Coffee and cancer risk: an update
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Introduction
The possible relationship between coffee and cancer risk has been extensively considered in epidemiological studies. The main cancer sites of interest are colorectal and liver on one side, for which inverse relationships have been reported, and bladder and pancreas on the other side, for which direct relationships have been suggested. Available evidence on these sites will be reviewed here, together with a brief mention of other relevant cancer sites. Focus will be on data published after 1990; that is, after Monograph 51 of the International Agency for Research on Cancer on Coffee (IARC, 1991).

Colorectal cancer
The 1990 IARC Working Group (IARC, 1991) concluded that in humans ‘there is some evidence of an inverse relationship between coffee drinking and cancer of the large bowel’.

The literature from 1990 to 2005 on the relationship between coffee, decaffeinated coffee and colorectal cancer risk is summarized here. At least four cohort (total number of cases: 1694) and nine case–control studies (7555 cases) analysed colon cancer, four cohort (568 cases) and four case–control studies (2704 cases) analysed rectal cancer, and six case–control studies (854 cases) analysed colorectal cancer combined (Tavani and La Vecchia, 2000, 2004; Michels \textit{et al.}, 2005). For colon cancer, most case–control studies found risk estimates below unity; the results are less clear for cohort studies. No consistent relationship emerged for rectal cancer. Decaffeinated coffee was not related to either colon or rectal cancer in one cohort and three case–control studies (Tavani and La Vecchia, 2004). One cohort study found an inverse relationship for decaffeinated coffee only (Michels \textit{et al.}, 2005).

Various possible reasons exist for the apparent inverse association between coffee intake and colon cancer risk observed in case–control but not in cohort studies. One of these is the presence of some bias or residual confounding in case–control studies. Any obvious methodological bias, however, is unlikely to account for the consistent results in different countries and settings. Likewise, major publication bias is unlikely, as negative results on the issue have also attracted interest over the last few years. Most papers allowed for several potential confounding risk factors, but multivariate analyses did not substantially modify the results.

A biological interpretation of the potential inverse association between coffee and large bowel cancer has been related to reductions of cholesterol, bile acid and neutral sterol secretion in the colon by coffee, as bile acids are promoters of colon carcinogenesis (Potter, 1992). This would also be consistent with the association being stronger for (or restricted to) colon rather than for rectal cancer. Furthermore, coffee intake increases colonic motility, which has been inversely related to colon cancer risk by influencing the exposure to colonic carcinogens (Brown \textit{et al.}, 1990). Coffee beans also contain several phenolic compounds with antioxidant properties [such as caffeic acid and chlorogenic acid (Daglia \textit{et al.}, 2000; Anese and Nicoli, 2003)] and diterpenes (such as cafestol and kahweol) with anticarcinogenic activity (Cavin \textit{et al.}, 2002).

Liver cancer
Several data on a potentially favourable effect of coffee on liver function and liver diseases have accumulated over the last two decades. These span from liver enzymes, to cirrhosis and to hepatocellular carcinoma (HCC), and therefore constitute a continuous spectrum not only of epidemiological data, but also of biological and clinical evidence.

Coffee consumption, in fact, has been inversely related to \(\gamma\)-glutamyltransferase and alanine aminotransferase activity in studies from Norway, Italy, Finland, France, Japan and the United States. Such inverse relationships were particularly strong in high-risk individuals, including heavy alcohol drinkers (La Vecchia, 2005). Coffee drinking has also been inversely related to the risk of cirrhosis in studies from North America and Europe (La Vecchia, 2005).

Cirrhosis is a major correlate of HCC, and the relationship between coffee drinking and the risk of primary liver cancer has been examined in at least six studies. An Italian case–control study based on 151 cases of HCC reported a multivariate relative risk (RR) of 0.78 for drinkers of three or more cups of coffee per day,
compared with noncoffee drinkers (La Vecchia et al., 1989). In a Greek case–control study (Kuper et al., 2000), including 333 cases, the age and sex-adjusted RR was 0.7 for drinkers of ≥ 20 cups of coffee per week compared with that of nondrinkers. The combined analysis of the two studies gave a RR of 0.7 [95% confidence interval (CI): 0.5–1.0] for three or more cups per day (Gallus et al., 2002).

In another Italian case–control study of 250 cases (Gelati et al., 2005), compared with noncoffee drinkers, the RRs were 0.8 for drinkers of one to two cups per day, 0.4 for those of three to four cups and 0.3 for drinkers of five or more cups per day.

In a prospective study of 334 cases from Japan, individuals who consumed coffee on a daily basis had lower HCC risk than those who almost never drank coffee (RR = 0.49, 95% CI: 0.36–0.66). The risk decreased with the amount of coffee consumed (compared with nondrinkers, the RR for one to two cups per day = 0.52; for three to four cups per day = 0.48; for five or more cups per day = 0.24) (Inoue et al., 2005). A pooled analysis of two other Japanese studies including a total of 117 cases gave a RR of 0.58 (95% CI: 0.36–0.96) for drinkers of one or more cups per day compared with never drinkers (Shimazu et al., 2005). In another cohort investigation, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), including 258 cases, the multivariate RR was 0.83 (95% CI: 0.54–1.25) for occasional and 0.50 (95% CI: 0.31–0.79) for regular (one or more cups per day) coffee drinkers. The inverse relationship was similar in men and women, and in those without and with a history of liver disease (Kurozawa et al., 2005).

The favourable effect of coffee consumption on HCC may be due to its inverse relationship with cirrhosis, but allowance for clinical history of cirrhosis did not totally account for the inverse association. Given its effects on liver enzymes and cirrhosis, and the weight of epidemiological evidence, coffee appears therefore to have a real effect in reducing the risk of HCC, as suggested also by data on rodents (Tanaka et al., 1990). Various components of coffee have been related to such a favourable effect, including caffeine, coffee oils kahweol or cafestol, and antioxidant substances from coffee beans, but no definite evidence is available.

Bladder cancer

The IARC Monograph 51 evaluated 22 studies published before 1990 (IARC, 1991). Of these, 16 found moderately increased RRs of bladder cancer in coffee drinkers compared with nondrinkers; in seven of these, the association was significant and in three there was also evidence of a dose–risk relation. No relation was observed in six other studies. As smoking is an important risk factor for bladder cancer, lifelong nonsmokers were also considered separately to obtain information on the potential distorting effect of tobacco. Some relation with coffee was still observed, although it was less clear, possibly because of smaller numbers.

After the publication of the IARC Monograph, at least four cohort (Mills et al., 1991; Chyou et al., 1993; Stensvold and Jacobsen, 1994; Zeegers et al., 2001a) and 13 case–control studies (Clavel and Cordier, 1991; Nomura et al., 1991; D’Avanzo et al., 1992; Kunze et al., 1992; Escolar Pujolar et al., 1993; McGeehin et al., 1993; Vena et al., 1993; Monas et al., 1994; Brown et al., 1995; Bruemmer et al., 1997; Donato et al., 1997; Pohlmann, 1999; Geoffroy-Perez and Cordier, 2001) provided information on coffee and bladder cancer.

Three cohort studies found moderately increased risk of bladder cancer in coffee drinkers, in the absence of a dose–risk relationship. In the Californian Seventh-Day Adventists’ cohort, which included 52 cases, the smoking-adjusted RR was 1.99 (nonsignificant) for two or more cups of coffee per day compared with noncoffee drinkers, with a stronger relation in never smokers (Mills et al., 1991). In a cohort of Japanese-Americans living in Hawaii (including 92 cases), a high consumption of coffee nonsignificantly increased risk (Chyou et al., 1993), and, in a Norwegian cohort of 43 000 men and women, the RR for drinkers of seven or more cups of coffee per day was 1.5 in men (based on 40 cases) and 2.4 in women (based on 13 cases) (Stensvold and Jacobsen, 1994). In the Netherlands cohort study based on 569 cases, the RR for an increment of one cup of coffee per day was 1.03 in men and 0.84 in women (Zeegers et al., 2001a).

In a pooled analysis of 10 European studies restricted to 564 nonsmokers, there was no excess risk in coffee drinkers (odds ratio: 1.0) (Sala et al., 2000). Another meta-analysis, which included three cohort and 34 case–control studies, estimated that coffee consumption increased urinary tract (mainly bladder) cancers risk by approximately 20%; the RR, adjusted for age, sex and smoking, was 1.18 (95% CI: 1.03–1.36) for coffee and 1.18 (95% CI: 0.99–1.40) for decaffeinated coffee (Zeegers et al., 2001b).

Thus, the large amount of epidemiological data on coffee and bladder cancer risk allows one to exclude a strong association. It is not clear whether the moderate association reported in many studies is causal. The major potential confounding factor is cigarette smoking, which is related to both coffee consumption and bladder cancer risk; however, misclassification of smoking status or residual confounding are unlikely to completely explain the association. Other possible sources of residual...
confounding include diet or occupational exposure to bladder carcinogens, although the similar associations found in men and women suggest that occupation is unlikely to be a major confounder.

Pancreatic cancer
In the early 1980s, a case–control study from North America showed a direct association between coffee consumption and pancreatic cancer risk (MacMahon et al., 1981). Overall, 21 case–control studies on pancreatic cancer relationship were reviewed in the IARC Monograph 51 (IARC, 1991). Among them, 10 found moderate positive associations, which were weaker after allowance for smoking, and the remaining studies found no association.

The results of at least seven cohort studies have been published after the IARC Monograph 51 (IARC, 1991). No association emerged in a cohort of 17,633 American men (RR 0.9 for intake of seven or more cups per day, based on 56 cases) (Zheng et al., 1993); in a Norwegian cohort of 43,000 men and women (RR 0.6 in men for seven or more cups per day and 1.2 in women for more than six cups per day, based on 26 and 13 cases, respectively) (Stensvold and Jacobsen, 1994); in a cohort of nearly 14,000 residents of a retirement community from the United States (RR 0.88 for four or more cups per day; based on 65 cases) (Shibata et al., 1994); in the Health Professionals’ Follow-up Study (RR 0.37 for more than three cups of coffee per day and 0.99 for decaffeinated coffee, based on 130 cases) (Michaud et al., 2001); in the Nurses’ Health Study (RR 0.88 for more than three cups of coffee per day and 0.85 for decaffeinated coffee, based on 158 cases) (Michaud et al., 2001) and in the Japan collaborative cohort study for evaluation of cancer risk, where no trend in risk with number of cups emerged (Lin et al., 2002). Conversely, in the Iowa Women’s Health Study cohort on nearly 34,000 women and including 66 incident cases of pancreatic cancer, the RR was 2.15 for drinkers of more than 17.5 cups of coffee per week. The association was not significant in never smokers (Harnack et al., 1997).

Most case–control studies published after the IARC monograph found no significant association between coffee and pancreatic cancer risk (Tavani and La Vecchia, 2000, 2004), and one study found an inverse association (Bueno de Mesquita et al., 1992).

It is possible therefore that any relationship between coffee and pancreatic cancer is not causal but explainable through selection or recall bias, residual confounding with cigarette smoking (the major recognized risk factor for pancreatic cancer) or other sources of confounding. In any case, a strong association between coffee and pancreatic cancer can now be excluded.

Other cancers
The IARC Monograph 51 included data on coffee and gastric cancer from five case–control studies (IARC, 1991). No evidence of association was found in any of them. More recently, a Norwegian cohort study observed no association between coffee intake and gastric cancer risk (RR 0.5 in men and in women, not significant, based on 78 cases) (Stensvold and Jacobsen, 1994). A cohort study of Japanese residents in Hawaii, including 108 cases, found that men who drank one cup of coffee per day had an elevated risk of gastric cancer compared with noncoffee drinkers (RR = 2.5) (Galanis et al., 1998). No association between coffee drinking and gastric cancer risk was found in four case–control studies: a Spanish study based on 354 cases (Agudo et al., 1992), a Swedish study based on 338 cases (Hansson et al., 1993), a Japanese one based on 893 cases (Inoue et al., 1998) and a Polish study based on 464 cases (Chow et al., 1999). Thus, it is now clear that coffee is unlikely to have any major effect on gastric carcinogenesis.

Six studies providing data on cancers of the oral cavity, pharynx and oesophagus were considered in the IARC monograph (IARC, 1991). No evidence of association with coffee consumption was found in any of them. Since then, at least one cohort (Stensvold and Jacobsen, 1994) and five case–control studies (La Vecchia et al., 1990; Franceschi et al., 1991; Pintos et al., 1994; Bundgaard et al., 1995; Castellsague et al., 2000) found no association for these cancers, whereas a case–control study based on 749 cases of oral and pharyngeal cancer and 395 of oesophageal cancer from Italy (Tavani et al., 2003) found that risk approximately halved in the highest quintile compared with the lowest quintile of coffee intake.

With relevance to breast cancer, of the seven case–control studies considered in the IARC monograph (IARC, 1991), none found an association with coffee consumption (IARC, 1991). More recently, three cohort and four case–control studies, including an Italian one with nearly 6000 cases (Tavani et al., 1998), found no association (Tavani and La Vecchia, 2000, 2004).

Likewise, no consistent relationship was observed between coffee, ovarian, laryngeal, lung, prostate, cervical, endometrial and thyroid cancers, Hodgkin’s and non-Hodgkin lymphomas, sarcoma, multiple myeloma and skin melanoma (Tavani et al., 2003; Naldi et al., 2004; Tavani and La Vecchia, 2004).

Conclusions
The large amount of epidemiological data on bladder cancer allows one to exclude a strong association with coffee intake, and the lack of dose–response relation does not support causality. Likewise, an association between coffee and pancreatic cancer risk can now be excluded.
For colorectal cancer, most case-control but not cohort studies reported an inverse association. Epidemiological data indicate an inverse relation between coffee, liver and probably oral and oesophageal cancers.

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References


