Alcohol and breast cancer: A study in weak associations
A three part paper by Erik Skovenborg MD
Part I

Alcoholic beverages were declared "carcinogenic to humans" (Group 1) by the IARC Monographs Programme, first in 1988 and then again in 2007 and 2010. (IARC. Alcohol drinking. IARC Monogr Eval Carcinog Risks Hum 1988;44:1-378.) In the same year Harris et al. published a study on breast cancer and alcohol consumption. (Harris RE et al. Breast cancer and alcohol consumption – A study in weak associations. JAMA 1988;259:2867-71.) "Recent epidemiologic investigations have indicated that moderate alcohol consumption slightly increases the risk of breast cancer. However, only a weak association is suggested, with reported odds ratios generally being less than 2.0 for women who drink vs those who abstain."The results from the Harris et al. case-control study of 1467 women with breast cancer and 10 178 sex- and age-matched hospital controls "did not provide compelling evidence that alcohol has a role in this malignancy".

Relative risks below 3 are considered moderate or weak – in comparison smokers' risk of lung cancer is 20 or more times higher than that of non-smokers. (Wynder EL. Workshop on guidelines to the epidemiology of weak associations. Prev Med 1987;16:139-141.) "In the workshop on the epidemiology of weak associations various problems were reviewed, including case-control selection, confounders, biases, subgroup analysis, criteria of judgment, and biologic plausibility. Clearly, when it comes to alcohol consumption and breast cancer, we are dealing with a weak association. Findings are not consistent from study to study. There is no definitive dose response. The association appears to be limited to certain subgroups, and there appears to be a lack of external consistency in that countries such as France and Italy, with the highest per capita intake of alcohol (about 16 and 12 L, respectively), do not have correspondingly high rates of breast cancer (about 16 and 15 deaths per 100000, approximate rank = 50th percentile)."

Alcoholic drinks and the risk of cancer

The Expert Panel investigating alcohol and breast cancer associations in the "Continuous Update Project Expert Report 2018" was less sceptical. (World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. Available at dietandcancerreport.org) The CUP Panel concluded: Consumption of alcoholic drinks is a convincing cause of postmenopausal breast cancer and a probable cause of premenopausal breast cancer. The dose-response meta-analysis showed a significant 5% increased risk per 10 grams of ethanol per day: RR 1.05 (1.02-1.08). The dose-response meta-analysis for postmenopausal breast cancer showed a significant 9% increased risk per 10 grams of ethanol per day: RR 1.09 (1.07-1.12).

Cancer is caused by an interaction of risk factors, including internal (genetic susceptibility and hormonal factors) and external factors (lifestyle and environmental factors). Breast cancer is the most common cancer in women worldwide and the fifth most common cause of death from cancer in women, so the association of alcohol intake and breast cancer risk has to be taken seriously. The question is how to interpret the statement on page 59 in the "Alcoholic drinks and the risk of cancer" report (World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Alcoholic drinks and the risk of cancer. Available at dietandcancerreport.org): "Current evidence does not identify a generally "safe" threshold for consumption of alcoholic drinks for breast cancer. That is, there does not seem to be a threshold below which an effect on cancer risk is not observed." However, there is some confusion as to the alcohol content of a drink in the texts. In the CUP Expert Report 2018 "Alcoholic drinks and risk of cancer" the alcohol content of a drink is presented with three different figures: 1) The intake of drinks was rescaled to grams of ethanol per day using 13 grams as the average content of one drink; 2) The dose-response analysis is reported as risk per 10 grams increase in alcohol consumed per day; and 3) The association of alcohol intake and kidney cancer is based on evidence for alcohol intakes up to 30 grams per day (about two drinks a day).

According to WHO no generally "safe" threshold for consumption of alcoholic drinks for breast cancer means "that any reduction in alcohol

consumption will be beneficial for health through the reduction of cancer risk". (World Cancer Report 2014). The WHO Report do not take account of the robust J-shaped relation between moderate alcohol consumption, CHD and all-cause mortality. (Skovenborg, E, Grønbæk M, Ellison RC. Benefits and hazards of alcohol – the J-shaped curve and public health. Drugs and Alcohol Today 2020:21(1)54-69.) In the large EPIC study (268 442 European women) light to moderate intake of alcohol was not related to incidence of alcohol-related cancer in women. With lifetime light alcohol users of ≤ 1 g/day as reference group instead of nondrinkers ("because these women consume alcohol at a level that is so low and infrequent that it presumably could not affect disease risk") lifetime alcohol consumption of one drink per day in women was associated with lower risk of all-cause mortality: HR 0.92 (0.86-0.98). (Bergmann et al. The association of pattern of lifetime alcohol use and cause of death in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Epidemiol 2013;42:1772-90.)

Causality, bias and confounders

With the one drink per day limit, that worked so favourably for the EPIC-women adhering to the limit, incorporated in many sensible drinking guidelines, an obvious question is whether WHO (and many national Cancer Societies) really have sufficient valid evidence for a message of total abstinence. "It is best not to drink alcohol," American Cancer Society recommends in its latest cancer prevention guidelines. With the 18th-century empiricist David Hume's observation that "proof is impossible in empirical science" in mind, how do epidemiologists separate out the causal from the noncausal explanations? (Rothman et al. Causation and Causal Inference in Epidemiology. Am J Public Health 2005;95:S144-S150.) "Scientific evidence can usually be viewed as a form of measurement. If an epidemiologic study sets out to assess the relation between exposure to alcoholic drinks and breast cancer risk, the results can and should be framed as a measure of causal effect, such as the ratio of the risk of breast cancer among drinkers to the risk among nondrinkers. Like any measurement, the measurement of a causal effect is subject to measurement error. In addition to statistical errors, the measurement error subsumes problems that relate to study design, including subject selection and retention, information acquisition, and uncontrolled confounding and other sources of bias. Nearly every study will have nearly every type of error. The real issue is to quantify the errors." First, one has to discriminate between evidence for no causal relationship, and no evidence of a causal relationship. The former expresses an important piece of evidence that may have substantial consequences, whereas the latter simply expresses lack of knowledge. Because of the by far higher demands on quality and size of studies set out to dismiss the assumption of carcinogenicity, there is an inherent imbalance of classification concerning carcinogenicity and lack of carcinogenicity. (Kundi M. Causality and the Interpretation of Epidemiologic Evidence. Environ Health Perspect 2006;114:969-74.)

Cancer epidemiology is, to a large extent, the determination of small effects and weak associations and poses major challenges. (Boffetta P. Causation in the presence of weak associations. Critical Reviews in Food Science and Nutrition 2010;50:13-16.) So let us apply thorough criticism of the evidence on light drinking and risk of breast cancer. A commonly used set of criteria, proposed by Bradford Hill, was an expansion of a set of criteria offered previously in the landmark surgeon general's report (1964) on smoking and health. Hill suggested that the following aspects of an association be considered in attempting to distinguish causal from noncausal associations: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy. These criteria should be considered only as aids to thought and practical tools; in fact, scientific causal assessment is a never-ending process centered around measurement of the exposure-disease relationship.

Strength. Strong associations are more likely to be causal than weak associations because, if they could be explained by some other factor, the effect of that factor would have to be even stronger than the observed association and therefore would have become evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. The alcohol-breast cancer association is weak and several bias and effect modifiers have been identified.

Information bias: Underreporting of alcohol intake is a general and serious problem.

- It is generally agreed that alcohol consumption is substantially underestimated when estimations are based on self-reports. In most studies self-reported consumption amounts to only 40-60% compared to sales figures. (Høyer et al. The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 1995;90:539-44.)
- In a study of alcohol measures derived from the Cognitive Lifetime Drinking History among 2142 respondents, current alcohol consumption accounted for only about 10-25% of the variability in lifetime alcohol consumption. (Russell et al. Relations among alcohol consumption measures derived from the Cognitive Lifetime Drinking History. Drug Alcohol Rev 1998;17:377-87.) Most studies that have quantified the effect of alcohol of the risk for cancers of the female breast have captured only current drinking.
- The actual Spanish consumption was 9.5 l of pure alcohol/person-year in 2011, however the coverage of WHO availability, Tax Agency availability, self-reported purchases, and self-reported consumption was 99.5, 99.5, 66.3, and 28.0 %, respectively. To obtain conservative estimates of alcohol-attributable disease burden, self-reported consumption should be shifted upwards by more than 85 % of Tax Agency or WHO availability figures. The underreporting identified can probably also be found worldwide, thus much empirical work remains to be done to improve estimates of per capita alcohol consumption. (Sordo et al. Estimating average alcohol consumption in the population using multiple sources: the case of Spain. Population Health Metrics 2016;14:21.)
- In a cohort of 127,176 persons, participants reporting light–moderate drinking had increased cancer risk in this cohort: HR for risk of any cancer were 1.10 (1.04–1.17) at <1 drink per day and 1.15 (1.08–1.23) at 1–2 drinks per day. However, the increased risk of cancer was concentrated in the stratum suspected of underreporting. (Klatsky et al. Moderate alcohol intake and cancer: the role of underreporting. Cancer Causes Control 2014;25(6):693-9.)

Detection bias: The increased risk of incident breast cancer in moderate alcohol consumers may be overestimated by more intensive screening.

- In the Maryland Behavioral Risk Factor Survey of 946 women ages 50 years and older, women who drank alcoholic beverages had higher mammography rates than nondrinkers: OR = 1.37 (1.03–1.83). (Fredman et al. Cigarette Smoking, Alcohol Consumption, and Screening Mammography among Women Ages 50 and Older. Preventive Medicine 1999;28:407-17.)
- Women who drank alcoholic beverages had significantly higher mammography rates than women who abstained from alcoholic beverages among respondents to the 1990 National Health Interview Survey. (Rakowski et al. Integrating behavior and intention regarding mammography by respondents in the 1990 National Health Interview Survey of Health Promotion and Disease Prevention. Public Health Rep 1993;108:605-24).
- In six iterations (2002–2012) of the Behavioral Risk Factor Surveillance System, a telephone survey of US adults conducted by the Centers for Disease Control and Prevention, participants reported their alcohol use and recent screening for several cancers. Moderate alcohol consumers were 84.7% more likely to report mammography screening than non-consumers. Among binge consumers the weighted prevalence of screening was lower than in non-binge consumers (binge vs non-binge moderate consumers 80.5 vs 85.5%). (Mu et al. Alcohol consumption and rates of screening: Is cancer risk overestimated? Cancer causes Control 2016;27:281-89.)

Effect modification: Uniform adjustments for effect modifiers have not been made in the observational studies of alcohol intake and breast cancer risk.

- Folate intake: Prospective studies indicated a U-shaped relationship for the dietary intake of folate intake: Increased dietary folate intake reduced breast cancer risk for women with higher alcohol intake level, but not for those with lower alcohol intake. (Chen et al. Higher dietary folate intake reduces the breast cancer risk: a systematic review and meta-analysis. British Journal of Cancer 2014;110:2327-38.) A dose-response meta-analysis of observational studies found folate intake inversely correlated

with the breast cancer risk when the highest and lowest categories were compared: OR = 0.85 (0.79–0.92), and the dose-response result showed that folate intake had a linear correlation with the breast cancer risk. A higher folate intake correlated with a lower breast cancer risk in premenopausal women: OR = 0.80 (0.66–0.97), but not significantly in postmenopausal women: OR = 0.94 (0.83–1.06). (Ren et al. Association of folate intake and plasma folate level with the risk of breast cancer: a dose-response meta-analysis of observational studies. Aging 2020;12(21):21355-375.)

- Diet: In the Norwegian Women and Cancer study a significantly higher risk of breast cancer was found in women with high consumption of alcohol and low consumption of fruit and vegetables and low consumption of fatty fish. (Engeset et al. Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study. European Journal of Cancer Prevention 2009;18:69-75.) A systematic review and meta-analysis found highest adherence to the MedDiet related to lower risk of cancer mortality in the general population and all-cause mortality among cancer survivors. The association of the MedDiet and cancer was only reflected by inverse associations between overall cancer risk and consumption of fruit, vegetables, whole grains and moderate intake of red wine. (Morze et al. An updated systematic review and meta-analysis on adherence to Mediterranean diet and risk of cancer. Eur J Nutr 2020.) A Randomized Clinical Trial to evaluate the effect of 2 interventions with Mediterranean diet vs the advice to follow a low-fat diet on breast cancer incidence found multivariable-adjusted hazard ratios vs control: HR = 0.31 (0.13-0.77) for the Mediterranean diet with extra-virgin olive oil group and HR = 0.53 (0.23-1.26) for the Mediterranean diet with nuts group. (Toledo et al. Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardio-vascular Risk in the PREDIMED Trial. JAMA Intern Med 2015;175(11):1752-60.)
- Drinking pattern: After controlling for cumulative alcohol intake, binge drinking was associated with increased breast cancer risk in Danish nurses (Mørch et al. Alcohol drinking, consumption patterns and breast cancer among Danish nurses: a cohort study. European Journal of Public Health 2007;17(6):624-29), US nurses (Chen et al. Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk. JAMA 2011;306(17):1884-90), Puerto Rico women with a sister with breast cancer (White et al. Lifetime Alcohol Intake, Binge Drinking Behaviors, and Breast Cancer Risk. Am J Epidemiol 2017;186(5):541-49) and Spanish university graduates (Sánchez-Bayona et al. Binge Drinking and Risk of Breast Cancer: Results from the SUN ('Seguimiento Universidad de Navarra') Project. Nutrients 2020;12:731). However, information on drinking patterns is almost non-existent in the evidence base for the CUP Expert Report 2018 "Alcoholic drinks and risk of cancer".
- Physical activity: An association of physical activity and cancer mortality risk was found in an analysis of data from participants aged 30 years and over in Health Surveys for England and the Scottish Health Surveys. Among the physical activity (PA) ≤ 7.5 MET-hour/week group, there was a significant association between alcohol consumption and risk of alcohol-related cancer mortality. Exdrinkers: HR = 1.53 (1.11 - 2.12), drinkers at hazardous levels: HR = 1.47 (1.07 - 2.02) and drinkers at harmful levels: HR = 1.64 (1.07 - 2.52) had significantly higher mortality risks than never-drinkers. The increased risks were eliminated among the PA > 7.5 MET-hour/week individuals. (Feng Y et al. Does adequate physical activity attenuate the associations of alcohol and alcohol-related cancer mortality? A pooled study of 54 686 British adults. Int J Cancer 2020;147(10):2754-63.)

Part II

While smokers' risk of lung cancer is 20 times higher (equal to 2000% higher) than that of nonsmokers, cancer epidemiology is, to a large extent, the determination of small effects and weak associations and poses major challenges. In comparison, a dose-response meta-analysis of alcohol and risk of postmenopausal breast cancer found a significant increased risk of 0.09 times (equal to 9%) per 10 grams per day compared to nondrinkers. (World Cancer Research Fund/ American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. Available at dietandcancerreport.org)

Sir Bradford Hill has proposed some features of the association we should consider before deciding that the most likely interpretation of the association is causation. (Hill AB. The environment and disease. Association or causation? J R Soc Med 2015;108(1):32-37.) With these nine features as aids to thought we will look at the proposed causal association of light alcohol consumption and breast cancer with a critical eye. Part I of this paper (published in our March edition) looked at the first of the nine viewpoints "from all of which we should study association before we cry causation" – Strength – with the conclusion that the alcohol-breast cancer association is weak and several bias and effect modifiers have been identified. Now we continue with the next eight features on the list.

Consistency. Next on Bradford Hill's list of features to be specially considered is the consistency of the observed association. Has the association been repeatedly observed by different persons, in different places, circumstances and times?

- The majority of the case-control studies and cohort studies published to date have shown a (modest) positive association between alcohol consumption and breast cancer. However, there is a considerable lack of consistency in results of the association between alcohol intake and breast cancer risk in retrospective as well as prospective observational studies. A large number of case-control studies have shown no association (n=34), non-significant positive associations (n=23) or negative associations (n=6). Regarding cohort studies 15 studies have shown no association, 12 studies a non-significant positive association and 1 study a negative association; e.g. among 2,764 women followed > 40 years in the Original Framingham Cohort and 2,284 followed up to 24 years in the Offspring Cohort, light consumption of alcohol or any type of alcoholic beverage was not associated with increased breast cancer risk. (Zhang et al. Alcohol consumption and risk of breast cancer: The Framingham Study revisited. Am J Epidemiol 1999;149(2):93-101.)
- It is likely that overall breast cancer risk in relation to alcohol intake varies among different ethnic groups and different regions. A meta-analysis of 4 case-control studies conducted in China found a significant inverse association between alcohol consumption and breast cancer risk. (Li Y et al. Association between alcohol consumption and cancers in the Chinese population: a systematic review and meta-analysis. PLoS One 2011;6:e18776.) Among the Japanese population, a qualitative review of the existing evidence has indicated that the association between alcohol consumption and breast cancer risk remains inconclusive. (Nagata C et al. Alcohol drinking and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2007;37:568-74.)
- Cohort studies with less than 10 years of follow-up gave estimates 11% higher than cohort studies with longer follow-up periods. (Curtis Ellison et al. Exploring the Relation of Alcohol Consumption to Risk of Breast Cancer. Am J Epidemiol 2001;154:740-47.)
- In the dose-response meta-analysis of 22 studies (n=35,221 cases) for postmenopausal breast cancer, high heterogeneity was observed. (dietandcancerreport.org)
- Two recent Mendelian Randomization studies did not find evidence for a causal relationship between genetically predicted alcohol consumption and risk of breast cancer.

  a) Zhu et al. Alcohol consumption and risk of breast and ovarian cancer: A Mendelian Randomization study. Cancer Genetics 2020;245:35-41.

  b) Ong et al. Evaluating the role of alcohol consumption in breast and ovarian cancer

susceptibility using population-based cohort studies and two-sample Mendelian randomization analyses. Int J Cancer 2021;148(6):1338-1350.

Specificity of the association is a strong argument in favour of causation. Harmful alcohol has been linked to more than 200 diseases and injury conditions including several other types of cancer while up to two drinks a day decreases kidney cancer. In comparison, the death rate of smokers is higher than the death rate of non-smokers from many causes of death, but specificity is demonstrated by the magnitude of the association of smoking and lung cancer. However, importance of the characteristic of specificity should not be over-emphasized.

Temporality. The question of temporal relationship of the association is particularly relevant with diseases of slow development. Regarding the association between alcohol consumption and breast cancer risk temporality is more a consideration of the extent to which alcohol affects breast cancer onset or breast cancer progression. There is no evidence of reverse causation (that early stages of breast cancer lead to change of drinking patterns) in the association of alcohol and breast cancer.

Biological gradient refers to the presence of a unidirectional dose–response curve.

- In the collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer, the relative risk of breast cancer increased with alcohol intake, increasing by 7.1% for each additional 10 g per day intake of alcohol consumed on a daily basis. Compared to women who drank no alcohol the relative risk was 1.03 for women whose alcohol consumption was 5-14 g/d, 1.13 for 15-24 g/d, 1.21 for 25-34 g/d, 1.32 for 35-44 g/d and 1.46 for >45 g/d. (Hamajima et al. Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. British Journal of Cancer 2002;87:1234-45.)
- Regular intake of wine with meals: A population-based case-control study of alcohol and breast cancer (250 cases and 499 controls) was conducted among women under the age of 75 residing in the Province of Vercelli, in northwestern Italy; an area where wine drinking is widespread and regarded by most as an acceptable habit. Wine is sometimes produced by the family for personal consumption and, in general, is economically affordable. In line with Italian customs, wine is consumed mainly during meals, in place of other drinks. As a consequence, levels of alcohol consumption were quite substantial; about 40% of the total study population, or more than 55% of drinkers, reported consumptions of alcohol in excess of 15 g/day and more than 20% of drinkers reported consumptions of 30 g/day or above. The dietary questionnaire was designed primarily for the purpose of estimating alcohol consumption in European countries, such as France, Spain, and Italy, where wine consumption is widespread and habitually consumed during meals. The questionnaire was therefore structured by meals. In comparison with abstainers (30% of women in the study) and after adjustment for potential confounders, no appreciable association was evident for alcohol consumptions as high as 30-40 g/day. Alcohol intake from wine (g/day) and RR (95% CI) of breast cancer: 0: 1.0, >0-10: 0.9 (0.5-1.5), >10-20: 1.2 (0.8-1.9), >20-30: 1.1 (0.7-3.0), >30-40: 1.4 (0.7-3.0), and >40: 2.1 (1.1-3.7). (Toniolo P et al. Breast cancer and alcohol consumption: a case-control study in northern Italy. Cancer Res 1989;49:5203-06.)
- The alcoholism paradox: Barmaids, who have a raised mortality from cirrhosis, have a low proportional mortality from breast cancer. (Office of Population Censuses and surveys. Women's occupational mortality 1970-72 (Series DHI no. I). London: HM Stationary Office 1985.) In a number of studies (3 from Sweden, 2 from Denmark, 1 from UK and 1 from the US) alcoholic women with a very high intake of alcohol had only a very modest increase (relative risk around 1.15) in breast cancer incidence compared to the general female population. (Kuper et al. Alcohol and breast cancer risk: the alcoholism paradox. British Journal of Cancer 2000;83:949-51). In a Russian retrospective case-control study of alcohol and cause-specific mortality in 48,557 adult deaths, the only significantly inverse association was with mortality from breast cancer (519 deaths), which was substantially

lower in the few women in the highest alcohol category (mean > 5 bottles of vodka or equivalent per week) than in women from the lower alcohol consumption categories. (Zaridse D et al. Alcohol and cause-specific mortality in Russia: a retrospective case–control study of 48 557 adult deaths. Lancet 2009; 373:2201–14.) The alcoholism paradox has not been explained away by confounding factors.

Plausibility. "It will be helpful if the causation we suspect is biologically plausible", Bradford Hill said in his President's Address. "But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day."

Tumor initiation and growth.

Cancer develops when the normal processes that regulate cell behaviour fail and a cell becomes the ancestor of a group of cells that share its functional abnormalities. More than one mutation is generally required to lead to cancer and most cancers result from the accumulation of genetic damage in cells over time. (Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10:789-99.)

- Oncogenes are mutated in ways that render the gene constitutively active or active under conditions in which the wild-type gene is not. A mutation in an oncogene is analogous to a stuck accelerator in an automobile; the car still moves forward even when the driver removes his foot from it.
- Tumor-suppressor genes mutations reduce the activity of the gene product. A mutation in a tumor-suppressor gene is analogous to a dysfunctional brake in an automobile; the car doesn't stop even when the driver attempts to engage it.
- Stability genes keep genetic alterations to a minimum, and thus when they are inactivated, mutations in other genes occur at a higher rate.

Mutations in these three classes of genes can occur in the germline, resulting in hereditary predispositions to cancer (e.g. inactivation of stability genes BRCA1 and BRCA2), or in single somatic cells, resulting in sporadic tumors. The cells of solid tumors must accumulate several rate-limiting mutations in cancer genes to achieve malignant status. These mutations occur over time, with each mutation engendering a clonal expansion resulting in a large number of cells that then form a substrate for subsequent mutations. It requires 30–40 years for a typical epithelial cell to accumulate the multiple genetic alterations required to progress to metastatic disease. Data-driven approaches provide a consistent estimate of contribution of extrinsic factors of 70-90% in most common cancer types. (Wu S et al. Substantial contribution of extrinsic risk factors to cancer development. Nature 2016;529(7584):43-47.) While numerous behavioral, reproductive, and medical breast cancer risk factors have been established, questions remain regarding the strength of associations with these, and other risk factors, due in part to the etiological heterogeneity among breast cancer subtypes.

A primary tumor starts from one single cell and monoclonality has been shown for the majority of human tumors. The first tumor cell multiplies exponentially with time: 1-2-4-8-16-32, and so forth. If the tumor cells have a diameter of 10 µm, the clone will have reached a volume of about 1 cm3 after 32 cell generations. The net growth of the tumor volume plotted on a semilogarithmic scale, it is linear and the inclination of the slope may be called the tumor volume doubling time (TVDT). (Friberg S, Mattson S. On the Growth Rates of Human Malignant Tumors: Implications for Medical Decision Making. J Surg Oncol 1997;65:284-97.) It takes 22 cell divisions (doublings) to reach a tumor size of 2 mm = the mammographically threshold size for diagnosis. About 32-33 doublings is needed for a tumor to reach a size of 109 cell and a volume of 1 cm3 = a tumor size that may give rise to symptoms and become detectable on palpation. With a TVDT of 150 days and assuming a constant generation time, the tumor is then about 12 years old.

Serial mammographies of untreated breast cancers during an observation period from 2 to 9 years showed great interindividual variability of the growth rates for different cancers of the breast, with TVDTs ranging from 88 days to 523 days. The average doubling time was 280 days, which means that more than 18 years were required from the first tumor cell (10 µm in diameter) to produce a tumor with a diameter of 2 mm (the lowest detection level). (Fournier D v et al. Growth rate of 147 mammary carcinomas. Cancer 1980;45:2198-2207.) In a study of faster growing interval breast

cancers average estimated TVDT was 167 days (95% CI 151-186). High grade, ER negativity and younger age were associated with shorter durations of TVDT. (MacInnes EG et al. Radiological audit of interval breast cancers: Estimation of tumour growth rates. The Breast 2020;51:114-19.)

Tumor induction and latent periods

Induction refers to the period between causal action and tumor initiation, and latent period to the period between disease initiation (when the cancer reaches a certain critical point of being irreversible without treatment) and detection. A causal model should contain a specification of the time required for an effect to become manifest and (with the evidence on breast cancer TVDT in mind) interpretation of some epidemiological data may need be reconsidered. If a tumor reaches the diagnostic level when it is 10 years old, it is not likely to have been initiated by a suspected carcinogen to which the patient was exposed only 5 years earlier. The causative agent must be searched for more than 10 years before the diagnosis. (Rothman KT. Induction and latent periods. Am J Epidemiol 1981;114:253-59.) In an analysis of the Copenhagen City Heart Study, in which alcohol intake was measured four times, 9,318 Danish women with no previous diagnosis of cancer were followed for breast cancer for 27 years, from 1976 to 2002. During follow-up, breast cancer was diagnosed in 476 women. The association between alcohol intake at first measurement (baseline alcohol intake) and breast cancer was positive and approximately linear. When alcohol intake was updated during follow-up, no association was observed between breast cancer and alcohol intake. It is suggested that this difference in results may be attributable to long latency time between alcohol intake and breast cancer occurrence. (Thygesen LC et al. Use of baseline and updated information on alcohol intake on risk for breast cancer: importance of latency. Int J Epidemiol 2008;37:669-77.)

Regarding alcohol as a risk factor for breast cancer, the question is whether alcohol is a weak cumulative breast carcinogen or a breast tumor growth promotor or both. (Brooks PJ, Zakhari S. Moderate Alcohol Consumption and Breast Cancer in Women: From Epidemiology to Mechanisms and Interventions. Alcohol Clin Exp Res 2013;37:23-30.) If alcohol acts as a cumulative carcinogen and alcohol consumption by postmenopausal women is a surrogate measure of lifetime alcohol consumption, then assessing alcohol consumption in postmenopausal women monitors lifetime exposure to a presumably cumulative carcinogen. If we presume that the only effect of alcohol drinking was to increase the growth rate of preexisting tumors, then the relationship between breast cancer risk and alcohol drinking would be limited to more recent drinking.

Some epidemiological studies suggest that drinking alcohol during adolescence and early adulthood has a strong impact on breast cancer risk (Liu Y et al. Alcohol Intake Between Menarche and First Pregnancy: A Prospective Study of Breast Cancer Risk. J Natl Cancer Inst 2013;105:1571-78. Romieu I et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. Int J Cancer 2015;137:1921-30.), while Swanson et al. found that only contemporary drinking (average intake during the recent 5-year interval) was associated with risk. (Swanson CA et al. Alcohol Consumption and Breast Cancer Risk among Women under Age 45 Years. Epidemiology 1997;8:231-37.) The results from 21,523 postmenopausal women who participated in the Diet, Cancer, and Health Study in two consecutive examinations in 1993-98 and 1999-2003 showed that women who increased their alcohol intake over the five-year period had a subsequent higher risk of breast cancer than women with stable alcohol intake. For women who reduced their alcohol intake over the five-year period, none of the hazard ratios was significantly associated with breast cancer. (Dam MK et al. Five year change in alcohol intake and risk of breast cancer and coronary heart disease among postmenopausal women: prospective cohort study. BMJ 2016;353:i2314.)

The results from a prospective observational study of 105,986 women enrolled in the Nurses' Health Study followed up from 1980 until 2008 with an early adult alcohol assessment and 8 updated alcohol assessments supports the lifetime carcinogen hypothesis, however when examined separately, alcohol consumption in early adulthood (18-40 years) and after 40 years were both strongly associated with the risk of breast cancer. These findings are consistent with a tumor-promoter type as well as a cumulative carcinogen type mechanism for alcohol and breast cancer. (Chen WY et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306:1884-90.)

Potential mechanisms for alcohol and breast cancer carcinogenesis

Ethanol is thought to potentially cause breast cancer through several mechanisms: by its metabolite acetaldehyde – a mutagenic and carcinogenic compound that causes formation of DNA adducts and inhibits DNA repair mechanisms, by cytochrome P450 2E1 mediated generation of ROS (reactive oxygen species), by enhancing levels of estrogen, by interference with one-carbon metabolism and by ethanol-induced dysregulation of epigenetic regulation of gene expression (particularly abnormal DNA methylation). All the above-described mechanisms by which ethanol is involved in breast carcinogenesis are important and support the complexity of the interaction between alcohol and breast cancer risk. (Dumitrescu RG et al. The etiology of alcohol-induced breast cancer. Alcohol 2005;35:213-25.)

- Acetaldehyde rapidly binds to DNA and produces DNA adducts, which results in DNA point mutations, DNA crosslinks and chromosomal aberrations. (Garcia CL et al. Relationship between DNA lesions, DNA repair and chromosomal damage induced by acetaldehyde. Mutat Res 2009;662:3-9.) Aldehydes are omnipresent in nature and are generated during normal metabolism. Most aldehydes are highly reactive and to prevent DNA damage, organisms have evolved aldehyde dehydrogenase enzymes that efficiently convert aldehydes into less noxious products. (Joenje H. Alcohol, DNA and disease. Nature 2011;475(7354):45-6.) Human breast epithelium is equipped with ADH and ALDH enzymes with a ratio of ADH to ALDH activity about 13:1. Class I ADH isoenzyme is the main ethanol-metabolising isoenzyme in breast tissues. (Jelski W et al. The activity of class I, II, III and IV alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in breast cancer. Clin Exp Med 2006;6:89-93.) The concentration of ethanol in the mammary parenchyma after ingestion of alcoholic beverages is supposed to equivalent to the BAC ranging from 2 to 10 mM (9 to 46 mg alcohol/100 ml blood) after moderate social drinking. Triano et al. found that ethanol metabolism in breast tissue homogenates is inhibited by ethanol in concentrations above 10 mM, so that after consumption of larger amounts of alcohol, other mechanisms for detoxification of ethanol would need to come into play. Cytochrome P450 2E1 is inducible by ethanol and has been shown to be expressed in human breast tissue. Reactions catalyzed by Cytochrome P450 2E1 enzymes are particularly prone to generate reactive oxygen species. (Triano EA et al. Class I Alcohol Dehydrogenase Is Highly Expressed in Normal Human Mammary Epithelium but not in Invasive Breast Cancer: Implications for Breast Carcinogenesis. Cancer Research 2003;63:3092-3100.)
- ADH and ALDH single nucleotide polymorphisms (SNPs).

  Alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) are subject to genetic variability by single nucleotide polymorphisms (SNPs). ADH polymorphisms associated with fast metabolism would result in higher systemic acetaldehyde levels that could potentially affect breast tissue. Only large changes in kinetic properties are likely to contribute to a relevant change in breast cancer risk. For example, for ADH1B rs1229984, the increase in velocity of ethanol turnover is almost by a factor of 90 in variant allele homozygotes compared with wild-type homozygotes. (Hurley TD et al. Genes encoding enzymes involved in ethanol metabolism. Alcohol Res 2012;34:339-44.) A meta-analysis of 12 case–control studies showed no direct effect on breast cancer risk of these ADH SNPs. (Wang L et al. Lack of association of ADH1C genotype with breast cancer susceptibility in Caucasian population: a pooled analysis of case-control studies. Breast 2012;21:435-39.) In a large prospective cohort study with a considerably high coverage of 76% of common genetic variability in ADH1B and 96% in ADH1C, alcohol intake was associated with overall postmenopausal breast cancer risk as well as with subtypes defined by ER and PR status, however, no significant effect modification of this association by ADH1B and AHD1C variability was observed. (Hahn M et al. Alcohol drinking, ADH1B and ADH1C genotypes and the risk of postmenopausal breast cancer by hormone receptor status: the Netherlands Cohort Study on diet and cancer. Carcinogenesis 2018;39:1342-51.)

  The ALDH2 rs671 polymorphism dramatically reduces ALDH2 enzyme activity: In carriers of

the ALDH2*2/*2 homozygous and ALDH2*1/*2 heterozygous genotypes the enzyme activity is nearly 0% and 17–38% of the normal activity, respectively. The ALDH2*2 variant is essentially absent among the Europeans, but is highly prevalent among East Asians: an estimated 560 million East Asians are carriers of ALDH2*2. Only three studies have examined the role of ALDH2*2 in the development of breast cancer and all found no association between ALDH2*2 and risk of breast cancer and observed no significant interaction between ALDH2*2 and alcohol consumption on the risk of breast cancer. (Chang et al. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. Journal of Biomedical Science 2017:24:19.)

- Estrogens. Estrogens stimulate the division of breast epithelial cells, which increases the risk of mutation thereby inducing or promoting breast cancer. A positive association between estrogens and breast cancer risk has been found in premenopausal women (Key T et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies related to elevated incidence of breast cancer in humans. Lancet Oncol 2013;14:1009-19.) and postmenopausal women (Key T et al. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606-16.) In comparison to abstainers, pre-menopausal women who consumed 91,4 g alcohol/week showed an 18% increase in serum estradiol. (Muti P et al. Alcohol consumption and total estradiol in premenopausal women. Cancer Epidemiol Biomarkers Prev 1998;7:189-93.) In postmenopausal women, after ovarian estrogen production has ceased, tissues such as adipose tissue, which express aromatase (an enzyme that converts androgens into estrogens) become the major source of estrogen. A meta-analysis of prospective studies among postmenopausal women showed that alcohol intake is positively associated with sex hormones, with the strongest association for dehydroepiandrosterone sulfate (DHEAS) – an androgen that can be metabolized to estrogen in the breast by aromatase. (Key TJ et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 2011;105:709-22). Ethanol stimulates proliferation of both normal breast tissue and ER+ breast cancer cells directly, causing a 10- to 15-fold increase in transcriptional activity of ER. Most studies observe an overall stronger association with ER+ and/or PR+ tumors compared with ER– and/or PR– tumors, for the highest versus the lowest alcohol consumption group. (Jung S et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol 2016;45:916-28.) The analysis of 2160 serum estradiol measurements in 275 postmenopausal women from the ELITE trial found higher BMI and alcohol use associated with higher estradiol levels, whereas current and past smoking were associated with lower estradiol levels. (Sriprasert I et al. Factors Associated With Serum Estradiol Levels Among Postmenopausal Women Using Hormone Therapy. Obstet Gynecol 2020;136:675-84.) While results of some studies indicate that postmenopausal women who are drinkers and use hormone replacement therapy (HRT) have an increased risk of breast cancer (Hvidtfeldt UA et al. Risk of Breast Cancer in Relation to Combined Effects of Hormone Therapy, Body Mass Index, and Alcohol Use, by Hormone-receptor Status. Epidemiology 2015;26:353-61.), findings from other studies do not support the effect of alcohol on HRT-related breast cancer risk. (Allen NE et al. Moderate Alcohol Intake and Cancer Incidence in Women. J Natl Cancer Inst 2009;101:296-305.) Estrogen and alcohol independently have been observed to contribute to angiogenesis – a regulated process used by breast cancer tumors to ensure a constant supply of oxygen and nutrients. (Maniyar R et al. Ethanol enhances estrogen mediated angiogenesis in breast cancer. Journal of Cancer 2018;9:3874-85.)
- Folate deficiency. Folate is a B vitamin that donates its methyl group for homocysteine remethylation to methionine as part of one-carbon metabolism. In turn, methionine is the methyl donor for DNA methylation via S-adenosyl methionine. Results from the Shanghai Breast Cancer Study (whose participants are not regular alcohol drinkers) support a protective role for folate: Dietary folate

intake was inversely associated with breast cancer risk with an adjusted OR of 0.71 (95% C, 0.56–0.92) observed among women who were in the highest quintile of intake. (Shrubsole MJ et al. Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. Cancer Res 2001;61:7136-41.) Alcohol can adversely affect folate metabolism by inhibiting the intestinal absorption, reducing the hepatic storage and increasing the renal excretion. (Halsted CH et al. Metabolic interactions of alcohol and folate. J Nutr 2002;132(8S):2367S–2372S). Modeling both exposures together revealed highly significant, independent associations between alcohol and folate and DNA methylation profile. (Christensen BC et al. Breast Cancer DNA Methylation Profiles Are Associated with Tumor Size and Alcohol and Folate Intake. PLoS Genet 2010;6(7):e1001043.) A meta-analysis of 16 prospective studies with a total of 744,068 participants and 26,205 breast cancer patients and 26 case–control studies with a total of 16,826 cases and 21,820 controls that have evaluated the association between folate intake and breast cancer risk, suggested that folate may have preventive effects against breast cancer risk. Prospective studies indicated a U-shaped relationship for the dietary folate intake and breast cancer risk. Women with daily dietary folate intake between 153 and 400 mg showed a significant reduced breast cancer risk compared with those <153 mg, but not for those >400 mg. The case–control studies also suggested a significantly negative correlation between the dietary folate intake level and the breast cancer risk. (Chen P et al. Higher dietary folate intake reduces the breast cancer risk: a systematic review and meta-analysis. Br J Cancer 2014;110:2327-38.)

Coherence: "In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, 'when you have eliminated the impossible, whatever remains, however improbable, must be the truth.' On the other hand, the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease - in the expression of the Advisory Committee to the Surgeon-General it should have coherence."

Experiment: "Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed."

Analogy: "In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy."

"Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and- effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (Bradford Hill A. The Environment and Disease: Association or Causation? Proc R Soc Med 1965;58(5):295-300.)

Part III
The case for action

Sir Austin Bradford Hill, an English epidemiologist and statistician, pioneered the randomised clinical trial and, together with Richard Doll, demonstrated the connection between cigarette smoking and lung cancer. To anyone involved in medical statistics, epidemiology or public health, Bradford Hill was simply the world's leading medical statistician. Hill's seminal 1965 Presidential Address to the Section of Occupational Medicine of the Royal Society of Medicine, where he presented what are now commonly called the "Bradford-Hill criteria", offered a timeless insightful analysis about how to interpret our observations. His Presidential address closed with important observations about critical methodological and policy issues about how to interpret conclusions about causality in "real life" situations (Bradford Hill A. The Environment and Disease: Association or Causation? Proc R Soc Med 1965;58(5):295-300.):

"Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it - or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually-to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day."

Should women should fear breast cancer after enjoying one glass of wine?

The evidence for a causal association between a light to moderate alcohol consumption and risk of breast cancer was reviewed in Part I and II of "Alcohol and breast cancer – a study in weak associations". Here we will focus attention on the evidence for a causal association between regular, light drinking, e.g. a glass of wine with your meal, and risk of breast cancer. "The association between alcohol and breast cancer is not strong and not necessarily causative, at least for moderate consumption." (McPherson K. Moderate Alcohol Consumption and Cancer. Ann Epidemiol 2007;17:S46–S48.) Despite a dose-dependent association between alcohol and breast cancer risk, there is some uncertainty on the point of a possible threshold level of alcohol consumption above which the increased risk of breast cancer becomes clinically significant. "But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like", Sir Bradford Hill concluded in his seminal paper on association or causation. The question is: Do we have very strong evidence that women should fear breast cancer after enjoying one glass of wine?

Methodological problems with information on low level alcohol intake

- **Underreporting** (Part I): Underreporting of alcohol intake is a general and serious problem that has not been addressed in the reports from e.g. International Agency for Research on Cancer, World Health Organization, World Cancer Research

Fund International and American Institute for Cancer Research. In a cohort study of cancer risk in participants reporting light–moderate drinking, the increased risk of cancer was concentrated in the stratum suspected of underreporting. (Klatsky et al. Moderate alcohol intake and cancer: the role of underreporting. Cancer Causes Control 2014;25(6):693-9.) In the important meta-analysis on alcohol, tobacco and breast cancer from 2002, the authors conclude: "Self-reported information on alcohol consumption is known to underestimate true consumption. Systematic under-reporting of consumption by both cases and controls would result in an overestimation of the relative risk of breast cancer for a given level of alcohol consumption. By contrast, random misclassification among both cases and controls would have the opposite effect, resulting in an underestimation of the relative risk. These two types of measurement error are inevitable, but counter-acting, and it is not possible to estimate their overall effect on the relative risks calculated here. Moreover, the shape of the dose-response relationship could be changed if, for example, heavy drinkers were more likely to under-report intake than moderate drinkers. Taken together, these reporting errors imply that some uncertainty remains about the true quantitative effect of an intake of a fixed amount of alcohol on the risk of developing breast cancer." (Hamajima et al. Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. British Journal of Cancer 2002;87:1234-45.)

• **Drinking pattern:** No information on the pattern of intake was collected by Hamajima et al. and information on drinking patterns is almost non-existent in the evidence base for the CUP Expert Report 2018 'Alcoholic drinks and risk of cancer'. There are three important aspects of drinking pattern regarding the association of alcohol intake and risk of breast cancer: 1) Regular drinking versus binge drinking; 2) Drinking a moderate amount of alcohol spread over most days/week versus a few days/week; and 3) Effect of fasting versus drinking with food on ethanol bioavailability.

1) Regular drinking versus binge drinking. After controlling for cumulative alcohol intake, binge drinking is associated with increased breast cancer risk (Part I).

2) Drinking a moderate amount of alcohol spread over most days of the week versus few days per week. Generally, there are two measures of alcohol exposure: the number of alcoholic drinks per time period, and ethanol intake in grams or millilitres per time period. In The Million Women Study, for example, women were categorized into five groups according to the total number of alcoholic drinks that contained about 10 g alcohol consumed per week, as reported in the recruitment questionnaire. The categories used were 0, less than or equal to 2, 3-6, 7-14, or greater than or equal to 15 drinks per week. In conclusion the study found regular consumption of low to moderate amounts of alcohol by women increases the risk of e.g. breast cancer. In the abstract the wording is: "for every additional drink regularly consumed per day…" although The Million Women Study had no data on drinking pattern regarding a consumption of ≥7 drinks per week.

3) Effect of fasting versus drinking with food on ethanol bioavailability. The decreased bioavailability of ethanol consumed with food versus drinking on an empty stomach is not addressed by the Continuous Update Project Expert Report 2018 for the simple reason that most studies do not collect information about drinking culture. An example of the important effect of drinking with food is the results of The Million Women Study (Simpson RF et al. Alcohol drinking patterns and liver cirrhosis risk: analysis of the prospective UK Million Women Study. Lancet Public Health 2019;4:e41–48.): At every level of alcohol consumption, cirrhosis incidence was lower in women who usually drank with meals compared with those who did not. After adjusting for the amount of alcohol consumed and potential confounding factors the relative risk for cirrhosis associated with usually drinking with meals compared with not drinking with meals was 0·69 (95% CI 0.62-0.77). An Italian case-control study of alcohol and breast cancer among women under the age of 75 (250 cases, 499 controls) was conducted in the Province of Vercelli, where wine drinking is widespread and wine is consumed mainly during meals. The alcohol questionnaire was structured by meals. In comparison with abstainers (30% of women in the study) and after adjustment for potential confounders, no appreciable breast cancer association was evident for alcohol consumptions below 30 g/day. (Toniolo

P et al. Breast cancer and alcohol consumption: a case-control study in northern Italy. Cancer Res 1989;49:5203-06.)

The systemic availability of ethanol – effects of First Pass Metabolism (FPM)

Human Class I Alcohol Dehydrogenase (ADH) has a low Km = 0.05-0.1 g/L for ethanol as substrate. Km (Michaelis constant for the affinity of an enzyme for its substrate) is the concentration of substrate which permits the enzyme to achieve half the maximum rate of reaction (Vmax.). When BAC exceeds 2 x ADH Km (0.1-0.2 g/L), the enzyme is saturated with substrate and is working at maximum velocity. (Bosron WF et al. Relationship between kinetics of liver alcohol dehydrogenase and alcohol metabolism. Pharmacology Biochemistry and Behavior 1983;18 (Suppl 1):223-27.) The hepatic ADH enzyme therefore becomes saturated after ≥0.2 g alcohol/kg bodyweight = just a couple of drinks. When the ADK enzyme is saturated, the rate of disappearance of ethanol from blood becomes virtually independent of the prevailing blood-ethanol concentration (zero-order kinetics). Consequently, the rate at which ethanol molecules reach the hepatic ADH enzymes becomes a major determinant of systemic availability. The slower the rate of absorption of ethanol molecules from the stomach to the hepatic portal vein, the smaller the amount of ingested alcohol that escapes first pass hepatic metabolism and enter the systemic circulation = a small AUC (area under the curve) for a given dose. The swifter the rate of absorption of ethanol molecules from the stomach to the hepatic portal vein, the larger the amount of ingested alcohol that escapes first pass hepatic metabolism and enter the systemic circulation = a larger AUC for a given dose. (Levitt MD, Levitt DG. The critical role of the rate of ethanol absorption in the interpretation of studies purporting to demonstrate gastric metabolism of ethanol. J Pharmacol Exp Ther 1994;269:297-304.)

The decrease of alcohol bioavailability via FPM is dependent on the rate of gastric emptying and the dose of alcohol. Liquids typically leave your stomach quickly; the half-time to gastric emptying (T1/2) after 300 ml black tea was 22.7 (95% CI 12.7-40.9) minutes. (Hillyard S et al. Does adding milk to tea delay gastric emptying? British Journal of Anaesthesia 2014;112 (1): 66-71.) After a steamed-rice with microwaved egg meal gastric emptying half time (T1/2) was 68.7 (95% CI 45.1-107.8) minutes. (Vasavid P et al. Normal Solid Gastric Emptying Values Measured by Scintigraphy Using Asian-style Meal: A Multicenter Study in Healthy Volunteers. J Neurogastroenterol Motil 2014;20:371-78) Increasing the energy content of the meal of fixed composition progressively delays the half time to gastric emptying: T1/2 = 57, 70, and 95 min. for 150 kcal, 300 kcal and 600 kcal, respectively. (Velchik MG at al. The effect of meal energy content on gastric emptying. J Nucl Med 1989;30(6):1106-10.) Intake of 400 ml beer (4.7 %vol), 200 ml red wine (13.7 %vol) or 100 ml whisky (43.5 %vol) or matching volumes of isotonic glucose solution after a solid 1485 kJ meal caused significant slowdown of gastric emptying (T1/2) in minutes: Beer 206 ±11 vs control 155 ±7; red wine 209 ±11 vs control 144±6; and whisky 248 ±16 vs control 144 ±8. (Kasicka-Jonderko A et al. Potent inhibitory effect of alcoholic beverages upon gastrointestinal passage of food and gallbladder emptying. J Gastroenterol 2013;48:1311-23.)

The FPM is increased after a substantial meal compared to a light meal. Forty-five ml of 95% alcohol, diluted to 150 ml with orange juice, was taken orally by six adult male volunteers under the following conditions: A (fasting), B (following a light breakfast) and C (following a heavy breakfast). Using treatment A (fasting) as a reference, the average area under the blood alcohol, time curve was reduced by 36% after a light breakfast and by 63% after a heavy breakfast. (Lin Y et al. Effects of solid food on blood levels of alcohol in man. Res Commun Chem Pathol Pharmacol 1976;13(4):713-22.) In a study with a low dose of alcohol (0.15 g alcohol/kg bodyweight = a 10 g dose for a woman weighing 66 kg) administered in a 5% dextrose solution (5 g/100 ml) perorally or intravenously 1 hour after a standard breakfast, FPM reduced the amount of ingested alcohol entering the systemic circulation (AUC) by 73%. (Fig. 1) When alcohol was given in the fasting state, there was no significant difference in blood ethanol level between the peroral and the intravenous dose. (DiPadova C et al. Effects of Fasting and Chronic Alcohol Consumption on the First-Pass Metabolism of Ethanol. Gastroenterology 1987;92:1169-73.)

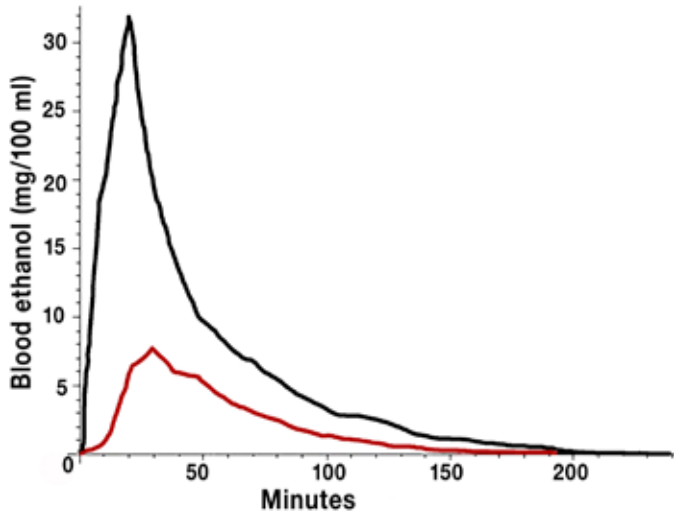

Fig. 1. Reduced systemic bioavailability (AUC = area under the curve) of a low dose of alcohol taken with a meal (red line) vs alcohol intake on an empty stomach (black line). The figure is redrawn after DiPadova et al.'s data.

A mathematical model for calculating the systemic availability of alcohol was used by Levitt to illustrate the dramatic effect of a concomitant meal on the blood levels resulting from an oral intake. The figure shows the blood alcohol levels for an oral intake of 12 g of ethanol equivalent to one 12 ounce can of beer (red line); and 2 (green) or 3 (blue) times this dose, all ingested for a 20 minute time period either with ("fed") or without ("fasted") a meal. (Fig. 2) Ingestion of a coincident meal with the ethanol can reduce the peak blood level by about 4 fold at low doses. (Levitt DG. PKQuest: measurement of intestinal absorption and first pass metabolism – application to human ethanol pharmacokinetics. BMC Clinical Pharmacology 2002;2:4.)

"The mechanisms whereby alcohol may increase the risk of breast cancer remains uncertain" the CUP Update Report 2018 concludes. "The potential mechanisms affecting breast carcinogenesis are diverse. Alcohol can also be metabolized in breast tissue to acetaldehyde producing reactive oxygen species associated with DNA damage." (World Cancer Research Fund/American Institute for Cancer Research, Continuous Update Project Expert Report 2018. Alcoholic drinks and the risk of cancer. Available at dietandcancerreport.org.) For alcohol metabolism in breast tissue to take place, systemic availability of alcohol is necessary. For a 170 cm height female weighing 66 kg the Widmark "r" factor would be 0.66 and her volume of distribution (body water) would be 66 x 0.66 = 43.56 litres. (Barbour A. Simplified estimation of Widmark "r" values by the method of Forrest. Science & Justice 2001;41(1):53-54.) Assuming a regular, moderate intake of alcohol an average alcohol elimination rate from blood would be 15 mg/100 ml/h. Consequently the woman would be able to metabolise 15 mg alcohol x 435.6 = 6534 mg (6.5 g) alcohol per hour.

When BAC exceeds 0.1-0.2 g/L (= 2 x Km), the hepatic ADH enzyme is saturated with substrate and at a higher BAC level some of the ethanol molecules that reach the hepatic ADH enzymes through the portal vein are not metabolized, and this fraction of ethanol molecules reaches the systemic circulation. The amount of alcohol leading to a BAC of 0.1-0.2 g ethanol/L is equivalent to 4.35-8.7 g ethanol in the female example mentioned above drunk within a few minutes on an empty stomach. When a 10 g dose of alcohol is taken during a meal (slowly, as small mouthfuls during 20-30 min.), BAC level will not exceed 0.1-0.2 g/L, the hepatic ADH enzyme will not be saturated, all ethanol molecules will undergo hepatic FPM and

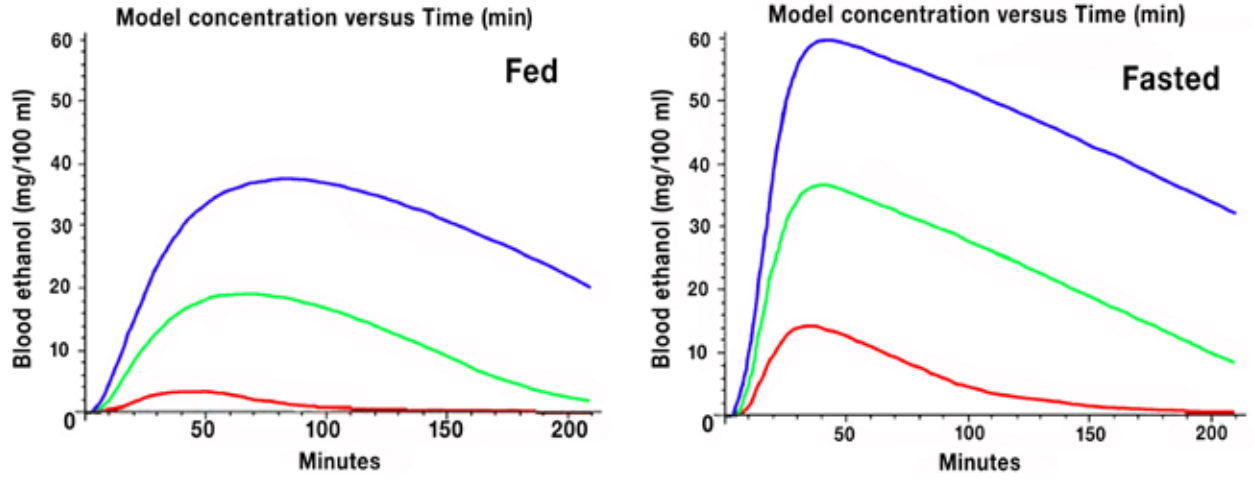

Fig. 2. The BAC curves are redrawn after data from the PKQuest model study by Levitt.

no (or very few) alcohol molecules will reach the breast tissue via systemic circulation.

Risk communication before and now

According to PubMed.gov, Albert J. Tuyns, a renowned French epidemiologist affiliated with the International Agency for Research on Cancer, Lyon, France, is the author of 27 papers on alcohol and cancer. In a chapter on cancer and alcoholic beverages in "Fermented Food Beverages in Nutrition" (Ed. Gastineau, Darby WJ, Turner TB. Academic Press, N.Y, 1979.) Tuyns in his summary considered what could be gained if a given population did not consume more alcohol and tobacco beyond a certain threshold. "In the case of Ille et Vilaine, if people kept within the reasonable limits of 10 cigarettes and half a liter wine (i.e. 40 gm of ethanol) per day, the incidence rate of esophageal cancer would be cut by 6/7 of what it is now." In a 2006 review on alcohol and cancer Boffetta & Hashibe suggested that "given the linear dose-response relation between alcohol intake and risk of cancer, control of heavy drinking remains the main target for cancer control. For example, the most recent version of the European code against cancer recommends keeping daily consumption within two drinks (i.e., 20-30 g alcohol) for men and one drink for women. Total avoidance of alcohol, although optimum for cancer control, cannot be recommended in terms of a broad perspective of public health, in particular in countries with high incidence of cardiovascular disease." (Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006;7:149-56.) Gerald Shaper presented a similar opinion: "The is no evidence that occasional or light drinking, i.e. 1-2 drinks per day in men and 1 drink per day in women, has any untoward effects and most would accept that this level of alcohol intake provides both individual and social pleasure." (Shaper AG. New baseline needed for alcohol and mortality studies. Addiction Research and Theory 2007;15:26-28.)

Today's warnings from Major International Health Organizations are presented without any reservations:

• "There is no safe level of alcohol – the cancer risk starts to increase even with low levels of alcohol consumption. For instance, drinking the amount of alcohol you would find in just a single glass of wine every day caused more than 4600 breast cancer cases in women in the WHO European Region in 2018" (Alcohol and cancer in the WHO European Region: an appeal for better prevention. Copenhagen: WHO Regional Office for Europe; 2020.)

Most of the studies presented by the International Agency for Research on cancer have no data on drinking pattern. The information about intake of alcohol is most often collected as number of drinks/grams of ethanol per week. The postulate of a certain definite breast cancer risk per glass of wine per day is a hypothesis without evidence and a furthermore a hypothesis that disregards methodological issues like underreporting and bioavailability of alcohol.

"In the absence of definite proof, judgments about causation and public health recommendations are at least partially value laden, with both scientific and extrascientific values playing roles. Indeed, causal inference appears by this account to be more subjective than objective. Two recent examples are induced abortion in relation to breast cancer and alcohol in relation to breast cancer. In both cases, 2 different reviewers examined the same evidence at the same time using similar approaches to causal inferences and yet came to exactly opposite conclusions about causation and public health recommendations. These stark differences can best be explained by the different rules of inference assigned to the criteria (i.e., scientific values) and by extrascientific values such as wish bias, moral stances, or political positions regarding the acceptability or appropriateness of the exposure." (Potischman N, Weed DL. Causal criteria in nutritional epidemiology. Am J Clin Nutr 1999;69(suppl):1309S–14S.). The "no safe level" message from WHO is an example of how generalized health risks lacking a clear evidence base can be officially promoted for the greater good of encouraging a healthier behaviour.

• "Current evidence does not identity a generally "safe" threshold for consumption of alcoholic drinks for breast cancer (pre and postmenopause)…" (World Cancer Research Fund/American Institute for Cancer Research, Continuous Update Project Expert Report 2018. Alcoholic drinks and the risk of cancer. Available at dietandcancerreport.org.)

The statement implies that it would be possible to establish a "safe threshold" for consumption of alcoholic drinks for breast cancer by scientific research. However, that is not possible, neither in theory nor in practice, to establish a "safe threshold" for activities that might involve a

risk. As pointed out by Weinberg, transscientific questions are those that can be asked of science but cannot be answered by science, such as whether the amount of electromagnetic energy to which we are normally exposed increases the risk of cancer. In one of his examples, a study of the spontaneous mutation rate in mice exposed to 150 milirem of X-rays would require 8 billion mice in order to show an increase of one half percent (as extrapolated from much higher radiation doses, assuming a linear regression). In other words, a potentially answerable question is unanswerable in real life. (Weinberg AM. Science and transcience. Minerva 1972;10:207-222.)

An example from the outbreak of bovine spongiform encephalopathy (BSE or "mad cow disease) in Europe. Regarding risk of infection with the BSA Health Information for International Travel: 2007 (https://www.cdc.gov/prions/vcjd/risk-travelers.htlm) concluded: "The current risk for infection with the BSE agent among travelers to Europe is extremely small, if it exists at all." Regarding prevention CDC suggested: "To reduce any risk of acquiring vCJD from food, concerned travelers to Europe or other areas with indigenous cases of BSE may consider either avoiding beef and beef products altogether or selecting beef or beef products, such as solid pieces of muscle meat (rather than brains or beef products like burgers and sausages) that might have a reduced opportunity for contamination with tissues that may harbor the BSE agent." Please note that while the risk is "extremely small, if it exists at all", no "safe threshold" for intake of burgers is suggested. An educated guess at that time compared the risk of eating a burger with the risk of riding 6 meters on a bicycle – a level of risk most people would find acceptable.

Another example: It has not been possible to identity a generally "safe" threshold for consumption of non-fermented milk products for breast cancer. In a prospective study of 33,780 women from the Swedish Mammography Cohort, high long-term non-fermented milk consumption was associated with increased ER+/PR+ breast cancer incidence, HR = 1.30 (95% CI:1.02 - 1.65) for the average of 1987 and 1997 intake of >2 vs. 0 servings/day and this increased risk was limited to women with BMI <25 kg/m2: HR = 1.55 (95%CI: 1.08 - 2.21). No significant associations with milk consumption were observed with ER-/PR- breast cancer. (Kaluza J et al. Long-term consumption of non-fermented and fermented dairy products and risk of breast cancer by estrogen receptor status – Population-based prospective cohort study. Clin Nutr 2021;40(4):1966-73.) Fraser et al. found similar results in a cohort study of 52 795 North American women. No clear associations were found between soy products and breast cancer, independently of dairy. However, higher intakes of dairy calories and dairy milk were associated with hazard ratios of 1.22 (95% CI: 1.05-1.40) and 1.50 (95% CI: 1.22-1.84), respectively, comparing 90th to 10th percentiles of intakes. Full fat and reduced fat milks produced similar results. Current guidelines for dairy milk consumption should be viewed with some caution. (Fraser GE et al. Dairy, soy, and risk of breast cancer: those confounded milks. Int J Epidemiol 2020;49(5):1526-37.)

• "Do as I do, think about cancer before you have a glass of wine." (Dame Sally Davies, CMO)

New British guidelines were introduced in 2016 which said that men and women should drink no more than 14 units a week - equivalent to six pints of beer or seven glasses of wine - and some days should be free of alcohol altogether. The UK's chief medical officers' advice was based on research which showed that any amount of alcohol can increase the risk of cancer. The new guidelines were criticized for sending a message that miscommunicates the risks of drinking to the public. "Except for the strong willed minority who will quit drinking entirely, the warning that "no alcohol is safe" will probably be counterproductive, as people might be happy to cut down but not to eliminate alcohol completely. In addition, why should people try to adhere to the new limits rather than the old ones if they are being told that the new recommended levels are not safe?" (Shaw DM. Drunk on risk: how the chief medical officers' alcohol guidelines are demonising drink. BMJ 2016;352:i1175.) The letter in BMJ went on the accuse the chief medical officers to be "drunk on risk": "Good guidelines give balanced information on risk and let people make their own choices. It is scaremongering to say that there's no safe amount when having a small or moderate amount increases risk only marginally. Sally Davies has even suggested that we should think about cancer every time we consider having a glass of wine; the

chief medical officers seem to be drunk on risk and demonising drink." (Donnelly L. Do as I do, think about cancer before you have a glass of wine, says chief medical office. Telegraph 2016. http://www.telegraph.co.uk/news/health/12136938/Doas-I-do-think-about-cancer-before-you-have-a-glass-of-wine-says-chief-medical-officer.html.)

Suggestions for future risk communication

A survey of 942 women in a screening mammography cohort sought to identify factors associated with women's unwillingness to decrease their alcohol intake to decrease their breast cancer risk. Levels of unwillingness to decrease alcohol intake differed by age – women who were 60 years and older were twice as unwilling to decrease their alcohol intake compared to the younger women, and household income – women who had an annual household income of >$200,000 were 1.75 times more unwilling to decrease their alcohol intake compared to the less affluent women. (Matin J et al. Factors Associated with Women's Unwillingness to Decrease Alcohol Intake to Decrease Breast Cancer Risk. J Prim Care Community Health 2021;12:21501327211000211.) The risk communication of the health agencies builds on the logic of 'a will to health', and some drinkers tend to prefer other rationales, associating alcohol use with socialisation, pleasure and relaxation. Understanding individual attitudes toward alcohol drinking and the influence of cultural and social factors will improve our assessment of the impact of alcohol drinking to tailor public health messages toward most susceptible population subgroups. (Scoccianti C et al. Female Breast Cancer and Alcohol Consumption. Am J Prev Med 2014;46(3S1):S16–S25.)

In an editorial with comments on a case-control study by Ferranoni et al., Klim McPherson observed that alcohol is clearly an integral part of many peoples civilized life. The advice given by Ferraroni et. al. was for pre-menopausal women who consume more than two drinks a day to consider a reduction in consumption. "Such a strategy would seem wise by any criterion, not least because of the known causative effects of alcohol on liver disease and digestive cancers." McPherson wrote, adding: "Clearly the notion, which is implicit in the 12% attributable risk figure, that all women should abstain from this prime cause of breast cancer, is neither sensible, achievable nor remotely justifiable on health grounds. The ACS study, for example, suggests that all cause mortality is a full 20% lower among middle aged women who drink one drink per day compared with women who abstain." (McPherson K. Alcohol and breast cancer. Eur J Cancer 1998;34(9):1307-8.) A strategy for future risk communication about alcohol and breast cancer might underline the low risk of light drinking – especially light drinking with a meal – like a glass of wine or beer sipped slowly during the meal as opposed to drinking alcoholic beverages on an empty stomach.

Erik Skovenborg is a Danish physician with a special interest in the health benefits of moderate alcohol consumption. His published work includes In Vino Sanitas, 1990; Lead in Wine throughout the Ages, 1994; Wine and Health – Myths and Facts, 2000. Member of the Social, Scientific and Medical Council of AIM (Alcohol in Moderation) from 1992 and co-founder of the Scandinavian Medical Alcohol Board (SMAB) in 1994. Chairman of the 1996 Copenhagen "Health and Alcohol Symposium" and the 1998 Stockholm "Women and Alcohol Symposium". For many years Erik Skovenborg has lectured extensively on alcohol and health to medical professionals and the general public and he is currently researching the effects of a moderate consumption of beer, wine and spirits.