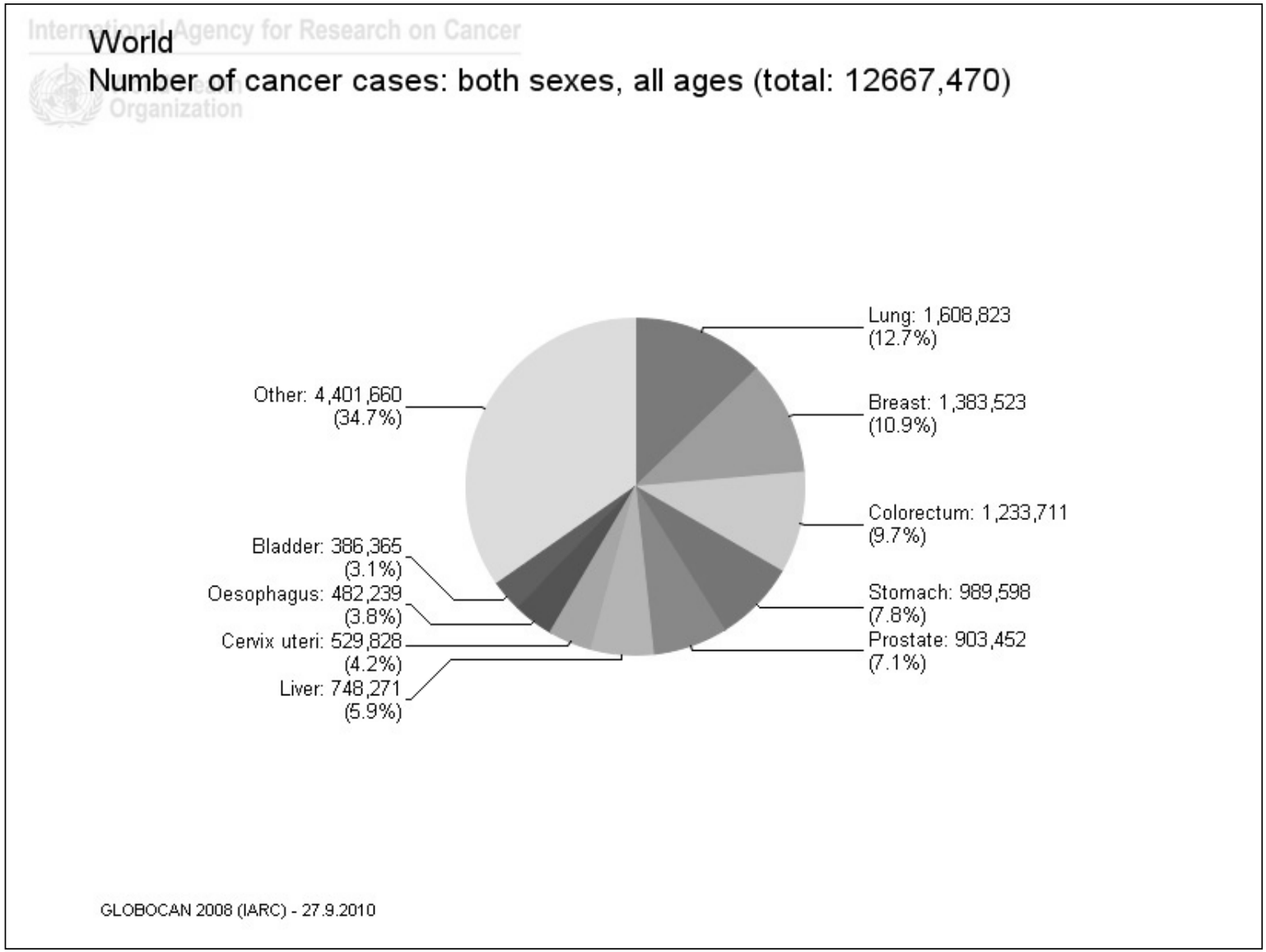


Figure 2 Number of cancer cases worldwide in year 2010 among men and women



World
Number of cancer deaths: both sexes, all ages (total: 7571,501)

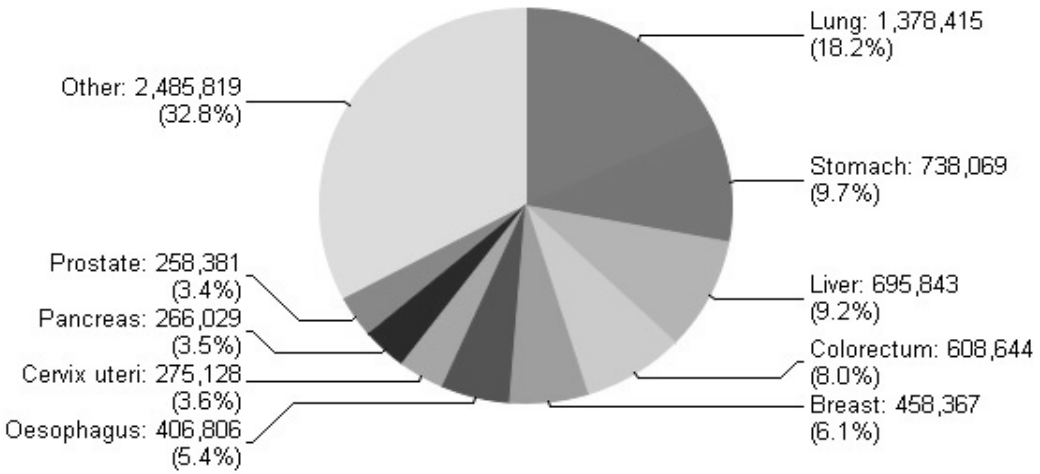
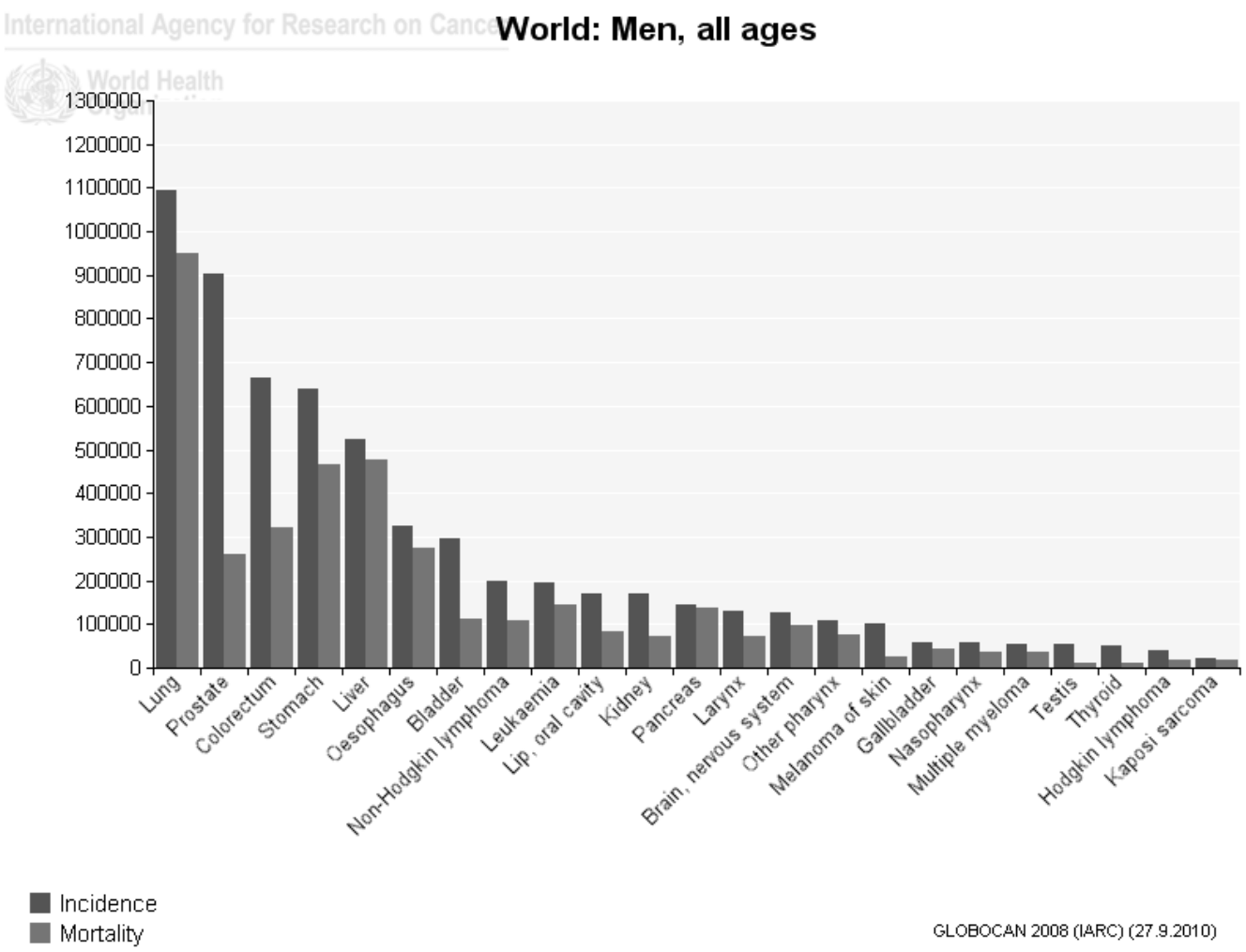


Figure 4 Most incident cancer cases among men worldwide in year 2010



2.2 DESCRIPTIVE EPIDEMIOLOGY OF THE FIVE MOST INCIDENT CANCER TYPES AMONG MEN

2.2.1 Lung cancer

With 1.1 million cases yearly, lung cancer accounts for 16.5% of cancers among men worldwide (Ferlay et al. 2010) (Figure 4). The highest rates are found in Europe especially Central and Eastern Europe and the lowest rates are found in Western and Middle Africa. It has a very high fatality rate, ranging from 0.80 to 0.86 in different parts of the world (Ferlay et al. 2010). The 5-year survival rate ranges from 49% to as little as 2% depending on the stage at diagnosis (Ries et al. 2005).

Cigarette smoking is the most important etiological risk factor for lung cancer with smokers having between 15 to 30-fold increased risk compared to non-smokers (Doll and Hill 1950, Levin et al. 1950, Alberg et al. 2007, Sasco et al. 2004, Freedman et al. 2008). Even though, tobacco consumption dates back to many centuries, lung cancer rates were relatively lower at the beginning of the 20th century (Alberg et al. 2007). The increased rates have been markedly associated with changing patterns, types and extent of cigarette consumption. The introduction of manufactured cigarettes with its additive properties and sustained delivery of carcinogens to the lungs has been one of the major reasons for the epidemic of lung cancer (Alberg et al. 2007). Tobacco smoke contains more than 4000 chemicals of which at least 50 are classified as carcinogens (Tobacco Atlas 2008). There is a marked dose-response relationship between cigarette smoking and lung cancer incidence, with risks increasing with amount smoked per day and the duration of smoking (Doll and Peto 1978, Peto 1986). Other forms of smoking such as cigar and pipe are also associated with increased risks of lung cancer but the magnitude is lower than that caused by cigarette because the frequency of smoking and depth of inhalation of these other forms are less than that of cigarette (Boffetta et al. 1999). Other factors associated with increased risk include genetic susceptibility, aging, and exposure to environmental and occupational

insults such as asbestos, chromates, chloromethyl ethers, polycyclic aromatic hydrocarbons, radon progeny, and air pollution (Doll 1955, Lemen et al. 1980, Doll and Peto 1981, Lubin et al. 1995, Darby et al. 2005, Matakidou et al. 2005, Alberg et al. 2007). Low socio-economic status, with its constellation of many unfavorable risk factors such as poor diet, smoking and exposure to occupational carcinogens is also a risk factor for lung cancer incidence and mortality (Mao et al. 2001, Li and Yu 2002). Of note also is the multiplicative action between cigarette smoking and the environmental insults in increasing lung cancer risk (Hammond et al. 1979, Lubin et al. 1995).

Increased physical activity and high intake of vegetables and fruits are suspected to be possible protective factors and the impact of micronutrients and anti-oxidants in foods in lung cancer prevention are still being investigated (Lee et al. 1999, Neuhouser et al. 2003, Miller et al. 2004, World Cancer Report 2008 Leitzman et al. 2009)

2.2.2 Prostate cancer

Prostate cancer accounts for 13.8% of all cancer cases among men (913,000 cases annually); it is the second most common cancer among men and the sixth leading cause of cancer death among men (Ferlay et al. 2010). Most cases of prostate cancer occur in the developed countries largely due to widespread adoption of prostate specific antigen (PSA) testing which has led to the cancer being diagnosed at an earlier stage and in younger men (Ferlay et al. 2010).

Incidence of prostate cancer increases with age (Hass and Sakr 1997, American Cancer Society 2003). In the United States of America (USA) more than 70% of the cases are diagnosed after the age of 65 years and the probability of developing prostate cancer increases from 1 in 45 for men aged between 40 and 59 years to 1 in 7 among men aged 60 to 79 years (American Cancer Society 2003). However, the histological evidence from autopsy suggests that the possibility of developing prostate cancer may be higher than

that seen in clinical practice (Carter et al. 1990). As many as 20% of men aged 50 to 60 years may have histological evidence of prostate cancer, rising to 50% among those aged 70 to 80 years (Carter et al. 1990).

There appears to be a strong familial risk to developing prostate cancer. Risk increases among men with a family history of prostate cancer especially an affected father or brother (Steiberg et al. 1990, Bratt 2002). Men with a family history of prostate cancer also tend to be diagnosed at an earlier age and a sizeable proportion of cases occurring before the age of fifty-five have an hereditary component (Carter et al. 1992, Bratt 2002).

The role of environmental factors in the aetiology of prostate cancer is obvious from immigration studies which have shown that the risk of prostate cancer among immigrants from low risk groups approaches that of their high risk host communities in a few generations (Shimizu et al. 1991, Crawford 2003). Diet has been implicated among the environmental factors. Whereas higher intake of saturated fat and meat are thought to be associated with higher risks of prostate cancer (Giovannucci et al. 1993), higher intakes of vegetables and diets rich in lycopene selenium, vitamin D, isoflavone are suspected to be protective but have not been fully confirmed in epidemiological studies (Giovannucci 2002, Vogts et al. 2003, Gilbert et al., Hollick et al. 2007, Kristal et al. 2010).

Since the growth of the prostate is under androgen control, it is believed that androgens may play a role in prostate carcinogenesis (Crawford 2003). This is further supported by evidence that androgenic blockade with 5α-reductase inhibitors is effective in treating benign prostatic hypertrophy (BPH) and androgen ablation is effective in treating advanced prostate cancer (Crawford 2003). However, epidemiological studies that have measured plasma testosterone prospectively before prostate cancer diagnosis have not convincingly linked pre-diagnostic serum testosterone levels with increased risk of prostate cancer (Hsing 2001, Parsons et al. 2005).

2.2.3 Colorectal cancer

With 663,000 cases annually, colorectal cancer accounts for 10% of all cancer cases among men and is the third most incident cancer among men worldwide (Ferlay et al. 2010). Incidence rates vary substantially worldwide with a 10-fold difference in incidence rates observed in different parts of the world (Ferlay et al. 2010, Jemal et al. 2010). The highest incidence rates are noted in the developed countries, especially Western Europe and Australia/New Zealand and the age standardized incidence rate among men is about 40% higher compared to women (Ferlay et al. 2010). Contrasting trends in incidence rates are being observed in areas that were traditionally low risk and those that were traditionally high risk. In some historical high risk areas such as the USA, incidence rates are stabilizing or even declining but in previously low risk areas such as Japan and Eastern European countries, the incidence rates are increasing in such a way that the peak rates observed in the Czech Republic and Japan have exceeded the peak rates observed in the traditionally high risk countries such as the USA and Australia (Center et al. 2009). The increase in incidence in the previously low risk countries has been mainly attributed to the adoption of dietary and lifestyle factors associated with westernization (Center et al. 2009). Likewise, while colorectal cancer mortality is decreasing in many developed countries mainly due to early detection from improved screening, and improved treatment, the situation is not the same in many developing countries (Sant et al. 2001, Center et al. 2009, Edwards et al. 2010). The 5-year survival rates approach 60% in the developed regions while it is lower than 42% in most developing regions (Coleman et al. 2008, Sankaranarayanan et al. 2010).

Colorectal carcinogenesis usually follows the multi-step adenoma to carcinoma sequence which takes between 10 to 15 years to fully ensue and during this period, a combination of genetic and environmental factors act together to promote it (Ullman and Itzkowitz 2011). Among the various dietary factors associated with increased risk of colorectal carcinogenesis are high intakes of animal fat, alcohol consumption, low intake of dietary

fiber, vegetables and fruits and folate (Armstrong and Doll 1975, Willet et al. 1990, Bingham et al. 2005, Koushik et al. 2007, World Cancer Report 2008, Key 2011). While a high level of physical activity, especially of moderate intensity have been found to be associated with lower risk of colorectal cancer, high body mass index (BMI) has been associated with increased risk (Wolin et al. 2009, Harris et al. 2009). The possible protective role of hormones and anti-inflammatory drugs are also being exploited as results from experimental and epidemiological studies have shown over time that non-steroidal anti-inflammatory drugs and in women, hormone replacement therapy are associated with reduced risk (Flossmann et al. 2007, Grau et al. 2009, Rennert et al. 2009).

2.2.4 Stomach cancer

Stomach cancer is the fourth leading cause of cancer and the second leading cause of cancer death among men (Ferlay et al. 2010). These figures represent an improvement in stomach cancer epidemiology compared to figures over 35 years ago when it was the most common cause of cancer worldwide (Parkin et al. 1984). Anatomically, stomach cancers are classified as cardia and non-cardia cancers. The non-cardia cancers constitute about 90% of cases, hence risk factors associated with the non-cardia cancers dominate the risk factor profiles for stomach cancers (Crew and Neuget 2006, Jemal et al. 2010). More than 70% of stomach cancer cases occur in developing countries with East Asia especially China contributing as much as 42% of the cases (Brenner et al. 2009, Ferlay et al. 2010). The geographical differences in the incidence rates are thought to be mainly due to differences in the prevalence of Helicobacter pylori infection which is thought to account for as much as 60% of all cases of non-cardia cancers (Uemura et al. 2001. Likewise, decrease in the incidence of non-cardia cancers in developing countries is thought to be due to decrease in the prevalence of H. pylori as a result of reduced transmission in childhood following improved sanitation and improvements in the preservation and storage of food (Howson et al. 1986, Roosendaal et al. 1997, Crew and Neugut 2006, Shibata and Parsonnet 2006). Given that H. pylori infection is an ubiquitous infection and up to half of the world

population must have been infected at one time or another (Marshall and Warren 1984, Rothenbacher and Brenner 2003), other risk factors such as genetic susceptibility among infected individuals must be at play. Other established risk factors for non-cardia stomach cancers are smoking, low socio-economic status, intake of processed meat, intake of salty and smoked food and low intake of fruits and vegetables (Gonzalez et al. 2003, Gonzalez et al. 2006, Crew and Neugut 2006, Brenner et al. 2009).

In contrast to the non-cardia cancers, incidence rates for cardia cancers have either remained stagnant or increased over time (Botterweck et al. 2000, Crew and Neugut 2006, Brenner et al. 2009, Jemal et al. 2010). Major risk factors are smoking, gastro-oesophageal reflux disease, pernicious anemia and obesity (Hsing et al. 1993, Calle et al. 2003, El-Sareg et al. 2007). The relationship between H. pylori infection and the risk of non-cardia cancers is, however, not clear.

2.2.5 Liver Cancer

Liver cancer is the fifth most common cancer among men accounting for 7.9% of all cancer cases in men (Ferlay et al. 2010, Jemal et al. 2011). Men have a higher risk of developing liver cancer compared to women; the male to female sex ratio is 2.4 (Ferlay et al. 2010). As many as 85% of all cases occur in the developing countries and as much as a 40-fold difference in incidence rates are observed between low and high incidence areas (Ferlay et al. 2010, Jemal et al. 2010). The highest rates are found in Asia, Western and Central Africa and the lowest rates in Europe and North America. The most important denominator for the wide ranging differences in incidence between the developed and the developing countries is infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) (Parkin 2006, Perz et al. 2006). Chronic infection with these two viruses accounts for 78% of liver cancer mortality worldwide which can rise to 90% in specific populations (Parkin 2006, Perz et al. 2006, London and McGlynn 2006).

While liver cancer rates have been decreasing in some Asian and Southern European countries, it has been increasing in some parts of Europe and the USA (Perz et al. 2006, Parkin 2002). The decrease in incidence rates in the Asian countries is mainly due to reduction in HBV infection during childhood as a result of better sanitary conditions and hepatitis B immunization programs while the decrease in Southern Europe is mainly due to screening of blood products for HBV and HCV infections, reductions in alcohol consumption in some areas (Bosch et al. 2004, Bosetti et al. 2008). On the contrary, increasing incidence rates are seen in many countries such as the USA because of HCV infection from injecting drug use (Bosch et al. 2004, Bosetti et al. 2008).

The other risk factors for liver cancer include dietary aflatoxins, alcoholic liver disease, steatosis, hemochromatosis, obesity and smoking (Bosetti et al. 2008). Most of these other factors have multiplicative effects in the presence of chronic HBV or HCV infections (Bosch et al. 2004, WHO 2008). The most important preventive measure for liver cancer is vaccination with the HBV vaccine and it is part of the routine national childhood immunization in many countries (WHO 2004). However, there is no vaccination against HCV as yet, thus the most important preventive efforts against HCV infection are proper screening of blood and other donor organs, establishment of ample infection control practices during medical and surgical procedures (Jemal et al. 2010, Bosetti et al. 2008).

2.3 RISK FACTORS FOR CANCER

Cancer is a multistage process characterized by uncontrolled cellular growth resulting from changes in genetic information of cells (Nowell 1974, WHO 2008). In normal situations, cellular division, differentiation and death are careful regulated and damaged cells are removed through apoptosis but when the damaged or abnormal cells escape from the inherent growth control, the groundwork for carcinogenesis is laid (WHO 2008). When

a normal cell is transformed into a cancerous cell, its phenotypic characteristics change from that of the parent cell (WHO 2008).

The changes in genetic information of the cells are usually accumulated over a long period of time and most cancers only manifest clinically many years after the initial DNA damage (Bishop 1991, WHO 2008). The DNA damage leading to cancerous transformations can be caused by endogenous or exogenous causes or a combination of the two (WHO 2008). Both endogenous and exogenous causes can interact with each other to increase or decrease cancer risk, they can also modify the actions of each other or act in a multiplicative fashion to increase risk of cancer (Ponder 2001, WHO 2008).

2.3.1 Endogenous causes

Age: Aging is associated with many genetic and epigenetic changes such as; decline in tissue repair capacity, increasing level of genomic abnormalities, telomere dysfunction and altered stromal milieu, all of which influence the risk of developing cancer (Curtis and Crowley 1963, Moriwaski et al. 1996, DePinho 2000). Cumulative lifetime exposure to DNA damaging agents from various sources leads to increase in somatic mutations in cells and tissues (DePinho 2000, WHO 2008). Cancer incidence rises exponentially in the final decades of life resulting in a lifetime risk of 1 in 2 for men and 1 in 3 for women (American Cancer Society 2000). One of the driving forces for increasing cancer burden is the increasing age of populations, both in developed and developing countries and it is presently estimated that the number of people age 65 years and above will increase worldwide from 418 million in 2000 to 1.36 billion in 2050 and since almost half of cancer cases are diagnosed among people older than 65 years, a corresponding increase in number of cancer cases is expected (Bray et al. 2006).

Genetic changes: These can be inherited or acquired (Ponder 2001). Inherited genetic changes are mutations in single genes passed on from parents to their offsprings and such

germline mutations are responsible for only a small proportion of cancers (WHO 2008). Individuals with such germline mutations, especially when they occur in the tumor suppressor genes, are predisposed to developing cancer at an earlier age compared to the general population (WHO 2008). Acquired genetic changes (somatic) arise from exposure to carcinogens which damage an individual's genetic make-up (Ponder 2001).

Other endogenous causes of cancer include:

(i) Oxidative stress from reactive oxygen species lead to DNA damage. Normally, the body has several mechanisms for dealing with and repairing the oxidative damage caused by the reactive oxygen species but when the body's repair mechanisms are overwhelmed, the result is an accumulation of DNA damage eventually leading to carcinogenic changes (Esme et al. 2008, WHO 2008, Lawless et al. 2010).

(ii) Chronic inflammation: chronic inflammation leading to cancer can arise from either an extrinsic or intrinsic pathway but whatever pathway is involved; the consequence is sustained activation of transcription factors such as nuclear factor-κB (NK-κB) and hypoxia-inducible factor 1α (HIF1α) (Coussens and Werb 2002, Karin 2006, Montavani et al. 2008). These transcription factors stimulate the production and recruitment of inflammatory factors and cytokines ultimately resulting in a cancer-related inflammatory micro-environment with increased cell proliferation, cell survival, angiogenesis, tumor-cell migration, inhibition of adaptive immunity (Montavani et al. 2008).

2.3.2 Exogenous causes

There are many exogenous causes of cancer and many are still yet to be characterized (WHO 2008). The exogenous causes usually have predilections for specific organ systems but some may have multi-systemic manifestations. Thus, the geographical distributions of many cancers reflect the prevalence of these risk factors within their populations. The risk factors range from addictive substances such as tobacco and alcohol, to diet, physical inactivity, obesity, sexual and reproductive health factors, environmental and

occupational risks such as air pollution, indoor smoke from solid fuels, aromatic amines, radiation, polychlorinated biphenyls etc. (Ezzati et al. 2005, Clapp et al. 2008).

2.3.2.1 Smoking

Tobacco use is the largest preventable cause of cancer and cancer mortality worldwide (Thun et al. 2010). As many as fifteen different cancers and cancer subtypes are known to be causally related to smoking, because constituents of tobacco smoke are multi-systemic carcinogens (IARC 2004, Thun et al. 2010). The cancer most causally related to smoking is lung cancer where the average relative risk (RR) among smokers in several studies range from 15 to 30 (Sasco et al. 2004) while lower relative risks (RR 1.5-2.5) have been reported in connection with cancers of the stomach, liver, kidney and upper aero-digestive tracts (Sasco et al. 2004).

It is estimated that while smoking causes 25% of all cancers and 32% of cancer deaths among men, it causes 4% of cancers and 8% of cancer deaths among women (Ezzati et al. 2005, Stewart and Kleihues 2003). The burden of cancer attributable to smoking differs between world regions also. In the developed regions, smoking causes 29% of cancer deaths while in developing regions, it is responsible for 16% of cancer deaths. The disparity in proportion of cancer deaths between developed and developing regions is believed to be due to the much longer history of smoking in the developed regions (Ezzati et al. 2005).

Since the first cigarette machines were invented in 1881, global cigarette consumption has been increasing over time (Tobacco atlas 2008). There are approximately 1.3 billion smokers in the world today and if present smoking trends continue, there will be 2 billion smokers in the world by the year 2030 (Tobacco atlas 2008). This is mainly fuelled by increasing uptake of smoking among young people in developing and emerging economies. According to estimates, 12 million cigarettes were smoked every minute in

2010 (Tobacco atlas 2008). While the smoking epidemic has peaked in many developed countries and is on a slow decline in many, especially among educated people, the epidemic appears to be increasing in developing countries. In 1965, 52% of men in the USA and 61% of men in the United Kingdom (UK) smoked but by 2007, this had reduced to 23% in both countries. Comparatively, nearly 60% of Chinese men presently smoke and China consumes about 37% of the world's cigarettes. The prevalence of smoking is however, highest in Eastern Europe and Central Asia and lowest in Africa and Middle East.

Apart from cigarette, the other major forms of tobacco are cigars, pipes, waterpipes and bidis (Tobacco atlas 2008). Even though, less consumed than cigarette, cigar and pipe smoking have also been found to be associated with increased risk of lung and upper aerodigestive tract cancers while bidis which is the most predominant type of tobacco smoked in India has been associated with increased risk of lung and cancers of the oral cavity (Sasco et al. 2004).

Tobacco smoke contains over 4,000 chemicals of which more than 50 are known carcinogens (Tobacco atlas 2008). Carcinogens from tobacco can be inhaled, ingested or absorbed through the circulation and there are various mechanisms by which they can lead to carcinogenesis (Kuper et al. 2002). A known mechanism is the metabolic activation of tobacco carcinogens by oxidative enzymes with the resultant compounds formed binding covalently to DNA to form DNA adducts (Hecht 1999). If these DNA adducts escape cellular repair mechanisms, they can cause miscoding, leading to mutations (Kuper et al. 2002). Likewise, free radicals in cigarette smoke can also induce oxidative damage to DNA leading to mutations, which can trigger activation of an oncogene or deactivation of a tumor suppressor gene (Kuper e 2002, IARC 1986). Other mechanisms by which smoking can increase cancer risk include altering the hormonal milieu and thus increasing

susceptibility to hormone responsive cancers and impairment of the immune system (Kuper et al. 2002, Sopori and Kozak 1998).

2.3.2.2 Diet

Although it is acknowledged that diet plays a role in the aetiology of cancer, either preventive in the case of fruits, vegetables, whole grains, dietary fibers and micronutrients in foods or contributing to excess risk in the case of fat, red meat and methods of food preparation; epidemiological studies over the years have yielded mixed results (Willet 2000, Key et al. 2002, Key 2011, WCR 2008). The major problem with epidemiological studies of diet and cancer is the inability to tease out the separate effects of each food type and nutrients as most food substances are consumed together and similar micronutrients may be present in different food types, and the inability to fully control for potential confounding lifestyle and genetic factors.

For example, the scientific evidence for a potential role of vegetable and fruit consumption in cancer prevention has undergone critical review over the last decade. Experimentally, it has been shown that various constituents of vegetables and fruits including phytochemicals, micronutrients and dietary fibers have anti-carcinogenic properties such as reducing oxidative DNA damage and increasing activity of enzymes needed to detoxify carcinogens (Armstrong and Doll 1975, Steinmetz and Potter 1991, World Cancer Report 2008). However, epidemiological studies have not been totally supportive at the population level.

Based on studies conducted prior to 1997, an expert panel concluded that there was convincing evidence that high intakes of fruits and vegetables were associated with reduced risk of total and specific cancers such as lung, colorectum, stomach, oesophagus and pharynx (World Cancer Research Fund/American Institute for Cancer Research 1997). However, the updated recommendations from the same expert panel have downgraded

the convincing evidence to probable and limited evidence (World Cancer Research Fund/American Institute for Cancer Research 2007). This is because most of the evidence from the earlier studies on vegetable and fruit consumption and cancer risk were derived from case-control studies, with potentials for recall and other types of bias, whereas the newer studies which have mainly failed to replicate the earlier protective findings are prospective cohort studies (Riboli and Norat 2003, Key 2011).

Four recent large prospective studies have investigated the association between fruits and vegetables and total cancer risk (Hung et al. 2004, Takachi et al. 2008, George et al. 2009, Boffetta et al. 2010). The European Prospective Investigation into Cancer and Nutrition (EPIC) study observed a small significant reduction in cancer risk among people with high intake of fruits and vegetables (Boffetta et al. 2010). In the NIH-AARP Diet and Health study, vegetables were inversely associated with cancer risk among men but not among women whereas fruits were not associated with cancer risk among men and women (George et al. 2009). The Japan Public Health Center-Based Prospective studies and two Harvard cohort studies observed no significant association between both vegetable and fruit consumptions and cancer risk (Takachi et al. 2008). Likewise, null or borderline results have been reported for specific cancers such as lung, colorectal and prostate (Park et al. 2007, Wright et al. 2008, Key 2011). Latest recommendations suggest that non-starch vegetables probably protect against mouth, larynx, esophageal and stomach cancers but limited evidence that they protect against lung, colorectal cancers. Fruits in general probably protect against cancers of the mouth, larynx, pharynx, esophagus, stomach and lung but there is limited evidence to suggest that fruits protect against cancers of the colorectum, liver and pancreas (World Cancer Research Fund/American Institute for Cancer Research 2007).

Many micronutrients present in various foods have been associated with reduced risk of cancer. They include vitamins C E and D, carotenoids (such as lycopene, α-carotene, ß-

carotene), calcium, selenium, folate, methionine, polyphenols and phyto-estrogens etc. (Greenwald et al. 2001, World Cancer Research Fund/American Institute for Cancer Research 2007). The micronutrients all reduce carcinogenesis through various diverse mechanisms in experimental conditions. Carotenoids have anti-oxidant properties and thus protect against oxidative damage to DNA, inhibit cell proliferation and oncogene expression and enhance cell to cell communication (IARC 1998, Greenwald et al. 2001, World Cancer Research Fund/American Institute for Cancer Research 2007). Polyphenols reduce carcinogen-DNA formation, inhibit cell proliferation and signal transduction pathways, induce cell cycle arrest and apoptosis. Vitamin D has anti-proliferative effects, induces apoptosis and reduces angiogenesis (Greenwald et al. 2001, World Cancer Research Fund/American Institute for Cancer Research 2007). Many studies, including randomized clinical trials have explored the association of these micronutrients with cancer risk and while some studies have reported significant inverse associations, many others have not (Greenwald et al. 2001).

Dietary fiber has been mainly associated with reduced risk of colorectal cancers and breast cancers in women (World Cancer Research Fund/American Institute for Cancer Research 2007). Dietary fibers increase fecal bulk, thereby diluting carcinogens; increase intestinal transit time, thereby reducing the likelihood, time and amount of carcinogens in contact with colonic mucosa and may bind directly with carcinogens and ensuring their elimination (Greenwald et al. 2001, World Cancer Research Fund/American Institute for Cancer Research 2007). On the other hand, there is convincing evidence that red and processed meat increases the risk of colorectal cancer but the evidence linking red and processed meat to increased risk of lung, prostate, esophageal, stomach and pancreatic cancers are limited (World Cancer Research Fund/American Institute for Cancer Research 2007).

2.3.2.3 Physical activity

Physical activity can be categorized by type into recreational, occupational, transport and household physical activities; by intensity into light, moderate and vigorous limited (World Cancer Research Fund/American Institute for Cancer Research 2007). Total amount of energy expended during physical activity depends on the frequency, intensity and duration of physical activity. Thus, high energy can be expended through low-intensity physical activity performed over a long period of time or high-intensity physical activity performed over a short period of time; however, both types have different physiological effects limited (World Cancer Research Fund/American Institute for Cancer Research 2007).

Physical activity has been shown to be inversely related to cancer (Friedenreich et al. 2010). Physical activity can influence cancer risk by (i) modifying circulating hormone and growth factor concentrations (IARC 2002, McTiernan 2002, Friedenreich et al. 2010). This is likely to be the biological mechanism in hormone responsive cancers such as prostate cancer. Testosterone may play a role in the etiology of prostate cancer and increasing physical activity has been associated with higher circulating concentrations of sex hormone binding globulin (SHBG), which binds to testosterone therefore decreasing plasma concentrations (Gaan et al. 1996, Haffner et al. 1995). Exercise also increases the production of insulin growth factor binding protein-3 (IGFBP-3), which binds to insulin growth factor (IGF), a known mitogen. Increased risk of colorectal, prostate and lung cancers have been associated with high levels of circulating IGF and low levels of circulating IGFBP-3 (McTiernan 2002, Rogers et al. 2008, Friedenreich et al. 2010).
(ii) Long term sustained physical activity also improves immune function by increasing the number and activity of macrophages and natural killer cells but to what extent this has on the anti-carcinogenic effect of physical activity is unknown (Shephard et al. 1995, Friedenreich et al. 2010).

(iii) Exercise has anti-oxidant effects by up-regulating the activities of free scavenger systems and anti-oxidant levels (Friedenreich et al. 2001). It also increases gut motility, thereby reducing mucosal exposure time to carcinogens, a mechanism deemed important in the prevention of colorectal cancer (Friedenreich 2001).
(iv) Physical activity promotes healthy weight and helps to prevent overweight and obesity by balancing caloric intake with energy expenditure (Friedenreich et al. 2001). Thus physical activity could help to prevent cancers that are due to overweight and obesity as the worldwide increase in obesity is mainly due to decreased physical activity and availability of calorie-dense foods (Thun et al. 2010).

Among men, physical activity is associated with reduced risk of colorectal, lung and pancreatic cancers but evidence has been most convincing for colorectal cancer where reduced risk has been observed with all forms of physical activity (World Cancer Research Fund/American Institute for Cancer Research 2007, Friedenreich et al. 2010). Even though the most optimal intensity and duration of physical activity necessary to prevent cancer is not fully ascertained, it is recommended that participating in moderate to vigorous physical activity of at least 45 minutes, five days a week may suffice (Byer et al. 2002). This is because moderate to vigorous physical activity is needed to metabolize stored fat and to modify physiological functions that affect hormones, insulin, prostaglandin and immune functions (Byers et al. 2002, Friedenreich et al. 2001). In a study in Finland, moderate intensity physical activity, at least 30 minutes a day was associated with reduced risk of dying from cancer among men (Laukkanen et al. 2011).

2.3.2.4 Body mass index

There is increasing evidence that overweight and obesity are associated with specific cancers, total cancer and cancer mortality (Renehan et al. 2008, Basen-Engquist and Chang 2011). In Europe, 2.5% of cancers among men and 4.1% of cancers among women are attributable to obesity compared to 4% and 7% among men and women respectively in the USA (Polednak 2008, Renehan et al. 2010). In a very large prospective study from the USA

involving more than 900,000 adults, obese men and women had 52% and 62% increased risk of dying from cancer compared to their normal weight counterparts (Calle et al. 2003). Likewise, a systematic analysis of prospective studies found that cancer mortality was lowest among men and women within normal BMI range and that every 5kg/m^2 increase in BMI was associated with a 10% increase in cancer mortality (Prospective Studies Collaboration 2009).

Among men and women, there is strong evidence that excess body weight increases the risk of colorectal, esophageal, pancreatic, kidney and thyroid cancers while there is probable evidence linking excess body weight to increased risk of leukemia, malignant melanoma, multiple myeloma and Non-Hodgkin's lymphoma in addition to the excess risk of endometrial and post-menopausal breast cancer risks among overweight women (World Cancer Research Fund/American Institute for Cancer Research 2007, Renehan et al. 2008, Basen-Engquist and Chang 2011). The relationship between obesity and lung cancer is however controversial. Studies suggest that an inverse relationship may exist but it has been suggested that these may be due to the residual confounding effects of smoking on body weight as smokers are more likely to be lean (Canoy et al. 2005, Kanashiki et al. 2005, Renehan et al. 2008). It has been suggested that anthropometric measurements such as waist to hip ratio may be better predictors of the relationship between adiposity and cancer risk but very few studies have investigated the relationship between such anthropometric measurements and cancer risk.

2.3.2.5 Infections

Chronic infections are estimated to be responsible for about 17.8% of cancers worldwide. Infection-related cancers are more common in developing countries where they account for 26% of cancer cases compared to developed countries where they account for 8% of cancer cases (Parkin 2006). The most common cancers caused by infections are liver

(hepatitis B and hepatitis C viruses), stomach (helicobacter pylori) and cervical cancer (human papilloma virus). Others such as Kaposi sarcoma (human herpes virus-8), lymphomas (Epstein-Barr virus), bladder cancer (schistosoma haematobium), and biliary tract cancer (onchocerciasis) are more common in certain regions of the world especially Asia and Africa (Parkin 2006, Thun et al. 2010). The low prevalence rates of these cancers in developed countries is an attestation to the preventive efforts such as improved standards of living, better hygiene and vaccination programs initiated over the last few decades in these countries (Thun et al. 2010).

2.4 ALCOHOL

2.4.1 Contexts of alcohol consumption

As many as 2 billion people consume alcoholic beverages in different forms worldwide (WHO Global status report 2004). In terms of cultural contexts, alcohol consumption in various societies has been described as "wet" and "dry" (Peele 1988, Room and Mäkelä 2000, Bloomfield et al. 2003). In wet cultures, usually observed in European countries bordering the Mediterranean, alcohol consumption is part of daily life; it is often consumed with meals, and is widely accessible. Wine is the preferred beverage and there are very few abstainers (Bloomfield et al. 2003). On the contrary, in dry cultures, access to alcohol is more restricted and alcohol consumption is less frequent but when drinking occurs, it is more likely to lead to intoxication and wine consumption is less common (Bloomfield et al. 2003). This type of drinking pattern is more frequently observed in the Scandinavian countries, and the United States of America (Bloomfield et al. 2003). The marked distinctions between wet and dry drinking cultures are however disappearing, leading to more homogenous drinking patterns in many cultures such that wine consumption is decreasing in the Mediterranean countries and overall alcohol consumption is increasing in the Scandinavian countries (Allamani et al. 2000, Leifman 2001).

2.4.2 Dimensions of alcohol consumption

There are two dimensions to alcohol consumption; average volume of consumption and patterns of drinking (Rehm et al. 2003). Both are related to health outcomes in separate ways and in order to reduce health burdens due to alcohol consumption, both dimensions must be taken into consideration (Rehm et al. 2003, Monteiro et al. 2008). Average volume of consumption or per capita consumption is more likely to be related to long-term health outcomes while patterns of drinking are more likely to predict acute health outcomes although average volume of consumption may also lead to acute health effects and there is emerging evidence that patterns of drinking may also be related to long-term health outcomes (Rehm et al. 1996).

Per capital alcohol consumption is the total alcohol production in a country (including imports and minus exports) in a year divided by the total population (WHO 2000). The World Health Organization (WHO) uses the adult (people 15 years and older) per capita to measure alcohol consumption instead of the per capita for the whole population. This is because in populations with a large proportion of young people, using per capita alcohol consumption for the whole population will underestimate the consumption among adults if it assumed that majority of people less than 15 years of age do not consume alcohol (WHO 2000). Since per capita alcohol consumption is a standardized form of measuring alcohol consumption, it is very useful for comparing consumptions between countries (WHO 2000). Per capita alcohol consumption figures are given in liters of 100% alcohol which takes into consideration the alcoholic content in each beverage (WHO 2000).

The three main sources of data for per capita estimates are national government data, data from international organizations and alcohol industry (WHO 2000, Rehm et al. 2003, Monteiro et al. 2008). The government data represent the most reliable data because it is usually based on sales figures, tax revenues and production data but nevertheless, it may

still be an underestimate since home production and smuggling cannot be accounted for (Rehm et al. 2003).

In order to understand individual levels of alcohol consumption, general population surveys are needed. These provide an array of information on prevalence of high-, moderate and low-drinkers, patterns of consumption, drinking occasion and socio-demographic correlates of drinking (Bloomfield et al. 2003, Monteiro et al. 2008). The most commonly used measure of alcohol consumption is the quantity-frequency index through which respondents can estimate how often they drink and how much they drink per drinking occasion (Bloomfield et al. 2003). However, this can underestimate amount of alcohol consumed because respondents tend to ignore occasional episodes of heavy consumption (Greenwald and Nephew 1994).

2.4.3 Regional differences in alcohol consumption

Taking both recorded and estimated unrecorded alcohol consumption into consideration, the highest amount of alcohol per resident aged 15 years and above (13.9L) is consumed in Europe C (Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine) (Rehm et al. 2009, Figure 5). A similar per capita consumption (12.9L) is observed for Europe A (Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom). The lowest per capita alcohol consumption (0.6L to 2L) is observed in the Eastern Mediterranean countries comprising Afghanistan, Pakistan, Iran, Saudi Arabia etc.

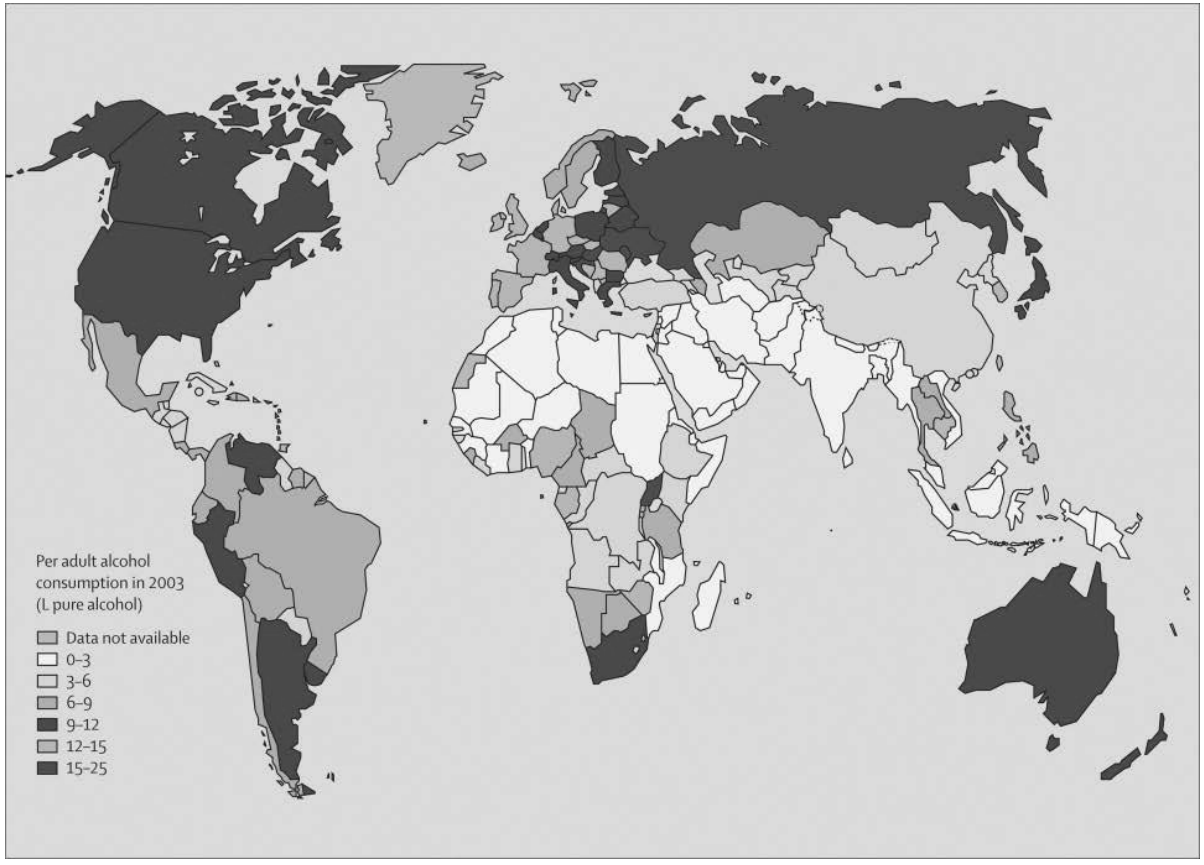
The proportion of heavy drinkers as defined as intake ≥ 40g/day among males and ≥ 20g/day among females mirrors that of per capita alcohol consumption (Rehm et al. 2003). As many as 18.6% of adults in Europe C, 15.7% in Europe A; and just 0.1% in the Eastern

Mediterranean are estimated as heavy drinkers. In all the regions, a higher proportion of males compared to females consume more alcohol. While the highest male (84%) to female (30%) disparity in alcohol consumption is observed in the Western Pacific B (Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam), the lowest is observed in Europe C (89% of men compared to 81% of women consume alcohol) (Rehm et al. 2003).

A proportion of adult per capita alcohol consumption is believed to be unrecorded. These can be home brewed beverages, smuggled products and travelers' import. This proportion ranges from as little as 10% in parts of Europe and North America to as much as 79% in the Southeast Asia (Rehm et al. 2003)

There is a wide geographical distribution in the type of alcoholic beverage consumed. The alcoholic beverage most commonly consumed globally in terms of pure ethanol content is spirits (Rehm et al. 2003, Monteiro et al. 2008). It dominates alcohol consumption in Europe and the Pacific regions. Beer is however more consumed in Southern America while locally fermented beverages predominate in many African countries. While spirit consumption has been growing globally over the last few years, wine consumption has been decreasing globally mainly because of decreased consumption in Southern Europe (Rehm et al. 2003, Monteiro et al. 2008).

Figure 5. Alcohol consumption worldwide- both recorded and unrecorded. Adapted from Rehm et al. Lancet 2009. Reproduced with the permission of Nature Publishers



2.4.4 Alcohol consumption trends

Alcohol consumption increased sharply worldwide during the 1960s till the early 1980s when it reached its peak. Since then, there had been a gradual decline in mean alcohol consumption until the late 1980s when a more stable rate was attained. However, there are regional differences in consumption trends such that while the countries with very high consumption levels are decreasing consumption, those with low consumption are increasing theirs; leading to a convergence in consumption rates (Hupkens et al. 1993, WHO 2004). Some of the stability/decreased in consumption rates observed in many developed countries has been attributed to alcohol control policies such as higher taxation enacted over the years to curb excessive consumption (Monteiro et al. 2008). Likewise, policy changes enacted in some other countries towards lower taxation and increased availability has led to increased consumption in countries such as Finland, Sweden, UK, Canada etc. (WHO 2004)

In Europe, beer consumption is increasing, wine consumption is reducing and spirit consumption appears to be stable because wine producing countries are consuming other beverages while non-wine producing countries are consuming more wine (Rehm et al. 2003, WHO 2004). In many developing economies, local beverages such as burukutu (Nigeria; Obot 2000), arrack (India; Mohan et al. 2001) made from the fermentation of grains, fruits, palm trees etc. are important components of total alcohol consumption especially in rural areas or poor neighborhoods. However, in the more affluent sections of these countries, beer consumption is increasing rapidly because of the social prestige attached to international beer brands and aggressive marketing by multinational alcohol beverage companies (Babor et al. 2003).

Of importance is the fact that large differences in consumption rates still exists within regions and within the same country but within a country, dramatic changes in alcohol

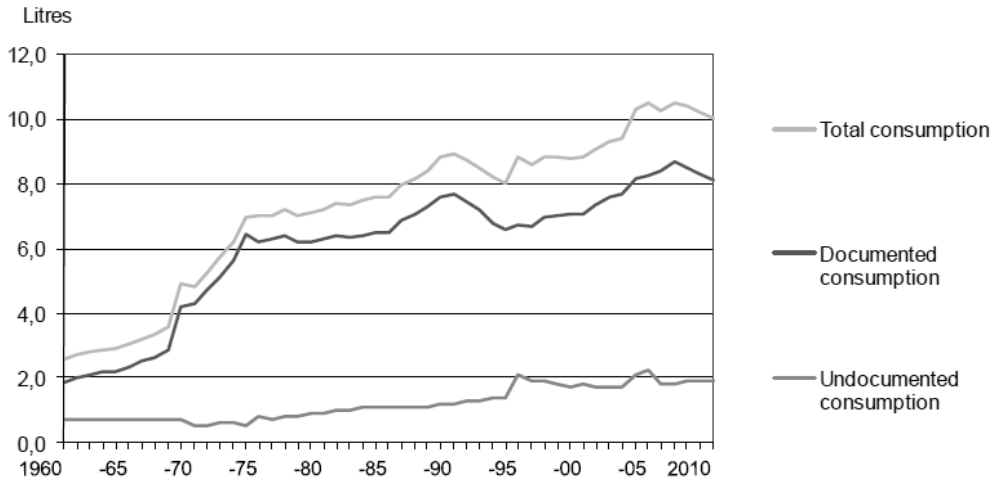
consumption are hardly observed. For example, a recent study in Europe (Sieri et al. 2002) observed that the type, volume and pattern of alcohol consumed in differed between the study regions. Wine was consumed mainly among Italian and Spanish men but men in Northern Italy and Northern Spain consumed more wine compared to those from the southern areas. In contrast, the beverage of preference in The German and Dutch centers was beer while Italian men consumed very little beer. In all the centers, women drank less than men and consumed different beverages (Sieri et al. 2002). In Finland, alcohol consumption has increased among women and women account for about a 3rd of alcohol consumed (Jääskeläinen and Virtanen 2010). The proportion of women who abstain from alcohol has reduced from 17% to 10% (Jääskeläinen and Virtanen 2010). Hazardous drinking habits have also increased among women in Finland, especially among young women. In survey carried out in 2000, 70% of young women aged 20-29 years drink to intoxication at least once a year (Jääskeläinen and Virtanen 2010).

2.4.4.1 Alcohol consumption in Finland

Alcohol consumption in Finland has increased steadily since the early 1960's (Ministry of Social Affairs and Health, 2005). From about 2.8 liters of 100% alcohol per capita in 1960, it increased to a high of about 8.9 liters of 100% alcohol per capita in 1990 (Ministry of Social Affairs and Health, 2005). However, per capita consumption reduced by about 10% over the next 3 to 4 years (Jääskeläinen and Virtanen 2010, Ministry of Social Affairs and Health, 2005). This reduction has been attributed to the economic recession at the time leading to lower purchasing power. However, an increase in per capita alcohol consumption was seen after 1994 due to the abolishment of time limits regarding alcohol purchased in third countries which led to increased imports from neighboring countries, specifically Russia and Estonia (Ministry of Social Affairs and Health, 2005). This steady increase was exacerbated in 2004 when tax on alcohol was reduced and quota on tax free alcohol import was abolished. Since 2005, alcohol consumption in Finland has consistently been more than 10 liters of 100% alcohol (Jääskeläinen and Virtanen 2010). However, latest

figures in 2010 indicate a slight decline in alcohol consumption but still at a high level of 10 liters of 100% (Jääskeläinen and Virtanen 2010).

Figure 6. Alcohol consumption in Finland over a 50-year period from 1960-2010. Adapted from Jääskeläinen and Virtanen 2010, Alcohol beverage consumption 2012. Available online at www.stakes.fi/tilastot/tilastotiedotteet/2011/Tr16_



Finland has been classified as a "former spirit-drinking country" (Ministry of Social Affairs and Health, 2005). This is because spirits accounted for most of the alcohol consumed the 1960's and a large part of the 1970's (Ministry of Social Affairs and Health, 2005). However, since the mid 1980's, beer has been the major alcoholic beverage in Finland and it presently accounts for about 46% of the proportion of alcohol consumed with spirits now the second choice accounting for about 26% of alcohol consumed (Ministry of Social Affairs and Health, 2005). Wine consumption in Finland has been increasing over the past 50 years. Fifty years ago, wine consumption accounted for less than 8% of per capita alcohol consumption but as of 2010, it accounted for as much as 15% (Jääskeläinen and Virtanen 2010, Ministry of Social Affairs and Health, 2005) and if drinking trends continue, wine and spirit consumption in Finland may converge in the not too distant future.

2.4.5 Alcohol metabolism

Upon ingestion, alcohol is quickly absorbed by passive diffusion in the stomach and small intestines and thereafter enters the portal circulation (Ferreira and Willoughby 2008). Alcohol has both lipophilic and hydrophilic properties, which facilitate its diffusion across cell membranes and also its extensive distribution throughout all body compartments (Koolman and Röhm 2005, Ferreira and Willoughby 2008). The alcohol molecule is primarily metabolized to acetaldehyde in the hepatocytes mainly by alcohol dehydrogenase (ADH) but sometimes by non-specific cytochrome P450 monooxygenase (MOX) (Lieber 1997, Ferreira and Willoughby 2008).

Acetaldehyde is a very reactive molecule, which is more toxic than alcohol itself. It is oxidized in the mitochondria by acetaldehyde dehydrogenase (ALDH) (Ferreira and Willoughby 2008). Both ADH and ALDH require NAD+ as a coenzyme and because the liver has a limited supply of NAD+, the detoxification rate is slowed down to about one drink per hour (15 g of ethanol) (Ferreira and Willoughby 2008). This can be circumvented by the induction of MOX enzymes but the downside is that induction of non-specific MOX enzymes also increases the metabolism of other weakly polar or non-polar compounds leading to generation of reactive oxygen species and deficiency of vitamins such as retinol (Lullman et al. 2000, Ferreira and Willoughby 2008).

2.4.6 Alcohol and health

Alcohol use is associated with a wide array of physical, mental and social problems and the international variations in alcohol attributable disease burden depends on the per capita consumption and pattern of consumption within the different countries (WHO 2004). Alcohol use is associated with acute (injuries, accidental poisoning, assault, interpersonal violence etc.) and chronic adverse health outcomes such as congenital anomalies, neuro-psychiatric disorders, liver diseases, polyneuropathy, cardiomyopathy,

hypertension, and cancers (WHO 2004). However, the health effects of alcohol use will not be complete without detailing its beneficial effects on health

2.4.6.1 Beneficial effects of alcohol on health

Evidence suggests that moderate alcohol consumption is associated with reduced risks of ischemic heart disease, ischemic stroke, diabetes mellitus and cholelithiasis (Rimm et al. 1995, English et al. 1995, Leitzmann et al. 1999, Rehm et al. 2004, Reynolds et al. 2003, Corrao et al. 2001).

The relationship between alcohol consumption and cardiovascular diseases is a complex one. While alcohol use has been associated with increased risk of hypertension, cardiac arrhythmias, and hemorrhagic stroke, majority of studies over the past 40 years have demonstrated a J-shaped relationship between alcohol consumption and ischemic heart disease wherein moderate drinkers are have lower risk compared to abstainers and those who drink excessively (WHO 2004). It has also been suggested that moderate drinking reduces the risk of disease progression in people who have ischemic heart disease (Niroomand et al. 2004).

The protective effect of alcohol on ischemic heart disease is plausible because moderate alcohol consumption causes changes in the plasma lipid profile such as increasing concentrations of high-density lipoprotein (HDL) and estimates reveal that as much as 40% of the protective effect may be mediated via these mechanisms (Suh et al. 1992, Criqui and Ringel 1994, Mukamal et al. 2005). Other putative mechanisms that have been suggested include the beneficial effects of moderate consumption on platelet function, fibrinolysis, anti-oxidative properties of some alcoholic beverages such as wine (Ridker et al. 1994, Zhang et al. 2000, Booyse et al. 2007). Although recent reviews seem to suggest that there may have been some misclassification in previous studies, especially with the appropriateness of using abstainers as the reference categories since abstainers may

actually be "sick quitters" who stopped drinking alcohol due to deteriorating health and the fact that healthy behaviors seem to cluster among moderate drinkers, the available scientific evidence appear to be in favor of a beneficial effect of moderate drinking on ischemic heart disease (Shaper et al. 1988, Fillmore et al. 1998, Fillmore et al. 2006, Ellison and Martinic 2007).

With regards to type 2 diabetes and alcohol use, a U-shaped relationship has been also been reported (Koppes et al. 2005). Likewise, patients with type 2 diabetes who consume moderate amounts of alcohol have been shown to be at lower risks of cardiovascular events (Koppes et al. 2006). The relationship between moderate alcohol consumption and type 2 diabetes is thought to be mediated by the effects of alcohol on glucose tolerance and insulin resistance (Rimms et al. 1995, Kiechl et al. 1996, Flanagan et al. 2000).

2.4.6.2 Burden of alcohol consumption on health

Despite the stated beneficial effects of alcohol on health, alcohol consumption contributes significantly to the global burden of diseases. According to the most recent estimates, 4.6% of the global burden of diseases and injury in 2004 can be attributed to alcohol consumption (Rehm et al. 2009). The burden is higher among men where alcohol use is responsible for 7.6% of diseases compared to 1.4% among women. This reflects the fact that men consume more alcohol than women and also indulge in heavier drinking (Rehm et al. 2009). The effect of alcohol on diseases and injury is seen in all age groups within the society but the relative effect of alcohol on health is most seen among people aged between 15 and 44 years where alcohol use was responsible for 10% of diseases in men and 3% in women (Rehm et al. 2009).

Likewise, 3.8% of global deaths in 2004 were attributable to alcohol use; 6.3% for men and 1.1% for women which represents an increase over values for the year 2000 due to an increasing number of women drinkers (Rehm et al. 2009). The sex differences in alcohol

attributed deaths were highest in the Southeast Asian region where men were ten times more likely to die from alcohol related causes than women. The proportion of deaths caused by alcohol was highest in Europe, especially for countries of the former Soviet Union where as many as 10% of deaths can be attributed to alcohol use (Rehm et al. 2009).

2.4.7 Alcohol and cancer

Since the beginning of the 20th century when Lamu (1910), a French pathologist noticed an increased risk of esophageal cancer among absinth drinkers, many experimental and epidemiological studies have been conducted on the possible association between alcohol and various cancers especially upper aero-digestive tract (UADT) cancers.

In the past, ethanol was not considered to be a carcinogen but a co-carcinogen and/or tumor promoter because ethanol did not induce carcinogenesis in animal experiments but more detailed analysis of these experiments revealed flaws in the study designs and execution (Seitz and Stickel 2007). Results of animal experiments on alcohol and cancer are influenced to a large extent by the study design, type of carcinogen used, duration of exposure, dosage and route of administration (Pöschl and Seitz 2004).

The carcinogenic effect of alcohol was mainly attributed to its metabolite, acetaldehyde. More recent animal experiments have revealed that when rats and mice were given alcohol in their drinking water, ethanol acted as a carcinogen especially in the UADT (Roy et al. 2002, Soffritti et al. 2002, Seitz and Stickel 2007). This led to the recent classification of ethanol by IARC as a carcinogen (Baan et al. 2007). The IARC concluded there is convincing evidence that alcohol intake ≥ 50g/day was associated with 2-3 fold increased risk of cancers of the oral cavity, pharynx, larynx and esophagus and smoking and alcohol acts multiplicatively to increase the risks of these cancers (Baan et al. 2007) but the effect of ethanol on different tissues in the body is still subject to debate.

2.4.7.1 Mechanisms of alcohol carcinogenesis

Ethanol and its metabolite acetaldehyde are now confirmed carcinogens but the precise mechanisms by which they cause cancer in various organs are still not fully understood. Apart from the systematic effects, it is believed that separate mechanisms are at play in most of the organs they affect.

2.4.7.2 Local effect

By acting as a solvent, alcohol increases the penetration of carcinogenic substances into the mucosa, thereby facilitating their uptake (Pöschl and Seitz 2004). It is also known that chronic alcohol intake causes atrophy and lipomatous metamorphosis of the parenchyma of the parotid and submaxillary gland resulting in a functional impairment and increased viscosity of saliva flow. This invariably leads to prolonged contact of carcinogens with the mucosa (Maier et al. 1986). Highly concentrated alcoholic drinks can also have a direct toxic effect on the epithelium. Chronic alcohol consumption can lead to reduced oesophageal motility; enhance gastro-oesophageal reflux which can lead to oesophagitis and metaplasia (Seitz et al. 1998). Previously, alcoholic beverages contained polycyclic hydrocarbons, asbestos fibres and nitrosamines which are all carcinogenic but these are no longer present in alcoholic beverages (Seitz et al. 1998).

2.4.7.3 Acetaldehyde

Acetaldehyde is classified as a carcinogen (IARC 1999, IARC 2007). In experimental studies, acetaldehyde inhalation in rats and hamsters resulted in cancers of the nasal mucosa and the larynx and when acetaldehyde is animals are given acetaldehyde in drinking water for a long time, it results in excessive cell growth of the mucosa cells of the upper digestive tract (Woutersen et al. 1986, Feron et al. 1982). Acetaldehyde has also been found to induce inflammatory and metaplastic changes in tracheal cells, interfere with

normal cell reproduction and enhances cellular damage to gastrointestinal mucosa (Seitz et al. 2001).

There are several pathways through which acetaldehyde can induce carcinogenesis. It can interfere with DNA replication by causing point mutations in in the hypoxanthine phosphoribosyltransferase 1 locus in human lymphocytes, and inducing sister chromatid exchanges and gross chromosomal anomalies (Obe et al. 1986, Dellarco 1988, Pöschl and Seitz 2004). It also interferes with DNA repair by inhibiting the activity of some enzymes such as O-6-methylguanine methyltransferase which are necessary for DNA repair (Espina et al. 1988, Pöschl and Seitz 2004). Acetaldehyde can interact with DNA building blocks to form DNA adducts which cause replication errors and/or mutations in oncogenes and tumour suppressor genes (Fang and Vaca 1995).

2.4.7.4 Oxidative stress

Chronic alcohol intake leads to the induction of CYP2E1, which is the other enzyme that metabolises ethanol to acetaldehyde (Baumgarten et al. 1996 in, Pöschl and Seitz 2004). Apart from acetaldehyde, CYP2E1 is also involved in the metabolism of xenobiotics and pro-carcinogens such as nitrosamines, aflatoxins, polycyclic hydrocarbons to their prospective carcinogens and the concentration of CYP2E1 in the liver is correlated with the generation of hydroxyethyl radical (Seitz et al. 1998). The induction of CYP2E1 is one of the mechanisms responsible for the synergistic effects of alcohol and smoking on cancers especially UADT cancers (Seitz et al. 1998). Ethanol also reduces the generation of glutathione, which is the major reductive compound that can counteract oxidative stress (Speisky et al. 1985, Seitz and Stickel 2007).

2.4.7.5 Nutritional factors

There may be nutritional impairment in heavy alcohol drinkers as they tend to derive most of their calories from alcohol consumption (Pöschl and Seitz 2004). Ethanol

metabolism increases oxidative stress leading to increased requirement for gluthatione and alpha-tocopherol (Pöschl and Seitz 2004). Acute and chronic alcohol consumption can also lead to folate deficiency, both from reduced intake and increased destruction by acetaldehyde (Stickel and Seitz 2004). Excessive alcohol intake can reduce folate bioavailability by reducing its intestinal absorption, increasing its urinary excretion and inducing cleavage of the folate molecule (Purohit et al. 2005). Alcohol intake can impair folate metabolism by inhibiting the activity of methionine synthase, the enzyme responsible for the transfer of a methyl group from folate to homocysteine, necessary for methionine reformation (Purohit et al. 2005). This results in the decreased production of S-adenosylmethionine which is a major methyl donor for proteins, DNA and RNA, ultimately causing global hypo-methylation (Purohit et al. 2005). Gene methylation is very important for controlling gene expression and hypomethylation of genes results in increased gene expression, which may be important in carcinogenesis (Baylin 2005, Seitz and Stickel 2007).

Another important nutritional factor is the effect of alcohol of retinoid metabolism. Retinoic acid is the most active form of vitamin A (Purohit et al. 2005). It controls cell proliferation, growth and differentiation and promotes apoptosis, thus any impairment in its functions can promote carcinogenesis (Purohit et al. 2005). Chronic alcohol intake can impair retinoic acid metabolism by inducing CYP2E1 activity and accelerating vitamin A catabolism and by inhibiting retinol metabolism to retinoic acid (Purohit et al. 2005, Seitz and Stickel 2007). Retinoic acid regulates gene transcription of many regulators of cell proliferation by signaling through its nuclear retinoic acid receptors (Seitz and Stickel 2007). Alcohol intake can also reduce the biological activity and signaling of retinoic acid by downregulating retinoid target gene expression and inhibiting retinoic acid receptor's binding activity to the retinoic acid response elements (RARE) (Purohit et al. 2005, Seitz and Stickel 2007).

Chronic alcohol intake can result in deficiency of other co-factors needed necessary for methyl group transfer such as vitamin B6 and B12 (Giovannucci et al. 1995, Seitz and Stickel 2007)

2.4.7.6 Genetic polymorphisms in alcohol metabolism and cancer risk

The importance of genetics in alcohol and cancer is underlined by the differences in the susceptibility of different races to the carcinogenic effects of alcohol and the fact that some people may be susceptible to the cancer-induced effects of alcohol at relatively low alcohol intakes. Because the conversion of ethanol to acetaldehyde and subsequently acetate depends on ADH and ALDH enzymes, it implies that genetic variations in the enzymes will lead to functional differences in their activities (Druesne-Percollo et al. 2009). Thus, the amount of acetaldehyde in the circulation following alcohol intake does not depend only on the amount of alcohol consumed but also on the genetic variants responsible for alcohol metabolism (Seitz and Stickel 2007).

The ADH oxidizes alcohol to acetaldehyde and about seven genes are known to encode for the ADH enzymes (Seitz and Becker 2007). Two of these enzymes, ADH1B and ADH1C exhibit considerable polymorphisms such that the amount of acetaldehyde generated differs substantially (Druesne-Percollo et al. 2009, Seitz and Becker 2007). For ADH1B, the mutant allele, ADH1B*2 encodes for an enzyme which is 40 times more active than the ADH1B*1 allele (Bosron and Li 1986, Druesne-Percollo et al. 2009). The ADH1B*2 allele is common in Asian populations where its frequency ranges from 10 to 90% but in African and European populations, the frequency does not exceed 15% (Quertermont 2004, Brennan et al. 2004). When individuals with the ADH1B*2 allele take alcohol, even in little amounts, acetaldehyde is produced in very large quantities leading to flush syndrome characterized by nausea, vomiting, facial flushing (Seitz and Stickel 2007). Thus, these individuals tend to avoid drinking alcohol because of the severe reactions. Studies in Asian populations have explored the relationship between alcohol consumption, ADH1B

polymorphisms and cancers of the UADT and most have found increased risk among moderate or heavy drinkers with ADH1B*1 compared to those with the ADH1B*2 polymorphism (Boonyaphiphat et al. 2002, Yokoyama et al. 2002, Chen et al. 2006,).

ALDH2 is the main enzyme that oxidizes acetaldehyde to acetate and is encoded by the ALDH2 gene which has two main alleles, ALDH2*1 (normal allele) and ALDH2*2 (inactive allele) (Crabb et al. 1989, Seitz and Stickel 2007, Druesne-Percollo et al. 2009). The ALDH2*2 is due to a point mutation in the ALDH2 gene resulting from the substitution of lysine for glutamine at position 487 of the protein (Seitz and Stickel 2007, Druesne-Percollo et al. 2009). People who are homozygous for the ALDH2*2 have null ALDH2 activity; cannot metabolize acetaldehyde and cannot tolerate alcohol due to the flush syndrome whereas heterozygotes have about 6% residual ALDH2 activity (Seitz and Stickel 2007, Druesne-Percollo et al. 2009). The proportion of Japanese people that are homozygous and heterozygous for ALDH2*2 allele are 10% and 40% respectively whereas the ALDH2 mutant alleles are extremely rare in European and African populations (Brennan et al. 2004, Seitz and Stickel 2007, Druesne-Percollo et al. 2009). Most studies on the association of these polymorphisms with alcohol associated cancer risk have been mainly related to the development of UADT, especially esophageal cancers, among Asians, where risks ranging from 11-fold to 50-fold have been reported among those with mutant alleles (Yokoyama et al. 1998, Yokoyama and Omori 2003, Asakage et al. 2007, Hiraki et al. 2007). A large study in Europe has confirmed these observations (Hashibe et al. 2006). The study reported an increased risk in UADT cancers among individuals who are homozygous or heterozygous for the ALDH2 alleles (Hashibe et al. 2006). Thus, there is compelling evidence to show that these genotypes modify an individual's risk of developing UADT cancers but their importance in the development of other cancers have not been investigated in detail.

3 AIMS OF THE THESIS

The major aims are to determine the relationship between alcohol consumption and cancer risk among men in Finland

The specific objectives of the study are:

1. To investigate the association between alcohol consumption and colorectal cancer (study I)
2. To determine if there is any relationship between binge drinking pattern and lung cancer (study II)
3. To elucidate the impact of alcohol consumption on total cancer risk and estimate the burden of cancer attributable to alcohol consumption (study III)
4. To investigate whether moderate alcohol consumption has an effect on cancer and cancer mortality beyond that observed for smoking (study IV)

4 MATERIAL AND METHODS

4.1 STUDY POPULATION

The men involved in this study were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). The KIHD is a prospective population-based study designed to investigate risk factors for cardiovascular diseases and other health related outcomes among middle-aged men from Eastern Finland. The study population consisted of men aged 42, 48, 54 and 60 years at the time of baseline examination which was conducted between March 1984 and December 1989. In all, 3,235 men were eligible to participate out of which 193 were excluded because of underlying serious diseases and 83% (2,682) volunteered to take part (Figure 7). Complete information on alcohol consumption and smoking was available for 2627 men. The study protocol was approved by the research ethics committee of the University of Kuopio. All participants gave written informed consent.

Figure 7. Kuopio Ischemic Heart Disease (KIHD) Risk Factor study cohort participation chart

4.2 ASCERTAINMENT OF CANCERS AND CANCER DEATHS

Cancer cases during the follow up period were ascertained by the Finnish Cancer Registry (FCR), which is nationwide. Cancer registration began in Finland in 1952 and since 1953 when the first complete nationwide cancer registration was conducted; over 950,000 cancer cases have been registered at the FCR (Pukkala 2001). From 1961, it became compulsory for physicians, laboratories and hospitals to notify all diagnosed or suspected cancer cases (Pukkala 2001, www.cancer.fi). The coverage of the FCR is virtually complete with no loss to follow-up and for solid tumours; the registration is over 99% complete (Teppo et al. 1994). The ICD-O-3 coding nomenclature which takes into consideration the tumour site, morphology, behaviour and grade has been used by the FCR since 2005. Coding is done by qualified secretaries under the supervision of the Registry physician.

Cancer deaths were ascertained by a computer linkage to the national death registry using the Finnish personal identity code. The personal identity code is a unique 11-digit personal identity code mandatory to every resident of Finland since 1961. The personal identity code is indicated on cancer registry forms. The cancer registry file containing personal identity codes is annually matched through computerized linkage with the cause of death register at the Statistics Finland so that dates and cause of deaths in cancer patients can be added to the FCR records (Pukkala 2001). It is also regularly linked with the Central Population Register to ensure that the personal identity codes are correct.

Standards are rigorously maintained to ensure that there is no breach of confidentiality and individual data are well protected. In order to use data from the FCR for linkage and research purposes, approval needs to be obtained from the relevant ethical research committee and other pertinent (e.g. data protection) authorities (Pukkala 2001).

4.3 ALCOHOL CONSUMPTION

Alcohol consumption was assessed with the Nordic alcohol consumption inventory which employs a structured quantity and frequency questionnaire model (Hauge and Irgens-Jensen 1981, Kauhanen et al. 1992). Four major alcoholic beverages were assessed (beer, wine, strong wine, spirits). For each type of alcoholic beverage, both the usual frequency of intake and usual dose (in glasses or bottles) were recorded using a structured response form which assessed both total alcohol intake and the timing or pattern of drinking (usual number of drinks per session). The measures of average weekly intake of all the alcoholic beverages were calculated on the basis of known alcohol content of each type of drink and reported doses and frequencies of drinking sessions. In Finland, a third of a liter bottle of ordinary beer (class III) contains 12g of ethanol, strong beer (class IV) contains 14g of ethanol and one portion of hard also contains 14g of ethanol.

For the study on binge drinking and lung cancer risk, we classified binge drinking as the consumption of more than 70g of alcohol on one drinking occasion. In literature, there is no consensus on the classification of binge drinking but binge drinking has been classified variously as (i) consumption of five or more alcoholic drinks at one drinking occasion, (ii) eight drinks within the same day, (iii) six or more bottles of beer at one drinking occasion (Wechsler and Austin 1998, Kauhanen et al. 1997, Murray et al. 2002). A previous study within this cohort that investigated the associations of binge drinking with mortality defined beer binging as consumption of 6 or more bottles of beer/drinking session (Kauhanen et al. 1997). In this study, we wanted to capture binge drinking from all alcoholic sources and not from beer alone. Therefore in the second study, we classified binge drinking based on the least amount of alcohol in 6 bottles of ordinary beer i.e. 70g. In terms of alcoholic content, this is also equivalent to (ii) ≥ 1 of big bottle (75cl) of mild wine, (iii) ≥ ¾ of 1 big bottle (75cl) of strong wine, (iv) ≥ 6 portions of hard liquor. This is because as previously described above, in Finland, a third of a liter bottle of ordinary beer (class III) contains 12g of ethanol, strong beer (class IV) contains 14g of ethanol and one portion of hard liquor contains 14g of ethanol.

In order to determine biomarkers of excessive alcohol use, serum gamma-glutamyl transpeptidase (GGT) and mean corpuscular volume (MCV) were measured from baseline blood samples. The questionnaire used to determine alcohol consumption was validated using the biomarkers of excessive alcohol use (MCV and GGT) and there was a correlation between alcohol intake and the biochemical markers (Kauhanen et al. 1992).

4.4 SMOKING

Smoking status was determined on the basis of recent use smoked cigarettes, cigars and pipes. Thus, a subject was described as a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or pipe within the past 30 days. The number of cigarettes, cigars, and pipes of tobacco currently smoked daily and the duration of regular smoking in years were recorded on a self-administered questionnaire that was checked by an interviewer. The life-long exposure to smoking was estimated as the product of the number of smoking years and the number of tobacco products smoked daily until the time of baseline examination

4.5 NUTRIENT INTAKE

Food consumption was assessed at the time of blood sampling during the baseline phase of the study. Collection of food data occurred over a 4 day period and subjects were instructed on the use of household measures for quantitative recording of their food intake (Rissanen et al. 2003). The instructions were given by a nutritionist who also cross-checked the completed food intake records. Dietary intake of foods and nutrients was calculated using NUTRICA software (version 2.5; National Public Health Institute, Turku). The software is compiled using mainly Finnish values of nutrient composition of foods, and takes into account losses of vitamins in food preparation (Rissanen et al. 2003). The nutrient composition of foods in the NUTRICA software used reflects data on vitamin contents of fruits and vegetables (Rissanen et al. 2003).

4.6 CARDIORESPIRATORY FITNESS AND PHYSICAL ACTIVITY

Cardiorespiratory fitness was assessed with a maximal, symptom-limited exercise tolerance test on an electrically baked bicycle ergometer between 8:00 a.m. and 10:00 a.m.

(Lakka et al. 1994, Laukkanen et al. 2009) The standardized testing protocol comprised of a linear increase in the workload of 20 W per minute (400 L bicycle ergometer, Medical Fitness Equipment, Mearn, The Netherlands) (Laukkanen et al. 2009). For safety reasons, and to obtain reliable information about exercise test variables, the tests were supervised by an experienced physician with the assistance of an experienced nurse. The electrocardiogram (ECG), blood pressure and heart rate were registered during the exercise stress test. Leisure-time physical activity was assessed using the KIHD 12-month leisure-time physical activity questionnaire (Lakka et al. 1994, Lakka and Salonen 1992). The checklist included the most common leisure-time physical activities of middle-aged Finnish men, selected based on a previous population study in Finland (Lakka and Salonen 1992). For each activity performed, subjects were asked to record the frequency (number of sessions per month), average duration (hours and minutes per session), and intensity (scored as 0 for recreational activity, 1 for conditioning activity, 2 for brisk conditioning activity, 3 for strenuous exercise) (Lakka et al. 1994).

4.7 STATISTICAL ANALYSES

All statistical analyses were conducted using SPSS for windows (SPSS Inc., Chicago IL). SPSS version 14 was used for the first study, version 15 for the second study, version 16 for the 3rd study and 18 for the 4th study. Two-sided $p< 0.05$ was considered statistically significant in all the studies. Descriptive statistics was calculated for all the variables in each study; presented as means (standard deviation or range) for normally distributed data and median (percentiles) for skewed data. In all studies, the Cox proportional hazards models were used to estimate the relationship between alcohol consumption and risks of cancers and cancer mortality. The results are presented as relative risks (RR) with 95% confidence interval (95%CI). The models in all the studies were appropriately adjusted for confounding factors based on the known relationship between those factors and the cancers under investigation. In studies III and IV, we calculated the population attributable fraction (PAF) of alcohol on total cancer risk using the formula: PAF= pd [(RR-

1)/RR] where pd is the proportion of cases exposed to a given exposure category of alcohol and RR is the adjusted relative risk for this category (Miettinen 1974, Greenland 1999) and the 95% confidence interval for the PAF was estimated using the formula 1-(1-AF) exp (±1.96VL1/2) (Greenland 1999).

Study I: alcohol consumption and colorectal cancer

The subjects were grouped into five quintiles based on the volume of alcohol consumed per week within the cohort; The five quintiles were (i) 1st quintile; men who consumed <3.3g of alcohol, this group consisted mainly of abstainers (ii) 2nd quintile; 3.3-17.2g/week, (iii) 3rd quintile; 17.3-48.8g/week (iv) 4th quintile; 48.9-115.3g/week, (v) 5th quintile >115.3g/week. To adjust for confounding factors, three different sets of co-variates were used n the proportional hazards models The first model included age and examination year; the second model included age, examination year, vegetable consumption, fruits and berries consumption, meat, milk, fibre and total energy intake; while the third model included age, examination year, vegetable consumption, fruits and berries consumption, meat, milk, fibre and total energy intake, family history of cancer, BMI, smoking, socio-economic status, leisure time physical activity and the use of aspirin medication. We carried out secondary analysis excluding colorectal cancer cases that were diagnosed within two years of study onset in order to exclude cases who might have had their cancers before the baseline phase of the study

Study II: relationship between binge drinking pattern and lung cancer

The relationship between binge drinking and lung cancer was first assessed in the whole population and the proportional hazards model was adjusted for age, examination year, family history of cancer, socio-economic status, leisure-time physical activity and BMI. Another proportional hazards model was fitted for only smokers in the cohort. In order to tease out the possible effects of smoking on the results, a more detailed analysis was

conducted according to smoking categories. The smoking categories were defined by the number of cigarettes smoked per day (1-19/day, 20-29/day and ≥30/day) and the duration of smoking in years (< 30 years, > 30 years).

Study III: the impact of alcohol consumption on total cancer risk

The subjects were divided into five groups based on the alcohol consumption within the cohort. As in study I, the five quintiles were (i) 1st quintile; men who consumed <3.3g of alcohol per week, this group consisted mainly of abstainers (ii) 2nd quintile; 1.3-17.2g/week, (iii) 3rd quintile; 17.3-48.8g/week (iv) 4th quintile; 48.9-115.3g/week, (v) 5th quintile >115.3g/week. Initially, the following confounders were included in the model age, examination year, family history of cancer, cigarette smoking, (4 categories, non-smoker, 110/day, 11-20/day and ≥21/day), cardiorespiratory fitness, socio-economic status, BMI in three categories (<25, 25-29, ≥30kg/m2), vegetable consumption and total energy intake. Likelihood ratio test was applied to assess the statistical significance of the variables, and possible interactions between them. Only age, smoking (4 categories), cardiorespiratory fitness and energy intake were included in the final model because they were the only variables that changed the risk estimates by up to 10%.

We carried out secondary analyses, excluding cancer cases diagnosed within the first two years of study onset. We also collapsed the cohort into 3 groups (i) abstainers (ii) quintiles 2 to 4 and a few men in quintile 1 who were technically not abstainers but consume very little alcohol (<1.3g/week) and (iii) quintile 5 but this did not materially change the risk estimates .

Study IV: the effect of moderate alcohol consumption and smoking on cancer and cancer mortality

We divided the cohort into two based on their weekly alcohol consumption. Because the overall alcohol consumption was low, with only 13% of the men consuming more than 14 units per week, we used the median alcohol consumption within the cohort (32g/week) as the cut-off. Men who consumed less than the median value are referred to as those consuming little alcohol while those who consumed >32g/week are referred to as consuming more alcohol. The men were categorized as smokers and non-smokers. We grouped the cohort into four based on the presence or otherwise of the two risk factors. (i) constituted non-smokers who consumed very little alcohol (reference group); (ii) men who were non-smoker who consumed more than 32g of alcohol/week; (iii) smokers who consumed little alcohol; (iv) smokers who consumed more than 32g of alcohol/week. We used Cox proportional hazards model to determine the relative risks of total cancer, cancer mortality and specific cancers adjusting for age, examination year, family history of cancer, total energy intake, fruit, vegetable consumption and cardiorespiratory fitness.

5 RESULTS

5.1 ALCOHOL CONSUMPTION INCREASES THE RISK OF COLORECTAL CANCER

The mean age of the men was 53 years and majority of the cohort, (59.3%) were 54 years at the time of baseline examination (Table 1). Alcohol consumption was generally low within the cohort as reflected by the low median weekly consumption of 31.5g/week. While only 15% of the men were abstainers, 13% consumed more than 168g/week (14 units/week). Thirty-three percent (n = 850) of the men smoked and the mean BMI of the cohort was 26.9 kg/m^2. Liquor was the preferred alcoholic beverage within the cohort, accounting for most of the ethanol intake in grams and wine was the least preferred, in particular, white wine.

The median alcohol intake among men who consumed the most alcohol in this cohort (men within the 5th quintile of alcohol consumption) was 198.8 g/week while that of men within the 1st quintile of alcohol consumption was 0 g/week. There was moderate correlation between alcohol consumption and biomarkers of alcohol consumption such as GGT (rs; 0.35, p-value = 0.001) and MCV (rs; 0.30, p-value = 0.001). Men within the highest quintile of alcohol consumption had the highest MCV (94.2 fl) and GGT (49.4 U/L). These men also had the highest BMI (27.7 kg/m^2), highest meat intake and smoked the most. They also consumed the least amount of fibres, vegetables, fruits, berries and milk.

There were 59 colorectal cancer cases after a follow-up period of 16.7 years. Alcohol consumption was associated with a significantly increased risk of colorectal cancer in all the models fitted (Table 2). The highest relative risk of colorectal cancer (4.4, 95%CI 1.6 –

11.9) was observed in the crude model and the multivariate adjusted model yielded a RR of 3.5 (95%CI 1.2–9.8, p-value=0.02) among men in the 5th quintile of alcohol consumption (>115.3g/week) compared to those in the 1st quintile (<3.3g/week). In order to exclude the residual effect of undiagnosed cancer cases during the baseline of the study, we conducted secondary analysis excluding the first two years of follow-up from the analysis but the point estimates were virtually unchanged.

In the updated follow-up, over a twenty-year period, 66 colorectal cases occurred within the cohort and the RR of colorectal cancer remained the same (3.6, 95%CI 1.4–9.3, p-value=0.02).

Table 1. **Baseline characteristics of men from the Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study expressed as median (10^{th} and 90^{th} percentiles)**

	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**
	<3.3	**3.3-17.2**	**17.3-48.8**	**48.9-115.3**	**>115.3g/week**
Age, years	54.3(48.3, 60.5)	54.3(42.9, 60.4)	54.3(42.8, 60.4)	54.3(42.7, 60.1)	54.3(42.5, 60.3)
Smokers (%)	14	26	32	39	50
Physical activity, kcal/day	69.9(0.1, 316.9)	91.2(6.1, 332.6)	87.9(8.7, 363.2)	94.7(10.6, 330.4)	78.4(1.8, 332.9)
Body mass index, kg/m^2	26.5(22.6, 31)	26.1(22.7, 30.8)	26.2(22.6, 31.1)	26.5(22.9, 31.3)	27.123.1, 33.2)
Socio-economic status	14(7, 19)	13(5, 19)	12(4, 19)	12(4, 19)	13(5, 19)
Vegetable consumption over 4 days, g	267.3(136.6, 444.5)	282.2(148.9, 447.5)	275.3(138, 430.9)	286.7(154, 444.8)	268.8(138, 442.1)
Fruits and berries consumption over 4 days, g	150(25.9, 373.3)	132.4(19.6, 343)	132.6(4.4, 338.2)	137.8(1.2, 357)	121.3(0, 310.7)
Energy intake over 4 days, KJ	9905(6990, 13649)	9837(7129, 13380)	9554(6692, 12932)	9613(6632, 12686)	9751(6761, 13166)
Blood glucose, mmol/l	4.6(4, 5.4)	4.6(4, 5.4)	4.5(4, 5.3)	4.6(4, 5.3)	4.7(4.1, 5.8)
Alcohol consumption, weekly, g	0(0, 1.4)	8.8(3.9, 15.4)	32(18.7, 45.5)	76(53, 105)	198(127.7, 450.8)
Gamma-Glutamyl Transaminase, U/l	16 (10, 34)	18(10, 44)	20(12, 47)	22(12, 51)	33(15, 88)
Mean Corpuscular Volume, fl	90.2(84.7, 95.5)	90.7(85.1, 96.2)	91.7(86.4, 97.7)	92.4(86.2, 98.6)	94.1(88.3, 100.4)

Table 2. **Risk Ratios and 95% CI of colorectal cancer by quintile of alcohol consumption at baseline among men from Eastern Finland who have been followed up for at 16.7 years**

	Number of cases	Incidence rate	(95% CI)		Model 1			Model 2			Model 3		
Quintile	n	/100,000			Risk ratio	(95% CI)	P-value	Risk ratio	(95% CI)	P-value	Risk ratio	(95% CI)	P-value
1st	5	56.8	7.0	106.6	1.0[a]			1.0[a]			1.0[a]		
2nd	13	142.9	65.2	220.6	2.6	(0.9-7.3)	0.07	2.6	(0.9-7.2)	0.08	2.4	(0.9-6.8)	0.10
3rd	13	148.4	67.7	229.1	2.9	(1.0-8.2)	0.04	2.7	(0.9-7.7)	0.07	2.5	(0.9-7.2)	0.09
4th	11	124.0	50.7	197.4	2.4	(0.8-6.9)	0.11	2.4	(0.8-6.9)	0.11	2.2	(0.8-6.4)	0.15
5th	17	210.4	110.4	310.4	4.4	(1.6-11.9)	0.004	3.8	(1.3-10.7)	0.01	3.5	(1.2-9.8)	0.02
Excluding the first 2 years of follow up													
1st	5	56.8	7.0	106.6	1[d]			1[d]			1[d]		
2nd	12	131.9	57.3	206.5	2.4	(0.8-6.8)	0.1	2.3	(0.8-6.6)	0.11	2.2	(0.8-6.3)	0.14
3rd	13	148.5	67.7	229.1	2.9	(1.0-8.1)	0.05	2.7	(0.9-7.7)	0.07	2.5	(0.8-7.2)	0.09
4th	7	78.7	20.5	137.4	1.5	(0.5-4.7)	0.49	1.5	(0.5-4.7)	0.48	1.4	(0.4-4.4)	0.59
5th	17	210.4	110.4	310.4	4.4	(1.6-11.9)	0.004	3.8	(1.3-10.7)	0.01	3.5	(1.2-9.8)	0.02

[a]Reference category
Model 1– adjusted for age and examination year
Model 2 - adjusted for age, examination year, vegetable consumption and fiber intake
Model 3 - adjusted for age, examination year, family history of cancer, vegetable consumption, fiber intake, socio-economic status and physical activity

5.2 RELATIONSHIP BETWEEN BINGE DRINKING AND LUNG CANCER MAY BE CONFOUNDED BY SMOKING

There were 65 lung cancer cases during the follow-up period of 16.7 years. As many as 27% of the men (n=621) reported a history of binge drinking in the preceding year and there were 27 lung cancer cases among them compared to 38 among men with no history of binge drinking in the preceding year. The mean age among men who reported binge drinking was similar to those who did not. However, binge drinkers were more likely to be smokers (51% vs 29%, p-value ≤ 0.001) and smoked more cigarettes (10/day vs 5/day) compared to non-binge drinkers. Binge drinkers were also more likely to consume more alcohol with median alcohol intake of 141 g/week compared to 16 g/week among non-binge drinkers and this was reflected in their comparatively higher GGT and MCV levels. They were also more likely to be of lower socio-economic status. Even though fruits and berries intake was higher among binge drinkers, there was no difference in their vegetable intake compared to non-binge drinkers.

In the multivariate adjusted model including smokers and non-smokers, binge drinkers had a higher risk of lung cancer (RR 1.89, 95%CI 1.10–3.20) compared to non-binge drinkers and analysis restricted to only smokers showed a similar point estimate; RR 1.79, 95% CI 1.03–3.12 (Table 3). However, in further stratified analysis, we observed no increased risk of lung cancer among binge drinking non-smokers compared to non-binge drinking non-smokers (RR 1.49, 95% CI 0.88–2.56). The association between binge drinking and lung cancer persisted with all categories smoking, with the highest relative risk seemingly among men who smoked between 1 and 19 cigarettes per day.

Similar results were obtained when the analysis was extended to include new cases diagnosed during an extended follow up period of twenty years.

***Table 3*. Relative risk (RR and 95% confidence interval, CI) of lung cancer by binge drinking among Finnish men who have been followed for 16.7 years**

	Number of subjects (cases)	Model 1 Relative Risk	95% CI	P-value	Model 2 Relative Risk	95% CI	P-value
In the whole cohort	2627 (67)	2.64	1.65-4.23	≤0.001	1.89	1.10-3.20	0.02
According to smoking categories							
Non-smokers	1812 (12)	1.48	0.89-2.47	0.13	1.49	0.88-2.56	0.14
1-19/day	367 (15)	2.68	1.63-4.41	≤0.001	2.70	1.61-4.53	≤0.001
20-29/day	329 (22)	2.21	1.33-3.70	0.002	2.35	1.38-3.96	0.002
≥30/day	119 (16)	2.22	1.34-3.73	0.002	2.24	1.29-3.80	0.004

Model 1 - Adjusted for age
Model 2 - Adjusted for age, examination year, family history of cancer, socio-economic status, leisure time physical activity and BMI

5.3 ALCOHOL INTAKE INCREASES THE RISK OF CANCER

There were 515 cancer cases, during a follow-up period of 20 years at the time of analysis of which 175, 73 and 66 were prostate, lung and colorectal cancers, respectively. Other less common cancers in the cohort were esophageal, stomach, liver, pancreatic and genito-urinary tract cancers. Incidence rate of total cancer was higher among men within the highest fifth of alcohol consumption (141/10,000) compared to those within the lowest fifth (97/10,000). The relative risk of cancer among men within the fifth quintile of alcohol consumption compared to the first was 1.42 (95%CI 1.07–1.88, p-trend=0.03) and exclusion of the first two years of follow-up did not affect the point estimate. The population attributable fraction of alcohol in this cohort was 6.7% (95%CI 3%–13%). In a more recent follow-up, which accrued 548 cancer cases (prostate cancer; 184, lung cancer; 81 and colorectal cancer, 66), the RR of cancer among men within the highest quintile of alcohol consumption was 1.44 (95%CI 1.1–1.9), yielding a PAF of 7.1% (Table 4).

In secondary analyses adjusting for the same variables used in the main analyses, we observed a slight elevated risk of cancer among men consumed more than 32g/week (median alcohol consumption) compared to those consuming less, suggesting that in this cohort, lower levels of alcohol consumption may also be associated with increased risk of cancer.

Table 4. RR[a] (95%CI) of total cancer according to quintiles of alcohol consumption among men from Finland who have been followed for 20 years

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
Analysis including 515 cancer cases[b]						
Number of subjects (cases)	525 (90)	526(102)	526(104)	525(101)	525(118)	
Relative Risk (95% CI)	1.0 (reference)	1.07(0.80-1.41)	1.18(0.89-1.57)	1.08(0.81-1.43)	1.42(1.07-1.88)	0.03
Analysis including 548 cancer cases[c]						
Number of subjects (cases)	525 (95)	526(108)	526(110)	525(9108)	525(127)	
Relative Risk (95% CI)	1.0 (reference)	1.07(0.81-1.40)	1.17(0.89-1.56)	1.09(0.82-1.44)	1.44(1.10-1.89)	0.01

[a]adjusted for age, cigarette smoking, cardio-respiratory fitness, energy intake and family history of cancer
[b]at initial follow up
[c]at latest follow up

5.4 MODERATE ALCOHOL CONSUMPTION HAS EFFECTS ON CANCER AND CANCER MORTALITY BEYOND THAT DUE TO SMOKING ALONE

There were 548 cancers and 230 cancer deaths during the 20 year follow up period. Compared to non-smokers who drank very little alcohol (< 32 g/week), non-smokers who drank more alcohol were at a borderline increased risk of cancer (1.24, 95%CI 0.99–1.54, p-value=0.06) (Table 5). However, smokers were at an increased risk of cancer irrespective of the amount of alcohol consumed. Nevertheless, higher RR was observed among smokers who consumed more alcohol (2.33, 95%CI 1.86–2.92). Moderate alcohol consumption was not independently associated with an increased risk of cancer mortality but smokers were at an increased risk of cancer mortality irrespective of the amount of alcohol consumed. The RR of cancer mortality among smokers who consumed more alcohol was 2.89 (95%CI 2.07–4.04), while among those who consumed less alcohol was 2.34 (95%CI 1.58–3.47). The PAF of cancer and cancer mortality among smokers who consumed more alcohol was 15.8 and 22.5 respectively.

Table 5. Relative Risk[a] (RR and 95% CI) of total cancer and cancer mortality according to categories of smoking and alcohol consumption among men from Finland who have been followed for 20 years

	Alcohol intake, grams/week							
	<32 g/week				> 32 g/week			
	No of subjects (cases)	**RR (95% CI)**	**P-value**	**PAF (%)**	**No of subjects (cases)**	**RR (95% CI)**	**P-value**	**PAF[b] (%)**
All cancers	(n = 548)							
Non-smoker	1020 (173)	1.0 (reference)			757 (146)	1.24 (0.99-1.54)	0.06	
Smoker	293 (77)	1.83 (1.40-2.39)	≤ 0.001	6.5	557 (152)	2.33(1.86-2.92)	≤ 0.001	15.8
Cancer mortality(n = 230)								
Non-smoker	1020 (66)	1.0 (reference)			757 (43)	0.94 (0.64-1.39)	0.77	
Smoker	293 (42)	2.34 (1.58-3.47)	≤ 0.001	10.5	557 (79)	2.89 (2.07-4.04)	≤ 0.001	22.5

[a]adjusted for age, examination year, cardiorespiratory fitness, total energy intake, vegetable, fruit, berry consumption and family history of cancer

[b]PAF- Population Attributable Fraction only presented for statistically significant groups

6 DISCUSSION

6.1 ALCOHOL CONSUMPTION AND COLORECTAL CANCER

The relationship between alcohol consumption and colorectal cancer has been rather difficult to establish. More than 60 studies have investigated the association over the years but the results have been inconsistent. A number of studies have reported a positive association (Wu et al. 1987, Longnecker et al. 1990, Choi et al. 1991, Chyou et al. 1996, Wakai et al. 2005, Ferrari et al. 2007, Thygesen et al. 2008, Gao et al. 2008, Bongaerts et al. 2008) while others have not observed any association (Barra et al. 1992, Murata et al. 1999, Ji et al. 2002, Chen et al. 2005, Akhter et al. 2007).

In our study, we observed a 3.5-fold increased risk of colorectal cancer, which is higher that the elevated risks reported in other cohort studies conducted among men only (Wu et al. 1987, Wakai et al. 2005, Thygesen et al. 2008). We speculate that this may be due to alcohol preference of our study population. This is because pure alcohol from liquor contributes to more than 50% of the total alcohol consumption in our study population. This proportion of liquor as a component of total alcohol intake is much higher than those seen in other study populations, where beer and wine are usually the preferred beverages of choice. It was once suggested that the main alcoholic beverages consumed in a population may have an impact on the risk. This is because a study in Denmark observed that wine consumption appears to attenuate the overall risks of colorectal cancer from alcohol consumption when wine consumption constitutes more than 30% of the total alcohol intake (Pedersen et al. 2003). However, there is strong evidence that rather than the specific constituents of the alcoholic beverages, it is ethanol and its major metabolite, acetaldehyde that are responsible for the carcinogenic effects of alcohol (Baan et al. 2007). In a large European study, both wine and beer were associated with increased risks of colorectal cancer and there were no significant difference in point estimates for colorectal cancer between beer and wine (Ferrari et al. 2007). In order to tease out the effect of

specific beverage on colorectal carcinogenesis, it would be ideal to conduct stratified analyses by beverage type; unfortunately, we had very few cases to enable stratified analyses.

The results from our study likely differ from those of some previous studies because of differences in study settings (whether they were case control or cohort studies, hospital or population based), differences in geographical location where the studies were conducted and the fact that our study included only men. Studies conducted in European, American and Japanese populations (Anderson et al. 2005, Sanjoaquin et al. 2004, Fedirko et al. 2011) have often supported a role for alcohol in colorectal carcinogenesis while studies conducted among Chinese subjects have rather not observed positive associations between alcohol consumption and colorectal cancer risk (Chen et al. 2005, Wang et al. 2001, Fedirko et al. 2011). Important factors that may be driving the differences observed among population groups may be genetic susceptibility, dietary modifications and amount of alcohol consumed in different populations. It was shown that among American and European subjects, alcohol intake >45g/day was associated with a 1.5-fold increased risk of colorectal cancer (Cho et al. 2004) whereas a similar intake among Japanese subjects was associated with a 2.1-fold increased risk (Otani et al. 2003). In support of the role of differing susceptibility within various populations, Moskal et al. (2006) observed that geographical area was a significant source of heterogeneity between alcohol and colorectal cancer in a dose-response meta-analysis of published cohort studies.

Another reason why the results from our study may have differed from other previous results is because our study population consisted of only men. Most other studies have included men and women. In studies conducted among women only, there are usually no or very weak associations between alcohol and colorectal cancer compared with studies among men (Kune and Vitetta 1992, Fedirko et al. 2011). Likewise, in studies (Kune and Vitetta 1992, Pöschl and Seitz 2004, Otani et al. 2001, Mizoue et al. 2006, Fedirko et al. 2011)

where the risks were assessed together in both sexes; inclusion of women in the analyses usually attenuates the associations between alcohol and colorectal cancer risk. The reason for this is that men consume more alcohol and are likely to undertake risky drinking habits compared to women. In the recent meta-analysis, alcohol consumption was associated with a 24% increased risk of colorectal cancer among men but an 8% increased among women (Fedirko et al. 2011).

In the largest, most recent and most-detailed meta-analysis to date involving more than 22,000 colorectal cancer patients from 57 published studies, moderate alcohol intake > 1 drink/day was associated with an increased risk of colorectal cancer (Fedirko et al. 2011). Moderate drinkers (1-4 drinks/day or 12.6 – 49.9g/day) and heavy drinkers (≥ 4 drinks/day or 50g/day) had 21% and 52% higher risks of colorectal cancer, respectively, compared to non-drinkers or occasional drinkers (Fedirko et al. 2011). Even though no increased risk of colorectal cancer was observed among light drinkers (<1/day), the dose-risk analysis revealed a significant 7% increase in risk among people who drank > 10g/day, which includes the upper bound of light drinkers which increased to 38% and 82% among people consuming >50g/day and 100g/day respectively (Fedirko et al. 2011). The increased risk observed among moderate drinkers was stronger for men (24%), than for women (8%) and stronger among Asians. Increased risks were noted for all parts of the colorectum but with regards to the colon, the risks were higher for the distal colon (RR 2.46) compared to the proximal colon (RR 1.38) even though the difference was not significant.

6.2 BINGE DRINKING AND LUNG CANCER

To the best of our knowledge, apart from our study, no other study has explored the relationship between alcohol consumption pattern and risk of lung cancer despite the fact that the health effects of binge drinking can be disaggregated from those of total alcohol consumption. The pattern of risk that we observed between binge drinking and lung cancer is however similar to that observed with total alcohol consumption. While there

were no apparent increased risk of lung cancer among binge drinking non-smokers, smokers who were binge drinkers had increased risk of lung cancer. This suggests that smoking is a very strong confounder of the relationship or that alcohol increases the baseline risk of smoking on lung cancer risk. However, the results could also be chance findings.

It is hypothesized that binge drinking, which can be a marker for excessive alcohol consumption can promote lung carcinogenesis by compromising liver function which may result in reduced detoxification of carcinogens and reduced delivery of protective nutrients (Korte et al. 2002), by inhibiting the activity of methionine synthase, leading to a decreased production of S-Adenosylmethionine ultimately causing global hypomethylation of DNA (Purohit et al. 2005). Experimentally, it has been shown that acute ethanol injection, analogous to binge drinking causes a significant increase in histone acetylation in the lungs (Kim and Shukla 2006) which causes changes in nucleosomal conformation thereby increasing the accessibility of transcriptional regulatory proteins to chromatin templates ultimately leading to carcinogenic transformations (Struhl 2001).

The relationship between alcohol consumption and lung cancer has been one of the most difficult to ascertain because of the difficulty in disentangling the effects of smoking from alcohol consumption especially among those with high alcohol consumption. While some studies have found a positive association between alcohol consumption and lung cancer (De Stefani et al. 1993, Doll et al. 1994, Dosemeci et al. 1997, Prescott et al. 1999, Bagnardi et al. 2010), others have not (Bandera et al. 1997, Woodson et al. 1999, Djousse et al. 2002, Rohrmann et al. 2006, Thun et al. 2009), and some studies have even reported inverse association between moderate alcohol intake, wine drinking and lung cancer (Rohrmann et al. 2006, Benedetti et al. 2006, Chao 2007, Chao et al. 2008). In some other studies, the positive association between alcohol and lung cancer was only evident among some subgroups in the population such as those with low vitamin A intake (Kvale et al. 1983) or

low fruit and vegetable intake (Benedetti et al. 2006). A non-significantly increased risk of lung cancer was reported in a pooled analysis of cohort studies among those who consumed ≥ 30g/day of alcohol (Freudenheim et al. 2005). In a dose-specific meta-analysis of cohort studies, it was reported that men who consumed ≥ 2,000g/month of alcohol had a 53% increased risk of lung cancer compared to non-drinkers (Korte et al. 2002). The same study also reported increased risk in case-controls studies but the elevated risks were only evident in hospital-based case-control studies and not in population-based case-control studies. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, neither alcohol consumption at baseline nor lifelong alcohol consumption was associated with increased risk of lung cancer (Rohrmann et al. 2006). The authors, nevertheless reported a lower risk of lung cancer among those with moderate alcohol intake (5 –14.9g/day) compared to those with low intake (0.1 – 4.9g/day) suggesting a J-shaped relationship.

Many studies, including the largest population-based case control study to date have reported a modification of the effect of smoking on the relationship between alcohol and lung cancer. The environment and genetics in lung cancer etiology (EAGLE) study is a population-based case-control study in Italy with 2,100 lung cancer cases (Bagnardi et al. 2010). In the study, using very light drinkers as reference categories, the authors observed increased risk of lung cancer among non-drinkers and very heavy drinkers (> 60g/day). The increased risk were only confined to ever smokers and was not evident among never smokers. The lower risks observed among light drinkers compared to non-drinkers in this study could also be due to residual confounding as the authors reported that light drinkers smoked less cigarette and were better educated compared to non-drinkers (Bagnardi et al. 2010).

Likewise, in an analysis stratified by histological type, significantly increased risks were observed for almost all other categories of alcohol intake compared to very light drinkers

among those with squamous cell carcinomas but not among those with adenocarcinomas and small cell lung cancers (Bagnardi et al. 2010). This tends to support a possible residual confounding effect of smoking, since squamous cell carcinomas are more likely to be related to smoking than adenocarcinomas (Bandera et al. 1997, Brennan et al. 2000).

Similarly, other studies have reported no relationship between alcohol consumption and lung cancer risk among non-smokers (Nishino et al. 2006, Shimazu et al. 2008, Thun et al. 2009). Shimazu and colleagues (2008) compared occasional drinkers to heavy drinkers in the Japan Public Health Center-based Prospective Study. In the total cohort, they reported a RR of 1.31 (95% CI 0.89-1.94), and a RR of 1.69 (95% CI 1.05-2.72) among smokers but a RR of 0.58 (95% CI 0.26-1.30) among non-smokers.

It is also possible that binge or heavy drinking may modify dietary patterns in such a way that binge drinkers are likely to substitute alcohol calories for calories obtained from food and may therefore consume less foods that have protective biological nutrients (Hillers and Massey 1985, Korte et al. 2002).

However, a particular limitation of our study on binge drinking and lung cancer risk needs to be noted. This is because our classification of binge drinking may miss some true binge drinkers and misclassify binge drinking since we used a composite measure of binge drinking and not a real measure as determined by response from participants. In order to determine the true extent of binge drinking, it would have been ideal to have the participants respond to a specific question asking about their binge drinking behaviour (e.g. consume more than 6 cans of beer, or 1 bottle of wine at a particular drinking occasion). We however did not have this specific question in our questionnaire, hence our decision to use a composite measure using the consumption of ≥70g of alcohol at a drinking occasion, which may lead to bias from misclassification of exposure.

Although we observed no associations between binge drinking and lung cancer in stratified analyses, we suggest that heavy drinking pattern needs to be considered in studies investigating the associations between alcohol and lung cancer. Lastly, larger studies are needed which can tease out the effects of smoking and possible interactions between binge drinking and smoking on lung cancer risk.

6.3 IMPACT OF ALCOHOL CONSUMPTION ON RISK OF CANCER

Very few studies have investigated the association between alcohol consumption and total cancer using cancer incidence as most studies exploring the association of alcohol on total cancer have focused more on cancer mortality. From cancer mortality studies, there is strong evidence that very high alcohol intake is associated with increased risk of dying from cancer (Blot 1992, Doll et al. 1994, Thun et al. 1997, Lin et al. 2005, Grønbaek et al. 2000, Theobald et al. 2001).

Similar to results from previous studies (Bagnardi et al. 2001, Nakaya et al. 2005, Inoue et al. 2005), we observed an increased risk of cancer among men with the highest amount of alcohol intake. Using occasional drinkers as reference, Inoue and colleagues observed a positive linear association between increased alcohol intake and cancer incidence among men, but not among women. They estimated that nearly 13% of the 3,403 cancer cases in their cohort was due to heavy drinking (≥ 300g/week). Another study from Japan (Nakaya et al. 2005) reported a dose-response relationship between the amount of alcohol consumed and total cancer risk among drinkers. Interestingly, they also noted that ex-drinkers had a significant 50% increased risk of cancer compared to never drinkers suggesting that the risk of cancer from drinking alcohol may persist for a while after stopping alcohol consumption. On the other hand, the increased risk among ex-drinkers may be due to reverse causality whereby the ex-drinkers stopped drinking because of ill-health such as cancer. Bagnardi and colleagues 2001 conducted a meta-analysis of 235 studies with over 117,000 cancer cases and observed a positive linear association between

alcohol consumption and total cancer. There was a significant 22% increased risk with alcohol intake of 50g/day which increased to 91% with intake of 100g/day.

We estimated that about 7% of the cancer cases within our cohort were due to alcohol consumption. This proportion is higher than the worldwide estimate. Using the WHO Global Burden of Disease project, it has been estimated that 3.6% of cancer cases (389,100 cases) and 3.5% of cancer deaths (232,900 cancer deaths) worldwide in 2002 are attributable to alcohol consumption (Boffetta et al. 2006). The percentage is expectedly higher among men (5.2%) compared to women (1.7%) due to the higher alcohol consumption among men (Boffetta et al. 2006). The alcohol-attributable fraction of cancers also exhibits large geographical variations. The lowest alcohol-attributable fractions of <1% are observed in the Eastern Mediterranean countries, rising to just below 2% in South East Asia (Boffetta et al. 2006). The highest alcohol-attributable fractions are observed for Europe C comprising the countries of the former Soviet Republic while for Europe A which Finland belongs to, the alcohol-attributable fractions of total cancer is about 6% (Boffetta et al. 2006).

6.4 EFFECTS OF MODERATE ALCOHOL CONSUMPTION SMOKING ON CANCER AND CANCER MORTALITY

Smoking and alcohol are two modifiable risk factors that are independently associated with increased risk of cancer and cancer mortality. Our results revealed that while smoking independently increased the risk of cancer and cancer mortality, moderate alcohol consumption was independently associated with increased risk of cancer but not cancer mortality. However, the risks of cancer and cancer mortality associated with moderate alcohol consumption and smoking together are more that due to either smoking or moderate alcohol consumption alone. It is worthwhile to note that because we investigated the effects of moderate alcohol consumption. It is possible and likely that the added risks on cancer and cancer morality would be higher if higher consumption

volumes, rather than moderate alcohol intakes are used. It is biologically plausible that alcohol and smoking cause more cancers that either alone given the fact that the alcohol metabolite, acetaldehyde is also a major constituent of tobacco smoke (Smith and Hansch 2000, Salaspuro and Salaspuro 2004). Alcohol consumption and smoking have been found to have synergistic effects on acetaldehyde concentrations in the saliva. Experimentally, it has been demonstrated that when smokers and non-smokers ingested comparable doses of ethanol, salivary acetaldehyde concentrations were seven times higher in active smokers compared to non-smokers. Among smokers, salivary acetaldehyde concentrations increased considerably more during active smoking with simultaneous ethanol intake than without simultaneous ethanol intake partly because smoking inhibits ALDH which results in less efficient acetaldehyde metabolism and subsequently higher acetaldehyde concentrations in the saliva (Helander and Curvall 1991).

6.5 STRENGTHS AND LIMITATIONS OF STUDY

Our study had the following strengths. It is prospective in nature whereby alcohol consumption was assessed at baseline before cancer diagnosis. Thus, the possibility of recall bias wherein men who had cancer may tend to recollect their alcohol intake and probably attribute their cancers to alcohol intake relative to men without cancer was greatly minimized. This was supported in secondary analysis where we excluded the first two years of follow-up to exclude cohort members who may have undiagnosed cancers from the analysis but the results were still the same. The study was population-based, with a long follow-up and minimal loss to follow-up ensuring that the results can be generalized beyond the study cohort to the general population. Cancer cases were ascertained from the high quality, nationwide Finnish Cancer Registry ensuring accurate ascertainment of cases. We had detailed information on a range of confounding factors which we controlled for. All these increase the confidence that the results from our study likely represent a true relationship between alcohol intake and cancer risk.

The following limitations also need to be taken into consideration when interpreting the results from our study. We assessed alcohol consumption using a questionnaire, thus alcohol intake among the subjects could have been under-reported. This could lead to reporting bias but we do not think the reporting bias will be systematically differential across drinking groups.

Likewise, the questionnaire had previously been validated using biochemical markers of excessive alcohol use such as MCV and GGT and there was a correlation between alcohol intake and the biochemical markers (Hauge and Irgens-Jensen 1981, Kauhanen et al. 1992), but nevertheless, the possibility of misclassification cannot be completely ruled out.

Another limitation relates the absence of information on alcohol intake after baseline examination, hence we do not know if drinking habits changed afterwards. This can lead to misclassification of exposures, which will most likely bias the estimates towards null if the misclassification is strong. A study in Denmark has however revealed that baseline, updated and cumulative average alcohol intake were all associated with increased risk of colorectal cancer with very little difference in risk estimates comparing the different analytical approaches, suggesting that there is a low intra-individual variation in alcohol consumption during follow-up (Thygesen et al. 2008).

Lastly, only a few site-specific cancers occurred during the follow-up period, which precluded us from exploring the association between alcohol consumption and site-specific cancers in greater detail that may enlighten us about specific groups that may be at higher risk, or specific histological types that may be more related to alcohol intake.

7 CONCLUSIONS

The following conclusions can be drawn from this prospective population-based study of alcohol consumption and cancer among men

1. The study lends support to the evidence that alcohol consumption increases the risk of colorectal cancer. Colorectal cancer is now one of the cancer sites for which the WHO has designated as being causally related to alcohol consumption.
2. Binge drinking does not increase the risk of lung cancer among non-smokers. Among smokers, binge drinking appears to increase the risk of lung cancer but this may be due to confounding, which cannot be totally controlled for. However, smoking and binge drinking may have a joint effect on lung cancer risk which deserves further evaluation.
3. Alcohol consumption is associated with an increased risk of total cancer and as much as 7% of the cancer cases among men in the cohort could be attributable to alcohol consumption. We also observed evidence suggestive of a slightly increased risk of all-cause cancer with consumption volumes that are hitherto deemed safe. Public health efforts to reduce the incidence of cancer will have to also incorporate reduction in alcohol consumption
4. Smoking is an independent risk factor for cancer and cancer mortality. However, smoking and moderate alcohol consumption cause more cancer than either smoking or alcohol would cause independently.

In summary, the results from this thesis have shown that alcohol consumption is associated with cancer risk. Public health strategies to reduce cancer burden in Finland

will need to incorporate strategies to reduce alcohol consumption, probably beyond the present recommended levels.

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Alcohol and Cancer Among Men

Public Health Impact and Perspectives

About 7% of cancer cases within this cohort of men from Eastern Finland could be attributable to alcohol consumption. For colorectal cancer, men who consumed the most alcohol had a 3.5-fold increased risk.
Smoking and moderate alcohol consumption cause more cancer than either would cause independently and smoking confounds the association between binge drinking and lung cancer risk.
Public health plans to reduce cancer burden in Finland will need to incorporate strategies to reduce alcohol consumption, probably beyond the present recommended levels.

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