We reviewed available evidence on coffee drinking and the risk of all cancers and selected cancers updated to May 2016. Coffee consumption is not associated with overall cancer risk. A meta-analysis reported a pooled relative risk (RR) for an increment of 1 cup of coffee/day of 1.00 [95% confidence interval (CI): 0.99–1.01] for all cancers. Coffee drinking is associated with a reduced risk of liver cancer. A meta-analysis of cohort studies found an RR for an increment of consumption of 1 cup/day of 0.85 (95% CI: 0.81–0.90) for liver cancer and a favorable effect on liver enzymes and cirrhosis. Another meta-analysis showed an inverse relation for endometrial cancer risk, with an RR of 0.92 (95% CI: 0.88–0.96) for an increment of 1 cup/day. A possible decreased risk was found in some studies for oral/pharyngeal cancer and for advanced prostate cancer. Although data are mixed, overall, there seems to be some favorable effect of coffee drinking on colorectal cancer in case-control studies, in the absence of a consistent relation in cohort studies. For bladder cancer, the results are not consistent; however, any possible direct association is not dose and duration related, and might depend on a residual confounding effect of smoking. A few studies suggest an increased risk of childhood leukemia after maternal coffee drinking during pregnancy, but data are limited and inconsistent. Although the results of studies are mixed, the overall evidence suggests no association of coffee intake with cancers of the stomach, pancreas, lung, breast, ovary, and prostate overall. Data are limited, with RR close to unity for other neoplasms, including those of the esophagus, small intestine, gallbladder and biliary tract, skin, kidney, brain, thyroid, as well as for soft tissue sarcoma and lymphohematopoietic cancer. European Journal of Cancer Prevention 26:424–432 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: cancer, coffee, incidence, mortality, review, risk

*Department of Clinical Sciences and Community Health, University of Milan and *Department of Epidemiology, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri*, Milan, Italy

Correspondence to Alessandra Tavani, SciD, Department of Epidemiology, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri*, Via G. La Masa 19, Milan 20156, Italy

Tel: + 39 023 901 4722; fax: + 39 023 320 0231; e-mail: alessandra.tavani@marionegri.it

Received 20 December 2016 Accepted 30 December 2016

European Journal of Cancer Prevention 2017, 26:424–432

Coffee and cancer risk: a summary overview

Gianfranco Alicandro, Alessandra Tavani and Carlo La Vecchia

Introduction

Coffee is one of the most widely consumed beverages in the world. It contains many bioactive substances and it is a major source of antioxidants from the beans (Pulido et al., 2003) – including polyphenols (such as chlorogenic, ferulic, coumaric, and caffeic acids), diterpenes (cafestol and kahweol) – and antioxidants produced during the roasting process, including melanoids (Borrelli et al., 2002; Vitaglione et al., 2012). The amount and type of compounds depend on the variety of the coffee blend (Arabica or Robusta), the roasting degree, the brewing method, and the serving size (Vitaglione et al., 2012).

Several epidemiological studies have evaluated the relationship between coffee consumption and cancer incidence or mortality. Most studies focused on selected organs of the gastrointestinal system, bladder, endometrium, ovary, breast, lung, and prostate, whereas a limited number of studies examined several other sites. In addition, a few studies evaluated the possible relationship between coffee consumption during pregnancy and the risk of childhood leukemia.

The results of these studies have been reviewed, and their key message has been analyzed and summarized in the present review, mainly on the basis of data of meta-analyses and collaborative reanalyses. We used the term relative risk (RR) for both cohort and case-control studies, where it is estimated by the odds ratio.

Results

Pooled estimates of RR by cancer site and level of coffee consumption derived from meta-analyses and collaborative reanalyses are shown in Table 1. The results of dose–risk analyses showing the RR for an increment of consumption of 1 cup/day are presented in Fig. 1.

Overall cancers

The relationship between coffee consumption and mortality from all cancers was evaluated in a meta-analysis (Malerba et al., 2013a) including 10 cohort studies. No significant association was reported between coffee consumption and mortality from cancer overall, with an RR of 1.03 [95% confidence interval (CI): 0.97–1.10] for the highest level of coffee drinking compared with nondrinkers or occasional drinkers (≤1 cup/day). The dose–risk analysis for the increment of 1 cup/day yielded an RR of 1.00 (95% CI: 0.99–1.01).

A meta-analysis (Crippa et al., 2014) based on nine cohorts, and aimed to verify a dose–risk association between coffee consumption and total mortality and mortality for wide groups of diseases, observed no
A cohort study (Hashibe et al., 2015) published after the above-mentioned meta-analyses evaluated cancer incidence in 97,334 patients enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) between 1992 and 2001 and followed up until 2011, including a total of 10,399 cancer cases. In this study, drinkers of at least 2 cups of coffee/day compared with those who consumed less than 1 cup/day had an RR of 1.00 (95% CI: 0.96–1.05). The RR for an increment of consumption of 1 cup/day was also 1.00 (95% CI: 0.99–1.01).

A slight reduction in the overall cancer incidence was reported in a recent Norwegian study (Lukic et al., 2016) on the basis of a cohort of 91,767 women with an average follow-up of 13 years. In that study, the mortality rate for all cancers was 9% lower in women who drank 3–7 cups of coffee/day compared with nondrinkers or occasional drinkers (<1 cup/day) (RR: 0.91, 95% CI: 0.86–0.97).

### Oral and pharyngeal cancers

A meta-analysis (Turati et al., 2011), which included nine studies (eight case–control studies and one cohort study), for a total of 2633 cases, reported an RR of 0.64 (95% CI: 0.51–0.80) for the highest compared with the lowest category of coffee consumption. Another meta-analysis (Li et al., 2016) including 11 case–control and four cohort studies for a total of more than 5000 cases of oral and pharyngeal cancer, confirmed the 34–40% lower risk of cancer, consistent in cohort and case–control studies.

In a collaborative reanalysis (Galeone et al., 2010a) of nine case–control studies including 3915 cancers of the oral cavity and pharynx and 9028 controls, carried out by the International Head and Neck Cancer Epidemiology Consortium (INHANCE), the RR was 0.61 (95% CI: 0.49–0.77) in drinkers of more than 4 cups of coffee/day compared with noncoffee drinkers.
Studies in cellular and animal models showed that the antioxidant effects of coffee may explain the risk reduction of oral cavity and pharynx cancers observed in coffee drinkers (Cavin et al., 2002; Huber et al., 2008). In particular, the antioxidant activity of coffee may prevent oxidative damage induced by smoking and alcohol, the main risk factors for these neoplasms. Accordingly, in the INHANCE study (Galeone et al., 2010a), the RR for drinkers of at least 4 cups of coffee/day was 0.72 (95% CI: 0.31–1.64) in never smokers and 0.51 (95% CI: 0.35–0.76) in heavy smokers.

Thus, there is evidence from several studies that coffee consumption is associated with a reduced risk of cancers of the oral cavity and pharynx.

**Stomach cancer**

At least 12 cohort studies and 14 case-control studies considered the relation of coffee drinking with stomach cancer, showing inconsistent results, but overall no increased risk. A recent meta-analysis (Li et al., 2015) of questionable methodological quality pooled the results of 13 cohort studies for a total of almost 3500 cases and found an RR of 1.06 (95% CI: 0.84–1.33) for the highest versus the lowest intake for the eight studies adjusting for smoking.

Thus, it is likely that coffee drinking is not related to gastric cancer risk, and that the slight increased risk found in some prospective studies depends on residual confounding by smoking.

**Colorectal cancer**

A meta-analysis of 24 case-control studies (Galeone et al., 2010b), which included 14 846 cases of colorectal cancers, reported an RR of 0.83 (95% CI: 0.73–0.95) in coffee drinkers and of 0.70 (95% CI: 0.60–0.81) in heavy drinkers compared with nondrinkers or occasional drinkers. In addition, the RR for an increase of coffee consumption of 1 cup/day was 0.94 (95% CI: 0.91–0.98). The inverse association was stronger for colon cancer (RR: 0.75, 95% CI: 0.64–0.88, for heavy drinkers compared with nondrinkers) than for rectal cancer (corresponding RR of 0.87, 95% CI: 0.75–1.00).

A case-control study (Schmit et al., 2016) carried out in Israel after the above-mentioned meta-analysis (Galeone et al., 2010b), including 5145 cases and 4097 controls, reported an RR of 0.74 (95% CI: 0.64–0.86) in coffee
drinkers compared with nondrinkers. An inverse association was also found in decaffeinated coffee drinkers, with an RR of 0.82 (95% CI: 0.68–0.99).

Therefore, case–control studies indicate that coffee consumption is associated with a reduced risk of colorectal cancer. The increased intestinal motility, induced partly by melanoindins (Boekema et al., 1999; Vitaglione et al., 2012), which may reduce exposure to carcinogens, is among the main biological mechanisms potentially involved in such a favorable effect. Moreover, polyphenols, diterpenes, and melanoindins may locally reduce oxidative damage induced by inflammation; one of the possible mechanisms of colorectal carcinogenesis (Sciril et al., 2003). Other potential beneficial effects on the large bowel of polyphenols in coffee include the reduction of procarcinogenic bile acid deoxycholic (Bernstein et al., 2003). Other potential beneficial effects on the possible mechanisms of colorectal carcinogenesis (Seril et al., 2015). However, cohort studies show no consistent association. A pooled analysis (Zhang et al., 2010), which combined the results of 13 cohort studies including 5604 cases, reported no relationship between coffee consumption and colon cancer, with an RR of 1.07 (95% CI: 0.89–1.30) for patients who consumed at least 6 cups/day compared with nondrinkers. Cohort studies published later reported conflicting results. In a Swedish cohort of 64603 individuals (Nilsson et al., 2010) followed up for 15 years and including 321 colorectal cancer cases, there was no significant association between coffee consumption and the risk of colorectal cancer, with an RR of 1.43 (95% CI: 0.86–2.38) for those who drank coffee at least four times a day compared with those who drank coffee less than once a day. In a cohort of 60041 Finns (Bidet et al., 2010) followed up on average for 18 years and that included 538 cases of colorectal cancer, there was no difference in the incidence of colorectal cancer for coffee drinkers of 1–10 cups/day compared with nondrinkers, with an RR of 1.03 (95% CI: 0.58–1.83) for nondrinkers versus drinkers of at least 10 cups/day. A Japanese study (Yamada et al., 2014), carried out on 58221 individuals and including 1001 cases of colorectal cancer, found an increase in risk for consumers of at least 4 cups of coffee/day compared with patients drinking less than 1 cup/day. The proportion of heavy coffee drinkers was, however, low and the association was significant only in men. Another cohort study of 307 Japanese patients (Nakamura et al., 2016) who underwent endoscopy to remove a colorectal tumor reported a lower risk of tumor recurrence over the subsequent 4 years in patients who consumed more than 3 cups of coffee/day compared with nondrinkers (RR: 0.21, 95% CI: 0.06–0.74). The European Prospective Investigation into Cancer and Nutrition (EPIC) study (Dik et al., 2014), based on more than 4200 cases, found a null association of coffee intake with colorectal cancer risk (RR: 1.06, 95% CI: 0.95–1.18), with a borderline increased risk for rectal cancer (RR: 1.20, 95% CI: 1.00–1.44). However, two prospective studies found an inverse association of coffee intake with colorectal cancer. In a cohort of 489706 elderly Americans (the NIH-AARP Diet and Health Study) (Sinha et al., 2012), including 6730 colorectal cancer cases, drinkers of 4–5 cups of coffee/day compared with nondrinkers had an RR of 0.85 (95% CI: 0.75–0.96) and those who consumed six or more cups had an RR of 0.74 (95% CI: 0.61–0.89). The decrease in risk was greater for proximal colon cancer (RR: 0.62, 95% CI: 0.49–0.81). In a Norwegian cohort study (Lukic et al., 2016) of 91767 women and overall 1266 colorectal cancer cases, the RR was 0.83 (95% CI: 0.70–0.98) in women who drank coffee more than 3–7 cups/day of coffee compared with nondrinkers or occasional coffee drinkers (<1 cup/day). In all these studies, the results were adjusted for smoking (La Vecchia et al., 1992).

Thus, although coffee has shown a favorable effect in case–control studies, the inconsistent association found in cohort studies does not allow conclusions on the relation of coffee intake and colorectal cancer risk, although an increased risk can be excluded.

**Liver cancer**

A meta-analysis (Bravi et al., 2013) of eight cohort and eight case–control studies, including a total of 3153 cases of hepatocellular carcinoma (HCC), reported an RR of 0.60 (95% CI: 0.50–0.71) in coffee drinkers compared with nondrinkers, with similar results in case–control (RR: 0.56, 95% CI: 0.42–0.75) and cohort studies (RR: 0.64, 95% CI: 0.52–0.78). In addition, a risk reduction was observed in patients either at low risk of HCC or at high risk (chronic carriers of hepatitis B and C markers, and heavy alcohol drinkers), and in studies from Europe, North America, and Asia. Time-trend analysis of RRs obtained from studies carried out since 2000 showed a consistency of risk reduction over time.

A meta-analysis of 12 cohort studies (Bravi et al., 2016), including 3414 cases of HCC, reported an RR of 0.66 (95% CI: 0.55–0.78) in habitual coffee drinkers compared with nondrinkers or occasional drinkers. The RR was 0.78 (95% CI: 0.66–0.91) in patients reporting moderate coffee consumption and 0.50 (95% CI: 0.43–0.58) in patients reporting high consumption. The same meta-analysis also considered five studies on cirrhosis, a condition associated with the pathogenesis of HCC. On the basis of a total of more than 1400 cases, the RRs of cirrhosis were 0.62 (95% CI: 0.47–0.82) in habitual coffee drinkers compared with nondrinkers or occasional drinkers, 0.72 (95% CI: 0.59–0.88) in moderate drinkers, and 0.35 (95% CI: 0.22–0.56) in heavy drinkers.

Coffee drinking has also a favorable effect on liver enzymes and other liver conditions. It reduces levels of transaminases and γ-glutamyl transpeptidase (indicators of hepatic disorders) (Ruhl and Everhart, 2005), the
degree of fibrosis in patients with chronic liver disease (Modi et al., 2010), and steatosis in patients with non-alcoholic steatohepatitis (Saab et al., 2014). Coffee increases the response to antiviral therapy in patients with hepatitis C (Freedman et al., 2011) and prevents liver fibrotic degeneration (Liu et al., 2015). This may be partly attributable to a reduction of oxidative stress in hepatocytes induced by chlorogenic acid (Shi et al., 2016).

Furthermore, data from experimental models and human studies showed beneficial effects of coffee on glucose metabolism and the risk of diabetes, which, in turn, is associated with the risk of HCC (La Vecchia et al., 1997; van Dam and Hu, 2012; Bosetti et al., 2014). Coffee modulates glucose metabolism by increasing insulin sensitivity (Shearer et al., 2003), slowing intestinal glucose absorption (Johnston et al., 2003), and reducing postprandial glycemic response (Jokura et al., 2015).

Thus, studies evaluating the relationship between coffee consumption and the risk of primary liver cancer, particularly HCC, reported a consistent risk reduction in coffee drinkers and a favorable role of coffee in some liver functions.

**Pancreatic cancer**

A study carried out at Harvard (MacMahon et al., 1981) suggested that coffee might be associated with pancreatic cancer, one of the most lethal cancers. However, studies published afterward found mixed results, mainly showing no association.

A meta-analysis (Turati et al., 2012), which included the results of 37 case–control studies and 17 cohort studies and overall 10,594 pancreatic cancer cases, found an RR of 1.13 (95% CI: 0.99–1.29) for the highest compared with the lowest coffee intake. The smoking-adjusted RR became 1.08 (95% CI: 0.94–1.25) when only studies adjusted for smoking were included in the meta-analysis. The RRs were consistent for the 22 case–control (RR: 1.10, 95% CI: 0.92–1.31) and for the 15 cohort studies (RR: 1.04, 95% CI: 0.80–1.36).

Other cohort studies published after the meta-analysis and carefully adjusted for smoking confirmed the null relationship between coffee consumption and pancreatic cancer. Particularly, the EPIC study (Bhoo-Pathy et al., 2013), including 865 cases, found an RR of 1.03 (95% CI: 0.83–1.27) for the highest compared with the lowest quartile of coffee consumption, with a similar estimate for decaffeinated coffee (RR: 1.12, 95% CI: 0.97–1.26), and the NIH-AARP Diet and Health Study, including 1541 cases, reported an RR of 1.00 (95% CI: 0.79–1.25) for 4–5 cups/day and 1.24 (95% CI: 0.93–1.65) for at least 6 cups/day (Guertin et al., 2015).

Thus, the evidence, on the basis of several studies and large number of cases, indicates that there is no relationship between coffee drinking and pancreatic cancer risk once smoking confounding is adequately taken into account (Klcoff et al., 2016).

**Lung cancer**

A meta-analysis of eight prospective cohorts and 13 case–control studies (Galarraga and Boffetta, 2016), including nearly 20,000 cases of lung cancer, found an RR of 1.09 (95% CI: 1.00–1.19) for drinkers versus never drinkers. However, the corresponding value among nonsmokers was 0.92 (95% CI: 0.75–1.10). The pooled RR for 1 cup/day increase was 1.04 (95% CI: 1.03–1.05) when unadjusted for smoking and 0.95 (95% CI: 0.83–1.09) among nonsmokers. The slightly increased risk found in cohort studies after adjustment for smoking (RR: 1.14, 95% CI: 1.01–1.28, Table 1), but not in case–control studies, may depend on residual confounding by smoking.

Thus, there is convincing evidence of a lack of association between coffee intake and lung cancer risk. The increased risk observed in some studies is likely due to residual confounding by smoking.

**Breast cancer**

More than 20 cohort and 20 case–control studies considered the relation between coffee intake and breast cancer risk. Most studies found no relation and among case–control studies, a few found a slight inverse association. The most recent meta-analysis based on 37 studies and about 59,000 cases (Jiang et al., 2013) found an overall RR of 0.97 (95% CI: 0.93–1.00) for the highest coffee consumption level compared with the lowest one, and no heterogeneity by menopausal status.

Thus, the overall evidence shows a null association on the basis of a large number of data.

**Endometrial cancer**

A meta-analysis of seven case–control studies and two cohort studies (Bravi et al., 2009), which included a total of 2610 endometrial cancer cases, reported an RR of 0.80 (95% CI: 0.68–0.94) among coffee drinkers compared with nondrinkers, with evidence of an inverse relation with exposure (RR: 0.93, 95% CI: 0.89–0.97 for an increment of 1 cup/day, considering both case-control and cohort studies).

Another meta-analysis (Je and Giovannucci, 2012), including six cohort (3144 cases) and 10 case–control studies (3484 cases), found pooled RRs for the study-specific highest versus the study-specific lowest drinking of 0.71 (95% CI: 0.62–0.81) on the basis of all studies, 0.70 (95% CI: 0.61–0.80) for the six cohort studies, and 0.69 (95% CI: 0.55–0.87) for the 10 case–control studies. The inverse association was similar in studies carried out in Europe (RR: 0.79, 95% CI: 0.63–0.99, based on eight studies) or North America (RR: 0.69, 95% CI: 0.60–0.79, based on five studies). The pooled RRs for an increment
of 1 cup/day were 0.92 (95% CI: 0.90–0.95, based on 14 studies), 0.94 (95% CI: 0.90–0.97) for cohort studies, and 0.90 (95% CI: 0.86–0.95) for case–control studies.

The most recent meta-analysis (Zhou et al., 2015) reported the results of 13 cohort studies including 10,100 cases. The RR was 0.80 (95% CI: 0.74–0.86) for the highest versus the lowest coffee intake and 0.95 (95% CI: 0.93–0.97) for an increment of 1 cup/day. The inverse association for the highest versus the lowest coffee intake was similar for regular (RR: 0.66, 95% CI: 0.52–0.85) and decaffeinated coffee (RR: 0.77, 95% CI: 0.63–0.94), and apparently stronger in women with a body mass index higher than 25 kg/m² and in those who never used hormone therapies. Similar results were reported in a cohort study (Hashibe et al., 2015) published after the above-mentioned meta-analyses and based on the PLCO cohort, which included 257 endometrial cancer cases. It reported an RR of 0.69 (95% CI: 0.52–0.91) in women who drank at least 2 cups of coffee/day compared with nondrinkers or occasional coffee drinkers.

Thus, the overall evidence indicates that coffee consumption is associated with a reduced risk of endometrial cancer. Besides the general antioxidant properties of coffee, a favorable role of coffee in endometrial cancerogenesis might be mediated through the reduction by coffee drinking of major risk factors of endometrial cancer, such as elevated body mass index and diabetes (Rosato et al., 2011; De Pergola and Silvestris, 2013; Lees and Leath, 2015).

**Ovarian cancer**

Although a slightly increased risk was observed for the relation between coffee drinking and ovarian cancer risk in some studies, these were generally the oldest and less controlled for confounding factors. A dose-related increased risk was found only in one old study (La Vecchia et al., 1984) in the absence of the relation with duration of the habit. However, most recent cohort and case–control studies found no association. A meta-analysis (Steevens et al., 2007) that considered five cohorts and 11 case–control studies found a pooled RR of 1.18 (95% CI: 0.97–1.44) for the highest coffee intake compared with the lowest, consistent for cohort and case–control studies. A more recent meta-analysis (Braem et al., 2012), based on seven cohort studies and including a total of 3,236 cases of ovarian cancer, found a pooled RR of 1.13 (95% CI: 0.89–1.43) for the highest versus the lowest coffee intake, and an RR of 1.02 (95% CI: 0.99–1.05) for an increment of 1 cup/day.

Thus, overall there is enough information, based on 11 cohorts, 19 case–control studies, and one case–control study nested in a cohort, to suggest a lack of relation between coffee intake and ovarian cancer risk.

**Prostate cancer**

More than 20 cohort and case–control studies have investigated the relation between coffee intake and prostate cancer risk, and they overall reported no relation. A meta-analysis (Discacciati et al., 2014) of five cohort and three case–control studies, which reported information on prostate cancer aggressiveness, found an overall RR for the increment of 3 cups/day of 0.89 (95% CI: 0.82–0.97) for fatal prostate cancer, whereas the RR for less aggressive prostate cancer was closer to unity.

Thus, there is clear evidence to support a lack of association of coffee intake with prostate cancer risk overall, with the suggestion of a possible slight inverse association for aggressive disease.

**Bladder cancer**

Several studies published in the 1970s and the 1980s (IARC, 1991) suggested an increased risk of bladder cancer in men, but not in women drinking coffee, in the absence, however, of a dose-dependent and duration-dependent relationship. This suggested a residual confounding effect of smoking, that, especially in the past, was correlated positively with coffee drinking (La Vecchia et al., 1992).

The association has now been considered in nearly 60 cohort and case–control studies conducted worldwide. The results of either cohort or case–control studies are mixed, with studies reporting direct, inverse, or null associations. Overall, the direct association was more often observed among men than women, which may suggest a residual confounding by smoking and occupational exposure, the major risk factors for bladder cancer. The information on never smokers comes from only a few studies, is based on a low number of cases, and is not conclusive, showing mixed results. The large majority of studies showing a direct association report no dose relation and results on time-related factors are very scarce.

A meta-analysis (Wu et al., 2015) of 34 case–control and six cohort studies, including 16,172 cases, reported an increased risk in coffee drinkers, significant in men (RR: 1.31, 95% CI: 1.08–1.59), but not in women (RR: 1.30, 95% CI: 0.87–1.96). The excess risk was greater in non-smokers (RR: 1.72, 95% CI: 1.25–2.35) than in smokers (RR: 1.24, 95% CI: 0.91–1.70). However, the separate analysis by study design showed that the association between coffee consumption and the risk of bladder cancer was observed in case–control, but not in cohort studies. Moreover, this meta-analysis presented some methodological limitations and did not include all the available data. The most recent multicentric case–control study (Turati et al., 2015), carried out in Italy on 690 cases of bladder cancer found an increased risk of bladder cancer with coffee drinking, which disappeared after careful adjustment for smoking. In the fully adjusted model, the RRs were 1.27 (95% CI: 0.84–1.94) for at least...
4 cups/day compared with nondrinkers or occasional drinkers (< 1 cup/day), and 1.03 (95% CI: 0.96–1.11) for an increment of intake of 1 cup/day. There was also no duration–risk relationship, with an RR of 1.03 (95% CI: 0.94–1.12) for a 10-year increase.

Thus, overall, the results are inconsistent and most likely the modest direct association observed in a few studies does not reflect a causal association, but can be attributed to a residual confounding of tobacco or other unidentified variables (IARC, 1991; La Vecchia and Tavani, 2007). This is further supported by the lack of evidence of a dose–risk and duration–risk relationship.

**Childhood leukemia after coffee consumption in pregnancy**

All studies considering the relation of childhood leukemia after coffee drinking during pregnancy have a case–control design and have been carried out in very few countries and by a limited number of research groups. Two meta-analyses (Cheng et al., 2014; Thomopoulos et al., 2015) reported some associations between coffee drinking during pregnancy and the risk of childhood leukemia. The most recent one (Thomopoulos et al., 2015) included nine case–control studies considering coffee, comprising a total of almost 3000 cases, and found pooled RRs for the highest versus the lowest maternal coffee drinking of 1.57 (95% CI: 1.16–2.11) for all leukemia, 1.43 (95% CI: 1.22–1.68) for acute lymphoblastic leukemia, and 1.81 (95% CI: 0.93–3.53) for acute myeloid leukemia.

The potential mechanism beyond the increasing risk of childhood leukemia may involve the inhibitory effect of caffeine on type II topoisomerases (Shin et al., 1990).

However, the results are generally inconsistent (Milne et al., 2011; Orsi et al., 2015). In a French nation-wide population case–control study (Orsi et al., 2015) of 747 cases of acute childhood leukemia, there was no association between maternal coffee drinking and overall childhood acute leukemia (RR: 0.90, 95% CI: 0.80–1.10), although high coffee consumption (>2 cups/day) was associated with acute lymphoblastic leukemia (RR: 1.30, 95% CI: 1.00–1.80). In an Australian case–control study (Milne et al., 2011) of 337 mothers with children with acute lymphoblastic leukemia, the overall RR was 0.89 (95% CI: 0.61–1.30) for coffee drinking versus nondrinking. However, the RR was significantly above the unit for childhood acute lymphoblastic leukemia with chromosomal translocations in nonsmoking mothers drinking more than 2 cups of coffee/day (RR: 2.55, 95% CI: 1.04–6.22).

In conclusion, the overall evidence is limited to case–control studies carried out by few research groups and inconsistent, with most studies showing a direct association between maternal coffee drinking during pregnancy and selected type of childhood leukemias. Thus, the evidence is still inconclusive.

**Other cancers**

The evidence of a potential relationship between coffee consumption and other cancers derives from a limited number of studies. In the INHANCE study (Galeone et al., 2010a), a collaborative reanalysis of case–control studies that included 1224 cases of laryngeal cancer and 7239 controls, there was no relationship between coffee consumption and laryngeal cancer, with an RR of 0.96 (95% CI: 0.64–1.45) for drinkers of more than 4 cups/day compared with nondrinkers.

Although based on very few studies and a very limited number of cases, no relation was found for cancers of the esophagus (Turati et al., 2011; Zamora-Ros et al., 2014), small intestine, gallbladder and biliary tract, skin (including melanoma) (Naldi et al., 2004), kidney (Huang et al., 2014), brain (Malerba et al., 2013b) and thyroid (Mack et al., 2003; Michikawa et al., 2011), and for soft tissue sarcoma and lymphohematopoietic neoplasms in adults.

**Conclusion**

The data considered in this review indicate that coffee consumption is not associated with an increased risk of any cancer, including most common cancer sites, such as lung, breast, and prostate cancers. Coffee consumption is associated with a significantly reduced risk of cancer of the liver and endometrium and possibly of the oral cavity and pharynx. There is also an indication of an inverse association with colorectal cancer, mainly from case–control studies. This result is difficult to interpret also given the consistency between case–control and cohort studies for other neoplasms.

The slight direct relation between coffee drinking and the risk of bladder cancer found in some studies is unlikely to be causal as there is no evidence of dose–risk and duration–risk relationship. The evidence of a possible direct relation between coffee intake during pregnancy and the risk of childhood leukemia comes from few studies and needs to be further investigated.

**Acknowledgements**

This work was funded by the Italian Ministry of Health, the general Directorate of European and International Relations, and the Italian Foundation of Research of Cancer (FIRC).

**Conflicts of interest**

There are no conflicts of interest.

**References**
