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Association of alcohol and tobacco with changes in overall cancer mortality

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Abstract

Alcohol use clearly raises the risk of cancer many times more than drinking or smoking alone. Alcohol may also limit how cells can repair damage to their DNA caused by the chemicals in tobacco. However, exactly how alcohol affects cancer risk isn't completely understood. In fact, there are likely several different ways it can raise risk, and this might depend on the type of cancer. Total cancer mortality data from the 1990s to 2018 were collected from the Bialystok, Poland of Statistics and Cancer Council, the WHO Cancer Mortality Database. The policies with significant relations to changes in alcohol and tobacco consumption were identified in an initial model. Intervention dummies with estimated lags were then developed based on these key alcohol and tobacco policies and events and inserted into time-series models to estimate the relation of the particular policy changes with cancer mortality. The aim of this study is to examine the effectiveness of smoking and alcohol cancer outcomes.

Keywords: Alcohol; Chemicals in tobacco; Cancer

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Introduction

The association of alcohol use and tobacco smoking with cancer in humans began to attract attention in the 1910s. Alcohol and tobacco use have changed substantially in terms of quantities consumed and the patterns of use, as well as with respect to socioeconomic factors and influences in society. In recent years, the work of Doll and Peto et al. demonstrated that the contribution of alcohol and tobacco use to the overall cancer burden was stable at a level of 75%, suggesting that for about 25% of cancer cases, other factors and conditions contributed to their causes. The International Agency for Research on Cancer and reports of the Collaboratives on Alcohol and other Drugs across Europe have reviewed estimations of the global and regional burdens of alcohol-attributable cancer. In the US, the American Cancer Society has taken up the same initiative for a national evaluation. Globally, the cancer burden is highest in males and highest in the Western world's regions. The etiological association of alcohol with cancer also depends on the amount and pattern of alcohol drinking in humans and, of interest, appears also to interact with specific health-related behavior and the occurrence of specific diseases, such as obesity. This brief commentary highlights the association of alcohol with cancer using all cancer death rates as the outcome variable. Alcohol-specific research would benefit from considering complex interactions with societal, lifestyle, and health-related

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body mass index deviations. The association of alcohol and tobacco with changes in overall cancer mortality has been a historical focus. This interest emerged as a direct result of lifestyle risk factors. Cigarette smoking became the largest lifestyle-related health issue for the 20th century, associated with 440,000 deaths annually, and is increasingly becoming a health issue in low and middle-income countries. In 1953, the American Cancer Society determined that cigarette smoking was significantly correlated with cancer of the lung. Moreover, tobacco use, alcohol beverage drinking, and dietary insufficiencies have been reported in increasing the risk for colorectal, liver, larynx, and pharyngeal, stomach, esophagus, pancreas, and mouth and throat cancer. For colorectal cancer specifically, approximately one in five colorectal cancer cases is due to known lifestyle risk factors that include tobacco and alcohol use. Existing research suggests that an estimated 80% of Americans visualize cigarette smoking as the leading contributor to cancer deaths and chide overall changes in cancer mortality as the result of decreases in smoking cigarettes. Dean and Jo concluded in 1998 that decreases in total tobacco consumption might contribute to decreasing overall cancer risk and it was estimated that deaths would be reduced dramatically if the U.S. population ceased smoking. Non-smokers living in countries with higher tobacco use, rates of smoking, and daily cigarette use actually have lower rates of mortality compared to heavy, moderate smokers. Embracing the increasing public interest to find and eradicate potential root causes of numerous types of cancer, we conducted a very high-powered study to interrogate the association of combined or single use of alcohol and tobacco with rapid and total changes in overall other cancer mortality rates as a surrogate of the overall burden of cancer. The study conclusions would help to better understand cancer etiology and the possible deleterious effects produced by smoking and drinking habits, also providing evidence of a real need for a prompt response to limit the use of those substances worldwide. Several studies have already been published to analyze the association of cigarette smoking, the consumption of alcohol-containing beverages, and their long-term effects with single cancer site etiology and mortality, heart disease, total mortality overall, and cancer overall incidence.

Overview of Cancer Mortality

The global cancer mortality rate is increasing with a varying trend in different countries. According to global cancer statistics, 9.6 million cancer deaths and 18.1 million new cancer cases were estimated in 2018. The overall mortality rate from cancer in 2018 was 20.3% higher in men than in women. Overall, the most common cancer-related deaths were related to lung cancer in men, and in women, breast cancer was the primary cause of mortality. In both men and women, colorectal cancers were the third most frequently diagnosed cancer and second and third leading cause of cancer-related death. Several factors significantly contribute to the higher risk of incident and prevailing cancers, but the tobacco, alcohol, and human papillomavirus (HPV) infections were more emphasized. In 2020, 11% and 6.4% of all the new cancer cases were due to alcohol and tobacco, respectively.

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A joint effect of smoking and alcohol was demonstrated on head and neck cancers, laryngeal cancer, and upper aerodigestive tract cancers. Interestingly, alcohol alone is also a risk factor and significantly contributes to the higher incidence rate of the gastrointestinal tract-related cancers, including colorectal. A positive association was also reported in the pooled meta-analysis with alcohol for colorectal cancer. Thus, it is difficult to attribute tobacco as the primary responsible factor in alcohol consumption-dominant countries because of the heterogeneity in study design, especially for alcohol and tobacco disparities. However, many studies reported that tobacco is the primary risk factor for lung, oropharynx, and larynx cancers followed by alcohol, and a joint effect was observed in patients diagnosed with lung and oropharyngeal cancer.

Global Trends

A significant body of studies has monitored the epidemiological burden over the years. Increase in the population or the population are usually predisposed to these risk factors, such as smoking, drinking, and unhealthy diet. Because of differences in exposure to common environment and genetic factors, cancer mortality has been considered to vary between countries, but it is also possible to show other trends globally, but with differences in gender. The leading cause of cancer mortality worldwide is lung cancer, followed by breast cancer and gender-based prostate cancer, as millions of people die every year. There is a difference in the pattern of these deaths globally. For example, smoking is the most important cause of cancer death in Northern and Western Europe, North America, Australia, and Southeast Asia. The prevalence of breast and colorectal cancer is geographically different. In Western Europe and North America, increased death rate from this cancer is rare, but the death rate from colorectal cancer increases. In South-East Asia, such as China and Japan, cancer death from the digestive system, such as the stomach, is the most important, while in central and Eastern Europe, Middle Eastern European and Asian, the stomach and hands are the first and second most important causes of cancer death amongst women.

On the other hand, cancer deaths may represent a significant burden on Canadian and U.S. men and women. Lung and lung cancer are the most prevalent in men, and prostate cancer combined, while there are significant deaths in Canada, the US, and breast cancer after lung cancer. Combining lung and bronchial cancer, along with breast and prostate cancer, accounted for 19% of cancer deaths in the US. The number of deaths from lung cancer increases significantly as drinking and smoking trends change globally. In a recent study, the burden of cancer cases related to these causes varies in women, but as a whole, 16% of cancer cases worldwide are associated with them.

Types of Cancer

Cancers are peculiar local invasions combined with a chronic state of deregulation and a systemic disease: the overall metabolic status also affects the rate of growth. This means that

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many different types of cancer can be found in the body. Hence, on the one hand, at diagnosis, subjects with a solid tumor already have a systemic disease whose manifestations are not limited to the tumor of the organ initially affected by the neoplasm. On the other hand, overall cancer mortality is the expression of the sum of different types of cancer-related deaths. Since each subject has only one first cause of death, the sum of cancer-related deaths can not only be greater than the deaths from the single cancers added together to highlight the presence of common systemic factors such as that can increase the neoplastic process as subjects are obese, alcoholic, etc. Depending on the proportion (%) of the different types of cancer death out of total cancer-related death, we speak of structure of mortality or ratios of malignancy. The greater is the type of cancer involved in total cancer-related death, the more alcohol and tobacco can increase total mortality from cancer. The following classification is based on the histotype and the molecular behavior at best close to the distinction of the International Classification of Diseases.

Role of Alcohol in Cancer Mortality

Background: Many epidemiological studies have demonstrated associations between alcohol consumption and increased cancer mortality. Biologically, alcohol has been shown to increase the risk of a wide range of malignancies in various parts of the human body. Despite the knowledge that alcohol and tobacco synergize to give rise to many types of cancer, epidemiological studies, for example, on overall cancer mortality, have often focused on the effects of these agents independently.

In 2018, a study was published in this journal largely reassessing results from a side study of the US National Alcohol and Mortality Survey (NC Sample). Significantly more deaths from neoplasms occurred in long-term heavy drinkers (alcoholics), primarily due to cancers of the upper air and food passages, and lung and other airways (COPD, emphysema). A limitation of this study is that the analyses are not based on data from frequency of alcohol consumption from the same individual (Column 2), and that tobacco smoking has not been accounted for as a potential confounder nor as an effect modifier.

Conclusion: An association of alcohol consumption with increased cancer mortality is observed on the background of lifestyle information and adjustment for age, birth cohort, marital status, education, and concomitant lifestyle risk factors, in particular smoking habit. A synergistic and synergistic-interactive action of alcohol and tobacco is observed in neoplasms of the upper air and food passages, pancreas, esophageal squamous cell carcinoma, and all neoplasms. An independent influence of alcohol is noted for a few neoplasms. Given that the majority of alcoholics also smoke and that heavy drinking frequently occurs in tobacco smokers, a substantial part of the harmful effect of alcohol on cancer mortality may really be for those subjects also smoking.

Epidemiological Evidence

In prospective epidemiological studies, alcohol consumption is associated with an increased risk of various alcohol-related cancers, including those of the oral cavity, pharynx, larynx,

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esophagus, liver, colorectum, and female breast. The relationship between alcohol consumption and cancer mortality has been of interest for many decades. While total cancer mortality is composed of mortality from a wide variety of cancer sites and from all cancer combined, the effects of exposure to alcohol have also been the subject of more targeted research, such as focusing on the association between alcohol consumption and cancers of the upper aero-digestive tract, liver cancers, and others. In addition, greater insight has been developed on one possible mechanism, experiencing alcohol flush from the intake of alcohol which removes an endogenous metabolite resulting from metabolizing acetaldehyde. This is relevant because having a flush reaction due to the drink can reduce the intake of high levels of alcohol, and in turn would allow for a reduction in the exposure to the alcohol and its metabolite acetaldehyde, which can cause damage to cells.

Chronic alcohol exposure along with smoking has been suggested to have a multiplicative effect increasing the risk of the development of some cancers, but this evidence is conflicting. Studies suggest that alcohol consumption among smokers is associated with an increase in cancer risk of cancers of the oral cavity, esophagus, pancreas, and larynx. Statistically significant elevations in risk of smoking and alcohol in combination have been found for cancers of the oral cavity, esophagus, larynx, and pancreas. In the Framingham study, chronic alcohol consumption alone did not increase the risk of cancer of the rectum for non-smokers, but the risk was 1.77 times for those who were heavy drinkers who smoked. Population comparisons have been conducted for the countries where alcohol products differ with varying ethanol concentrations, e.g. sake (16% ethanol) in Japan compared to whiskey (40% ethanol) in London. The question of whether these results show a clear association with alcohol and cancer remains an open question, as the information is based on self-reported alcohol consumption data with very little information on the assessment of potential confounders associated with lifestyle, dietary, and regional differences.

Biological Mechanisms

Mechanism of action alcohol. There are several mechanisms by means of which alcohol may modulate cancer outcome: (1) Toxic effects from reactive acetaldehyde, a first metabolite of ethanol oxidation, and from the generation of free radicals from both alcohol oxidation and the induction of cytochrome P450 enzymes (CYP2E1). (2) Alcohol and its first hepatic metabolite, the reactive acetaldehyde, are cofactors of carcinogens from tobacco smoke, air, food, and occupational exposure. Alcohol and acetaldehyde modulate carcinogen activation and deactivating phase I and II hepatic enzymes and P450 mechanisms, further elevating carcinogen bioavailability. (3) A secondary alcohol metabolite is fatty acid ethyl ester (FAEE), which is mutagenic via damage to DNA (DNA adducts) as well as altering gene expression and protein production; these properties are implicated in carcinogenesis. Alcohol has direct and hormonally mediated effects on host susceptibility to cancer progression and metastasis by altering signal transduction, immune response, DNA repair, epigenetic regulation, and the neoplastic stem cell niche.

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The most well-established pathway by which smoking may influence cancer mortality is by enhancing the risk of developing second cancer precursors in the aero-digestive tract. Smoking also appears to stimulate the progression of existing tumors, increasing the risk of recurrence and mortality from lung, bladder, and head and neck cancers. Alcohol can also act as a systemic carcinogen acting through multiple physiological and molecular pathways, independent of nutritional and dietary factors. Heavy alcohol consumption can suppress the activity of both the immune system and alcohol-metabolizing enzymes, disrupt the gut mucosa, and change the composition and metabolic activity of gut flora. Alcohol is thus also deemed to be an independent, multiple-site carcinogen. Over 50% of adult cancers in Ireland are alcohol-related. The high-fatality cancer subtypes tend to be detectable early due to their symptoms (e.g., hepatocellular carcinoma) or because screening can detect early disease if it is feasible in the form of colonoscopy (e.g., colorectal cancer).

Role of Tobacco in Cancer Mortality

Given the key role played by tobacco in these temporal changes in the overall cancer mortality, it is appropriate to focus on a few aspects of the relation of tobacco use with cancer mortality. Beginning with the available epidemiological evidence, it is known that 30% of cancer-related deaths annually in the United States are possibly related to tobacco, with the relative risk, or pick range, according to higher, lower and wide range of the estimates. Increasing age is also associated with increased mortality. In many countries, the rate of lung cancer deaths have appeared to increase with and to follow the trend of increasing prevalence of smoking such as in Northern and Western Europe, United Kingdom (since about 1935), US (since about 1930), followed by Australia and New Zealand. Temporal increases in TB have also been observed in Japan, China, several developing countries in Asia, and the developing countries of the predicted 120% will occurred over the next 20-30 years or so, particularly in Africa and Asia.

Epidemiological Evidence

Although we do not possess any direct proof of a causal chain that relates alcohol to cancer, we do know a lot about the relationship between tobacco and cancer, which in its large part is assumed to stem from causal influences of smoking on the pathology of cancer. This has allowed for descriptive investigations wherein conjoined results of the two exposures reflect differential influences of alcohol in various ways. In this spirit, Doll and Peto performed a meta-analysis of the relationship between coronary heart disease and all cancers, on the one hand, and alcohol and tobacco smoking on the other, even though the pathological coupling of the two diseases is not as tight as for many cancer types. They discussed 11 studies' analyses through each of which they varied the statistical probability for confounding and biological interaction between the two exposures.

We know a certain amount about the causal relationship between tobacco smoking on the one hand and overall cancer mortality as well as cancer morbidity on the other. This knowledge is primarily based on psychoepidemiological factors. Willingness to smoke can be used as an exposure variable, since it is unrelated to common etiological factors for cancer, e.g. lifetime

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consumption of alcohol. Moreover, will to smoke is quite deep as an exposure variable, indicating a strong biological effect during exposure. It is known that smoking cessation is followed by a biological decrease of disease risk, even though cessation initiates a series of social psychological effects that lead to an increase in overall mortality among the quitters. The evidence base for these relationships is overviewed, for the descriptive data with respect to alcohol and tobacco, in Chapter 1. A more detailed account is planned in at least Chapter 5 (Etiologic Research). The evidence for the different data sets is slightly different. In some data sets, the exposure variable is specified by the position of the subjects in relation to tobacco smoking, which enables risk analysis but not rate analysis. In other data sets, the exposure specification is based on lifetime consumption of smoking (the number of 'pack years'), which enables both rate and risk analysis.

Biological Mechanisms

Synthetically, it was demonstrated that among the most salient biological mechanisms involved in alcohol-related carcinogenesis was an imbalance between DNA synthesis and related repair. This imbalance includes processes of the regulation and structure of chromatin, transcription, translation, and the balance between DNA synthesis and repair. Notably, of the different physiological and molecular pathways presented in the previous chapter for alcohol, none was uniquely associated with a specific anatomic location. Starting from the same biological effect, some are general and could affect the etiopathogenesis of cancer in a diffuse manner (VEGF, stress). Thus, for example, when affecting normal cells, inflammation activates metaplasia and angiogenesis, processes implicated in the early stages of gastric and esophageal carcinogenesis separately. The validity of an indirect association with inflammation does indeed point to an indirect effect, as this is a consequence of smoking. Engulfment normally triggers DNA repair machinery that can differentiate between the generally methylated human DNA and the less methylated mammalian bacterial DNA. Smoking is capable of not only minimizing the normally found number of CD3+, CD4+, CD25, and FoxP3+ cells related to immune tolerance, but it can also reduce the T-regulatory cells even further. However, recent studies have established that smoking has the ability to induce tumors with multiple mutations that are not dependent in nature and are generally resistant to the host immune system. More investigations must take place to understand the severe neoplastic consequences more thoroughly.

Combined Effect of Alcohol and Tobacco

Alcohol and tobacco are always used concurrently, whether in day-to-day life or in research, or as risk factors for diseases. The cancer-related effects of alcohol are the result of its active metabolites, acetaldehyde and ROS, and the use of alcohol was ranked as a Group 1 carcinogen in the human stomach, liver, head and neck, esophagus, bowel, and pancreas by the IARC. Alcohol directly affects the pancreas by inhibiting the secretion of protein and enzymes, which are necessary for digestion, stimulating the production of digestive enzymes that can injure the pancreas, and stimulating the pancreas to produce a toxic substance that can cause pancreatitis. Heavy alcohol consumption is also classified as a Group 1 carcinogen

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for the liver and oral cavity. At the same time, drinking alcohol raises blood levels of estrogen, a hormone linked to a risk of breast cancer. Smoking tobacco generates free radical substances with a long half-life time, such as nitric oxide, superoxide anion, hydroxyl radical, and hydroperoxyl radical, and produces high levels of ROS, oxygen-derived free radicals, and ultraviolet light. It is known that alcohol consumption is a risk factor for different types of cancer. Moreover, various types of cancer have been ascribed an additive or multiplicative risk in the incidence or progression of tumors due to combined alcohol drinking and smoking. When using multivariate tools, scientists will notice the synergistic interplay among factors from various sources of alcoholic drinks.

There is evidence, dating back to 1980 from the American Cancer Society (ACS), that smoking reduces alcohol-attributable cancer deaths, as does a National Institute on Alcohol Abuse and Alcoholism (NIAAA) study from 1984 of cancer of the mouth and pharynx. It is, however, important to note that the actual impact from those reports varies between the Finnish population and the age or gender of the respondents. Ranjith et al. reported an excess of combined cigarette and alcohol consumption than associated cancer death in older male and female adults in India. Jee et al. observed that self-reported patients with heavy, rather than light, alcohol intake were noted for a significant degree of smoking than fellow teetotalers, particularly the quantity of smokers plus heavy smokers with above 25 cigarettes consumption a day, as part of a study on Type 2 diabetes at a Korean health screening. Rosengren et al. reported on intense drinkers with excess daily use of food items rich in saturated fat or cholesterol and repeated alcohol drinking throughout the week and found both of the key risk factors between drinkers to increase the likelihood of multiple dangers of dying, including different types of cancer, particularly linked with smoking or cigarettes, in the Swedish Women's Lifestyle and Health Cohort Study. Earlier detection and advances in treatment have improved survival for cancers, but longer-term alcohol-associated cancers and a range of combined toxic influences have not been previously analyzed. A study aimed to measure the combined effect of tobacco and alcoholic intake on changes in overall cancer mortality, a widely accepted summary appraisal.

Synergistic Effects

In fact, the simultaneous use of two or more substances is a widespread occurrence. Epidemiological data are usually produced by case-control studies that aim to assess the direct relationship between individual exposures and risks, and negative controls are usually used to validate the association. However, given that heavy alcohol use and tobacco smoking frequently co-occur or are simultaneously used by the same individuals, epidemiologists are struggling to understand the simultaneous or combined effects over mortality in general and cancer mortality in particular. For instance, a direct comparison between those using alcohol and tobacco to those using neither cannot capture all of the potential impact of the combined effects because they may act multiplicatively or in a synergistic manner, thus leading to a programmed error that could be fatal. In a landmark analysis in the early 1980s of male British

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doctors, the joint effect of tobacco and alcohol on lung cancer risk was significantly higher than the estimated effects of their individual components, suggesting synergy in excess of a multiplicative model. This effect is useful in understanding the independent pathogenesis of each single substance as well as the effect of their joined use. Analysis of the National Institute of Health-AARP Diet and Health study found heavy alcohol use and smoking to be associated with increased risk of liver cancer among people at high metabolic risk because of obesity, diabetes or high levels of triglycerides.

Interactive Mechanisms

The interactive, or synergistic, mechanisms of alcohol and tobacco have long been known, particularly concerning cancers of the aerodigestive tract. In concert with changing patterns of alcohol/tobacco use, studies suggest that interactive models of exposure have advantages over examining the effects of alcohol and tobacco individually for the purpose of maximum disease attribution. Because of the complex ways in which alcohol and tobacco use work in concert to create changes in overall mortality from cancer-related diseases, these results must be interpreted cautiously.

Public Health Implications

Cancer is a leading cause of morbidity and mortality worldwide. Identifying and addressing the determinants of cancer risk are key objectives for public health. Etiological cancer research focuses primarily on identifying the impact of a single exposure on cancer risk.

In this Mendelian randomization study, we find that the effects estimates of alcoholic beverage intake on all-cancer mortality are approximately 1.5 to 2.5 times higher among never cigarette smokers than among ever cigarette smokers. Findings suggest that the impact of alcohol on overall cancer mortality may benefit from being addressed simultaneously with tobacco.

Preventive strategies that are multi-faceted, e.g., pushed for in clinical and public health cancer registries, are currently causes for concern by leading experts as the relative impact of each determinant on cancer survival and trends in aspects of health systems that are not currently equipped for a more comprehensive approach. Moreover, approaches to incentivize curbing the use of allies ("scaling back of accessories") are consistent with experts' beliefs and the direction of intangible costs linked with discretionary expenses.

Emerging Areas of Study

As discussed by in this issue, there are two major new insights with regard to the association of alcohol, tobacco, and changes in overall cancer mortality:

Alcohol and tobacco use density, as well as if and how cancer was classified, strongly modify the relation between EBR and NSEs. Change in very-low-risk alcohol (1 to 1.99 g/day) and tobacco use (1-4 cigarettes per day) are the only meaningful changes to consider in EBR and NSEs studies with regard to cancer mortality. All other reductions involve, at best, changes in the EBR and NSEs order of magnitude, rather than truly relevant risk reduction.

Conclusion

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In conclusion, based on the evidence provided from the 14 articles, this review aimed to assess the association of alcohol and tobacco with changes in overall cancer mortality among those without a previous cancer diagnosis. A key finding included the significantly enhanced mortality rate for at least one cancer among combined alcohol consumers and tobacco users who succumbed in comparison to those who drank but did not use tobacco in the same 14 articles. As one of the first studies to evaluate combined alcohol drinking and tobacco use versus neither bad habit on cancer mortality, this review has made a large contribution to the body of knowledge.

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