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Alcohol and Gastrointestinal Cancers in Korea—Risk, Inactive Genes, and Missing Alcohol

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In a Korean cohort of more than 11.5 million participants (47.8% men), Yoo et al[1] explored the association between alcohol consumption and gastrointestinal (GI) cancers, paying particular attention to drinking patterns. They examined the separate associations between frequency of drinking and amount consumed per occasion on the one hand and risk of GI cancers on the other. Weekly alcohol consumption, drinking frequency, and amount per occasion were assessed for their association with incident cancers of the esophagus, stomach, colorectum, liver, biliary tract, and pancreas. Approximately 320 000 individuals developed GI cancers. The risk was higher among mild, moderate, and heavy drinkers than among nondrinkers and increased in a dose-dependent manner with drinking frequency. The risks of GI cancer remained flat for consumption higher than 5 to 7 units per occasion. The risks for the site-specific cancers were generally similar to those for all GI cancers. The size of the cohort facilitated the investigation of multiple outcomes and their association with several different aspects of alcohol consumption patterns simultaneously. It also allowed for the exclusion of the first 12 months of outcomes, thus reducing likelihood of what is sometimes called *reverse causation*—that is, removing from the analysis individuals with an undiagnosed cancer that has changed their drinking behavior. The authors concluded that frequency of drinking is a more important risk factor for incident GI cancers than the amount of alcohol consumed per occasion.

Alcohol consumption has been increasingly normalized in societies across the world, and Korea is no exception. Our gatherer-hunter ancestors would have consumed alcohol only on the rare occasions when they discovered a tree of overripe fruit before the chimpanzees found it. In many societies throughout our subsequent history, alcohol was a celebratory drug. In the 18th and 19th centuries, there were periods of high consumption among some groups in different countries. However, it is only recently that alcohol consumption has increased markedly worldwide—provoked by endless and devastatingly effective advertising, including routine "product placement" in films, and facilitated by extensive availability and low prices. Binge drinking, always a feature of male drinking but usually at infrequent intervals, has also become increasingly common and increasingly accepted, particularly among young people. Because our evolutionary and historic exposures to alcohol were low (and thus associated with infrequent deleterious effects), we have not developed biological curbs on consumption—with one intriguing exception, to which we will return shortly.

Daily alcohol consumption in Korea has almost doubled between 1998 and 2016-2018, increasing from 8.4 g in 1998 to 15.0 g during 2016-2018, a trend that was more marked among women (2.1 increasing to 5.8 g) than men (14.8 increasing to 23.9 g).[2] Approximately one-fourth (23.7%) of men and 5.8% of women consume alcohol at a harmful level (>60 g pure alcohol per drinking day for men and >40 g for women), decreasing slightly from 2007 to 2014 among men but increasing among women.[3] Thus, increasing our understanding of the association between alcohol and health in Korea is important.

Yoo et al[1] do this in 2 important ways. First, they expand the evidence for the association between alcohol consumption and GI cancers, not only providing data on cancers of the esophagus, colorectum, and liver (already well established as alcohol related[4]) but also strengthening the evidence for the association between alcohol consumption and cancers of the stomach, biliary tract, and pancreas. Because the researchers were able to control for tobacco, this last finding is

particularly informative. Second, Yoo et al[1] provide evidence that the frequency of consumption may be more important than the amount of alcohol consumed per session, perhaps suggesting that regularity of insult is more important than specific dose.

However, there is an interesting caveat to generalizing these findings beyond Korean and other Asian populations. As the authors themselves note, the Korean population has a high prevalence of an inactive form of aldehyde dehydrogenase (*ALDH2* [OMIM 100650]), a gene that encodes a major enzyme in alcohol metabolism, inasmuch as it eliminates acetaldehyde. In fact, 25% to 35% of Korean individuals have an inactive form of this gene. This common polymorphism in *ALDH2* (ALDH2 rs671 [c.1510G>A (Glu504Lys)]) has paradoxical effects—it increases the level of acetaldehyde in the blood of drinkers, which in turn increases the risk of cancer because acetaldehyde is a key player in the carcinogenicity of alcoholic beverages.[4] On the other hand, the accumulation of acetaldehyde and the resultant flushing response are sufficiently unpleasant that they tend to reduce alcohol consumption among those with the Lys allele.

In support of this yin-yang characteristic producing real-world effects, Koyanagi et al[5] conducted a case-control study in which they decomposed the total effect of the Lys allele on the risk of digestive tract cancer into a direct carcinogenic effect and an indirect effect mediated by drinking behavior. They reported that, although alcohol is a substantial risk factor for GI cancers, the presence of the Lys allele results in behavior that reduces this risk.

Thus, it is worthwhile to ask whether some of the differences in patterns of consumption seen in this cohort are associated with the *ALDH2* polymorphism. The study by Yoo et al[1] describes the habits of a specific subset of mild (0-13 units/week) and moderate (13-26 units/week) drinkers who, nonetheless, are binge drinkers, consuming more than 8 units at a session. The relevant genetic data are not available but those with the Lys allele may well be substantially overrepresented in this subset: they choose to drink alcohol but experience the devastating physiologic consequences and thus space out their binge-drinking sessions. If there are, indeed, major differences in the biology of Korean binge drinkers, it may not be possible to make easy recommendations about drinking patterns, even in Korea, until there is a better understanding of the nature of behavioral and biological influences on drinking.

From the Table in the study by Yoo et al,[1] it is possible to calculate the mean alcohol consumption for this whole population of approximately 12 million; it works out at 2.58 L of pure alcohol per person per year. However, the World Health Organization reports that, in 2016, among those 15 years or older in Korea, total alcohol consumption was 10.2 L of pure alcohol per person per year.[6] It is clear that there is substantial underreporting of alcohol consumption across the population studied by Yoo et al.[1] This finding is not unique to Korea—it is observable whenever we compare the alcohol intake of a study population with the known consumption data for the whole country. It implies (1) that the alcohol consumption of those who are not included in studies is massively different from that of the study participants; (2) that alcohol consumption is underreported in a uniform fashion (everyone underestimates their consumption to the same degree); or (3) that alcohol consumption is underreported in a biased manner, perhaps most plausibly with the heaviest drinkers being the worst reporters.

Scenario 1 seems relatively unlikely with a study population of almost 12 million individuals in a country of approximately 50 million. Scenarios 2 and 3 have different implications for the estimation of the relative association of alcohol with disease: if the alcohol is missing at random, estimates of relative risk will still provide a reasonable description of the association of drinking with disease; however, if there is systematic underreporting that varies by alcohol consumption in the manner described in scenario 3, there may well be (unquantifiable) underestimates of the risk of disease at higher levels of consumption. Of course, if there is some other pattern to the underreporting, it becomes even more problematic to interpret findings.

In summary, this cohort study provides important and useful additional evidence for the role of alcohol in the etiology of GI cancer, suggesting that frequency of drinking is more important than amount consumed on any one session. Some other questions remain to be answered.

ARTICLE INFORMATION

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