3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) *Perinatal exposure/oral administration*

Mouse: In a study available only as a preliminary report, groups of 150 male and 150 female Swiss mice (CRL:COBS, CD-1) were mated at 12 weeks of age, and mothers of mice to be allocated to treated groups received 1% instant coffee in the diet throughout gestation and lactation. After weaning, offspring were housed singly and received diets containing 0, 1, 2.5 or 5% (w/w) instant coffee [origin unspecified] until the end of the experiment at 720 days. Increasing levels of coffee in the diet impaired the growth of animals, but better survival was noted in animals that received the higher doses: at 24 months, the survival rate in the group receiving 5% instant coffee was 50% compared with about 25% in controls. Tumours of the liver, lung and lymphatic tissue were observed frequently. The incidences of benign liver-cell tumours in males were 42/150 controls, 38/150 receiving 1%, 20/150 receiving 2.5% and 16/150 receiving 5%; those in females were 2/150 controls, 2/150 receiving 1%, 1/150 receiving 2.5% and 1/150 receiving 5%. Two hepatocellular carcinomas were observed in one male mouse treated with 1% instant coffee and in one male mouse treated with 2.5%, but none was seen in mice receiving 5% or in controls. [The Working Group noted that hepatocellular tumours are common in Swiss mice.] No increase in the incidence of benign or malignant lung tumours was observed. Lymphosarcomas (all histological types) were observed in male and female control and treated animals. In males, the incidence of these tumours decreased from 32% in controls to 12% in the high-dose group. In females, no clear dose-dependent decrease was observed, although the incidence of lymphosarcomas was 46% in controls and 18% in the high-dose group (Stalder *et al.*, 1984). [The Working Group noted that the reduced numbers of liver adenomas in males and of lymphosarcomas in animals of each sex in the higher-dose groups might have been due to impaired growth; these animals also had longer survival. Neither of these factors was taken into account in the analysis.]

Rat: Groups of 55 male and 55 female F_1 Sprague-Dawley rats, five to six weeks old, were given 25, 50 or 100% freshly brewed coffee as drinking fluid *ad libitum* for two years, at which time all survivors were killed. The animals were derived from females given 50% coffee as drinking fluid for about five weeks before mating and throughout gestation and lactation. Parent males, parent control

females and two groups of F_1 control rats received tap-water only. Ten rats of each sex per group were killed at one year and were submitted to blood sampling and necropsy. Lower mean body weights were observed in males that received 100% coffee, and significantly increased mortality was seen in females given 50 and 100% coffee. Two statistical methods were used to adjust the incidence data for survival differences: In the first, which assumes that tumours are non-fatal (i.e., incidental), a significant increase in the number of tumour-bearing males was seen in the low-dose group (relative risk (RR), 1.26; $p < 0.05$) but in no other group. In the second analysis, which assumes that tumours are lethal, increased numbers of tumour-bearing animals were seen among males in the low- and mid-dose groups (RR, 1.71, $p < 0.01$ and 1.43, $p < 0.05$, respectively) and among females in the mid- and high-dose groups (RR, 1.47, $p < 0.05$ and 1.45, $p < 0.05$, respectively) (Palm *et al.*, 1984). [The Working Group noted that the first statistical analysis was more appropriate, since the tumours were not the cause of death.]

(*b*) *Oral administration*

Rat: In a study reported as a letter to the Editor of *The Lancet*, 144 male and 144 female Sprague-Dawley rats, 21 days of age, were administered 5% instant coffee in the diet for two years, at which time the survivors were killed. An untreated control group of 41 males and 41 females was available. The urinary bladders of 94 male and 99 female treated and 29 male and 29 female control animals were examined histologically. No hyperplasia or tumour of the urinary bladder was observed (Zeitlin, 1972). [The Working Group noted the incomplete reporting of the study: no information on survival was given, and only the bladder was examined histologically.]

Groups of 40 male and 40 female Sprague-Dawley rats, weighing approximately 100 g, were fed diets containing 6% of 13 different samples of instant coffee; caffeine had been removed by extraction with dichloromethane from seven of the samples, but in three of these the caffeine had been put back. Treatment was for two years, at which time all survivors were killed. A control group of 40 males and 40 females was available. Survival was similar in all groups, although males given the decaffeinated coffees had slightly lower death rates, but the body weights of treated males were lower than those of controls. No increase in the incidence of any type of tumour was noted. In males in two of the six groups given instant coffee and in one of the three groups given decaffeinated coffee plus caffeine (see also the monograph on caffeine p. 310), the incidence of benign and malignant tumours was significantly lowered (all $p < 0.05$); in females, the decrease was not statistically significant. A logistic regression analysis showed that the level of caffeine significantly lowered the incidence of tumours (Würzner *et al.*, 1977a,b). [The Working Group noted that only one control group was used for the 13 treatment

groups and that the reduced numbers of tumours might have been due to impaired growth.]

(*c*) *Administration with known carcinogens*

The Working Group was aware of various other experiments (e.g., Mori & Hirono, 1977; Fujii *et al.*, 1980; Wattenberg & Lam, 1984; Nishikawa *et al.*, 1986) that were part of studies on the modifying effects of coffee on the activity of known carcinogens, which are not included here since their design was inadequate to reveal any effect of coffee on tumour production (short duration of exposure and/or limited numbers of animals).

(i) *Azaserine*

Rat: Groups of 40 male SPF Wistar rats, 19 days of age, were given a single intraperitoneal injection of azaserine, a pancreatic carcinogen, at 30 mg/kg bw and were then fed a low-fat diet, a high-fat diet or a high-fat diet plus coffee solution as the drinking fluid. The concentration of coffee was increased gradually from 25% during the first two weeks to 100% within four weeks, which was continued for the life span of the animals. Animals were autopsied 15 months after the end of azaserine treatment. The mean body weight of rats given the high-fat diet and coffee was significantly lower than that of the high-fat controls. The number of pancreatic tumours was significantly smaller in the group maintained on the high-fat diet and coffee than in the group on a high-fat diet only (44 adenomas *versus* 176 [$p < 0.001$] and 28 carcinomas *versus* 57 [$p < 0.05$]) (Woutersen *et al.*, 1989). [The Working Group noted that the decrease could have been due, at least partly, to the impaired growth of the animals.]

(ii) *7,12-Dimethylbenz[a]anthracene*

Rat: Groups of 40-41 female Sprague-Dawley rats, 53-55 days of age, were given a single intravenous injection of 7,12-dimethylbenz[*a*]anthracene (DMBA) at 20 mg/kg bw. Coffee (moderate or full strength) and decaffeinated (97% caffeine-free) coffee were given instead of drinking-water 29 days before up to three days after DMBA treatment; the experiment was terminated 12-18 weeks after DMBA treatment. Further groups of 80 or 84 female rats received a single dose of DMBA at 5 mg by gavage at 54 or 55 days of age and three days later were given coffee in the drinking fluid until 18-21 weeks after DMBA treatment. After DMBA treatment, all rats were palpated at two-week intervals for the presence of mammary tumours. When tumours reached 2 cm in diameter, they were excised surgically, and the rat was placed back in the experiment. In rats treated by intravenous administration of DMBA, moderate and high doses of coffee significantly ($p < 0.05$) reduced the number of mammary carcinomas per rat. Consumption of high

and moderate doses of decaffeinated coffee did not have this effect, but addition of caffeine at 860 mg to decaffeinated coffee resulted in a significant reduction ($p < 0.05$) in the number of mammary carcinomas per animal. Coffee consumption did not significantly affect the percentage of rats with mammary tumours. Administration of coffee to rats treated with DMBA by gavage did not significantly affect the number of mammary carcinomas per animal (Welsch *et al.*, 1988).

In a subsequent study with the same experimental protocol (intravenous and gastric administration of DMBA) but with administration of a chemically defined diet containing 5% unsaturated fat (corn oil) *ad libitum*, similar results with coffee were obtained, i.e., a reduction in the number of mammary tumours per rat but no effect on the percentage of rats with tumours (Welsch & DeHoog, 1988).

Hamster: Groups of 20 female Syrian golden hamsters, weighing approximately 70 g, were fed powdered chow or chow supplemented with 20% powdered green coffee beans. Two weeks later, the right buccal pouch of 16 animals from each group was painted three times with a 0.5% solution of DMBA in heavy mineral oil; the remaining four animals per group were treated three times weekly with heavy mineral oil alone and served as controls. The experiment was terminated after a total of 50 treatments (16.5 weeks). At the end of the experiment, 12/16 animals given chow alone and 9/16 also given green coffee beans were still alive; most of the losses were due to respiratory infections or ether anaesthesia. Tumours of the buccal pouch were seen in 9/12 animals receiving chow (eight had multiple tumours) and 2/9 also receiving green coffee beans. Two hamsters receiving chow had mild to moderate dysplasia of the right buccal pouch and one had dysplasia, including carcinoma *in situ*; the buccal pouches of the nine remaining animals had various grades of dysplasia, including carcinoma *in situ* and papillary carcinomas. Of the animals receiving green coffee beans, only two had carcinomas of the right buccal pouch; the remaining seven showed dysplasia. A statistically significant reduction in average tumour mass was observed in the latter group (Miller *et al.*, 1988). [The Working Group noted that survival was low.]

(iii) N-*Nitrosobis(2-oxypropyl)amine*

Hamster: Groups of 40 male Syrian golden hamsters, six weeks old, received two weekly subcutaneous injections of 20 mg/kg bw *N*-nitrosobis(2-oxypropyl)-amine and were then fed a low-fat diet, a high-fat diet or a high-fat diet plus daily preparations of coffee as the drinking fluid. The concentration of coffee was gradually increased from 25% during the first two weeks to 100% within four weeks, which was continued for the life span of the animals. The hamsters were killed 12 months after the second injection of nitrosamine, and autopsied. Mean body weights of animals on high-fat diet alone were significantly greater than those of animals on low-fat diet; those of hamsters fed high-fat diets with caffeine did not

differ significantly from those of animals on the high-fat diet alone. The total number of ductal/ductular adenocarcinomas of the pancreas was significantly increased in the high-fat group (eight; $p < 0.05$) as compared to the low-fat group (two). The total number of adenocarcinomas in the group receiving high-fat diet plus coffee (five) was slightly but not significantly smaller than that in the group on high-fat diet alone (Woutersen *et al.*, 1989).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, metabolism and excretion*

No data were available to the Working Group (see the monograph on caffeine p. 321).

(ii) *Toxic effects*

Groups of male Wistar rats were given 4 or 8% brewed or decaffeinated coffee in the drinking-water for six to eight months. Body weights of coffee-treated rats were 6-7% lower than those of controls receiving water only. Coffee induced 'no untoward effect' on the liver (Strubelt *et al.*, 1973).

Weanling male Sprague-Dawley rats were fed starch-based diets supplemented with either brewed coffee, decaffeinated coffee, tea, caffeine or nothing (controls). Compared with controls, rats consuming coffee or caffeine had elevated concentrations of cholesterol and phospholipids. In addition, both groups had lower levels of triglycerides, although the difference was significant only for the group receiving caffeine (Naismith *et al.*, 1969).

Six male and nine female adult rhesus monkeys were fed an atherogenic diet *ad libitum* for 12 months. Major changes in the profiles of total plasma lipids and lipoproteins occurred within three to six months and remained at the higher level thereafter. Four females and three males were then given 50% coffee as drinking fluid for 12 months, while the remaining animals were given water. The authors reported no significant difference in total plasma protein or lipids between coffee-treated and control animals after 15 and 18 months (Callahan *et al.*, 1979).

In a study reported as an abstract, coffee did not enhance the number or size of pancreatic atypical acinar-cell foci induced in rats by azaserine (Roebuck *et al.*, 1985).

(iii) *Effects on reproduction and prenatal toxicity*

Brewed coffee: In a combined subchronic, reproductive and developmental toxicity study, Sprague-Dawley rats were given 12.5, 25 or 50% freshly percolated

coffee as the drinking fluid (daily caffeine intake, 9, 19 or 38 mg/kg bw) for five weeks before mating, throughout gestation and until 27 days after parturition. No effect on fertility, litter size, neonatal growth or survival was observed with any dose level. Among the offspring, underdevelopment of the renal pelvis was observed in the mid- and high-dose groups; cleft palate and delayed ossification were also observed in the offspring, but these were not clearly dose-related (Palm *et al.*, 1978).

In a similarly designed study, Sprague-Dawley rats received 25, 50 or 100% percolated coffee as the drinking fluid (approximate daily caffeine intake, 20, 40 or 80 mg/kg bw) for 91 days, after which they were mated to produce F_{1a} litters, while the administration of coffee continued. Female rats were mated again ten days after their first litters had been weaned to produce F_{1b} litters, which were used for teratological examination. Parent rats treated with 50 and 100% coffee had enlarged livers and kidneys, but no significant effect on reproduction or lactation was observed. Body weights of F_{1a} offspring of the high-dose rats were comparable to those of controls at four days of age but had decreased significantly by weaning at 21 days of age. No teratogenic effect or decrease in neonatal body weight was observed in F_{1b} pups delivered by caesarean section, although offspring of rats given the mid- and high doses showed a significantly increased incidence of delayed ossification of the sternebrae (Nolen, 1981).

In a behavioural teratology study, Sprague-Dawley rats were given either drinking-water or fresh drip coffee as drinking fluid from the time of mating until parturition. The average daily dose of caffeine was 122 mg/kg bw. Significant decreases in body, liver and brain weights were observed in the offspring of the coffee-treated group at birth but not at 30 days of age. In addition, a significant increase in motor activity and a decrease in grooming time and time spent with a novel object were observed in this group at 30 days of age (Groisser *et al.*, 1982).

In another behavioural study, Sprague-Dawley rats received 0, 25 or 100% brewed coffee as the drinking fluid from 60 days before mating until weaning of the F_1 offspring. No effect on reproduction was observed. Among the offspring of treated rats, there were delays in the eruption of incisor teeth and maturation of swimming skills. A significant decrease in running wheel and preweaning open-field activities was also observed, but no effect was seen on learning, memory or motor function. On the basis of post-weaning measurements, the authors concluded that the treatment did not result in a significant risk for irreversible damage in the offspring (Butcher *et al.*, 1984).

Instant coffee: In a combined subchronic, reproductive and developmental toxicity study of instant coffee (Nolen, 1981), described above, the body weights of F_{1a} offspring of high-dose dams were comparable to those of controls at four days of age but had decreased significantly by weaning at 21 days of age. No teratogenic effect or decrease in fetal body weight was observed in F_{1b} pups delivered by

caesarean section, although offspring of the high-dose group had a significantly increased incidence of delayed ossification of the sternebrae.

Groups of white mice [strain unspecified] were fed instant coffee crystals in the diet, at doses equivalent to human consumption of 0, 4, 8, 12, 16 or 20 cups of coffee per day, from the time of mating to parturition. No abnormality or gross malformation of the alimentary tract was observed in the offspring, but pup body weight and length were significantly decreased at doses equivalent to eight cups of coffee or more (Murphy & Benjamin, 1981).

Sprague-Dawley rats were given 1.5% (w/v) solvent-free, freeze-dried coffee solution as the drinking fluid from the time of mating until gestation day 21 or postnatal day 14. When treatment was continued until postnatal day 14, offspring of coffee-treated and control groups were cross-fostered. No gross malformation, difference in organ or fetal body weights, or change in iron, zinc or copper levels in maternal plasma, liver or kidney or in fetal liver were observed. Offspring of dams treated with coffee prenatally had significantly decreased birth weights; no change in body weight was observed three or four days after birth (Muñoz *et al.*, 1986).

Decaffeinated coffee: In a combined subchronic, reproductive and developmental toxicity study, Sprague-Dawley rats received 25, 50 or 100% decaffeinated brewed and instant coffee as the drinking fluid (equivalent to 12, 25 or 50 cups of coffee per day) with the same study design as described previously (Nolen, 1981). No effect on reproduction, litter size or postnatal viability of the F_{1a} litters was observed. Body weights of offspring of mid- and high-dose dams were comparable to those of controls at four days of age but were significantly decreased at weaning. No malformation or variation was observed in F_{1b} offspring, and no delay in ossification was seen (Nolen, 1982).

In a behavioural teratology study, Sprague-Dawley rats received freshly brewed decaffeinated coffee (average daily caffeine intake, 4.5 mg/kg bw) as the drinking fluid from the time of mating until parturition. A significant decrease in the liver weights of the offspring was observed at birth, and a significant increase in motor activity and a decrease in time spent grooming or with a novel object were seen (Groisser *et al.*, 1982).

(iv) *Genetic and related effects*

The genetic and related effects of various types of coffee have been reviewed (Sugimura, 1982; Sugimura & Sato, 1983; Aeschbacher *et al.*, 1984a; Nagao *et al.*, 1984; Sugimura *et al.*, 1984; Nagao *et al.*, 1986b; Aeschbacher, 1990). In bacteria, there is evidence that dicarbonyls (e.g., methylglyoxal) and hydrogen peroxide acting together contribute to the mutagenic activity of roasted coffee (Nagao *et al.*, 1984; Fujita *et al.*, 1985a,b). Both the dicarbonyls and hydrogen peroxide may be deactivated by enzymes present in cells and tissue, such as glyoxalase, glutathione

(for methylglyoxal), catalase and peroxidase (for hydrogen peroxide) (Nagao *et al.*, 1984; Friederich *et al.*, 1985; Fujita *et al.*, 1985b; Tucker *et al.*, 1989). In mammalian cells, coffee aroma stripped from roasted coffee and the dicarbonyls contained therein may contribute to the genetic effects (Aeschbacher *et al.*, 1985; Tucker *et al.*, 1989). There is substantial evidence in various genetic test systems, with one exception (Graf & Würgler, 1986), that caffeine is not involved in the genetic activity observed (Nagao *et al.*, 1979; Aeschbacher, 1990).

Coffee has been studied in experimental genetic and related systems as both instant coffee powders and as finely ground roasted coffee beans prepared with water in the normal way for drinking and then lyophilized. The doses are expressed as mass of coffee powder used in the treatment, which generally required the powder to be dissolved in the treatment solvent. Sterilization of preparations to be tested for bacterial mutagenicity, by filtration or autoclaving, did not influence the results significantly (Aeschbacher *et al.*, 1980). Time between sample preparation and test may affect the genetic response. In several studies, where specifically noted, the coffee was solvent-extracted or chemically fractionated. Studies in bacteria of green coffee beans indicate a lack of mutagenic activity (Kosugi *et al.*, 1983; Albertini *et al.*, 1985; Dorado *et al.*, 1987); similar comparisons of roasted and unroasted beans have not been made with other systems.

The results of the studies on genetic and related effects are listed at the end of this section in Table 29, with the evaluation of the Working Group, as positive, negative or inconclusive, as defined in the footnotes. The results are tabulated separately for the presence and absence of an exogenous metabolic activation system. The lowest effective dose (LED), in the case of positive results, and the highest ineffective dose (HID), in the case of negative results, are shown together with the appropriate reference. The studies are summarized briefly below.

Brewed coffee: Freshly brewed coffee induced prophage lambda in lysogenic *Escherichia coli* K12.

A number of studies have been conducted on the mutagenicity of coffees to *Salmonella typhimurium* under different conditions. Brewed coffee consistently induced mutations in *S. typhimurium* TA100, and mutations were also induced in TA102 and TA104, which are more sensitive to oxidative mutagens, and in *E. coli* WP2 *uvrA*/pKM101. There are conflicting reports on the mutagenicity of coffee to *S. typhimurium* TA98. [The Working Group noted the inadequate reporting of several of the studies with TA98.] Coffee gave negative results in standard strains of *S. typhimurium*, which do not contain the pKM101 plasmid. Brewed coffee was also mutagenic in the *S. typhimurium* L-arabinose-resistance forward mutation assay in strain BA13.

There was no significant response in tests for sex-linked recessive lethal mutation, dominant lethal mutation or chromosome loss in *Drosophila*

melanogaster, but weak activity was observed in the somatic cell (wing imaginal disc) mutation and mitotic recombination tests following larval feeding. These effects were attributed to caffeine.

Treatment of cultured human lymphocytes with brewed coffee induced sister chromatid exchange, gaps, breaks and total chromosomal aberrations. Endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells. Bisulfite, which complexes carbonyls, reduced the frequency of sister chromatid exchange and endoreduplicated cells, while catalase and peroxidase treatment had no effect (Tucker *et al.*, 1989). Coffee aroma stripped from roasted coffee beans also induced gaps, breaks and total chromosomal aberrations in human peripheral lymphocytes.

Instant coffee: Instant coffee induced prophage lambda in lysogenic *E. coli* K12, strain GY5027 but did not induce SOS activity in *S. typhimurium* TA1535/pSK1002.

Instant coffee induced mutations in *S. typhimurium* TA100 but not in TA98, TA1535, TA1537 or TA1538. Instant coffees were mutagenic to *S. typhimurium* strains TA102 and TA104, which are more sensitive to oxidative mutagens. Instant coffee was also active in the *S. typhimurium* L-arabinose-resistance forward mutation assay in strain BA13. The mutagens in coffee are inactivated by the cytosolic fraction of exogenous metabolic systems from rat liver, by heat in the presence of oxygen (Friederich *et al.*, 1985), by sodium sulfite (Suwa *et al.*, 1982) and by catalase (Fujita *et al.*, 1985b). This evidence, together with that from other studies, led to the conclusion that an interaction of methylglyoxal with hydrogen peroxide accounts for most of the mutagenicity of instant coffee (Fujita *et al.*, 1985a,b).

Negative results were obtained in host-mediated assays in which coffee was administered to male Swiss mice by gavage after intraperitoneal injection of *S. typhimurium* TA1530. Similarly, negative results were obtained in the intrasanguinous test following intravenous injection of *E. coli* K12 into male Swiss mice and assaying for reverse and forward mutation at the *nia*$^+$ and *gal*$^+$ loci, respectively.

Treatment of Chinese hamster lung cells with instant coffee increased the frequency of mutations in the diphtheria toxin resistance assay. Most of the mutagenicity was suppressed by sodium bisulfite. Methylglyoxal was shown to account for less than 3% of the mutagenicity (Nakasato *et al.*, 1984).

There was no significant response in tests for sex-linked recessive lethal mutation, dominant lethal mutation or chromosome loss in *Drosophila melanogaster*, but weak activity was observed in the somatic cell (wing imaginal

disc) mutation and mitotic recombination tests following larval feeding. These effects were attributed to caffeine.

Treatment of cultured human lymphocytes with instant coffee induced gaps, breaks and total chromosomal aberrations. Sister chromatid exchange and endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells (Tucker *et al.*, 1989).

Instant coffee administered to Chinese hamsters as a single oral dose did not increase the frequency of sister chromatid exchange. In a micronucleus test, Swiss mice were given five consecutive daily oral doses of instant coffee; no significant induction of micronuclei above spontaneous levels was observed. Two oral doses to Swiss mice of coffee aroma (up to 50 ml/kg bw) also gave negative results (Aeschbacher *et al.*, 1984b). In another study, no significant increase in the frequency of micronuclei was induced by single or multiple administrations of instant coffee by gavage (Shimizu & Yano, 1987). [The Working Group noted that the authors reported a tendency for the number of micronuclei to increase in a dose-related fashion.]

Decaffeinated coffee: Decaffeinated coffee induced prophage lambda in lysogenic *E. coli* K12, strain GY5027. It induced mutation in *S. typhimurium* TA98, TA100, TA102 and TA104, which are sensitive to oxidative mutagens. No effect was observed in *Drosophila melanogaster* when decaffeinated coffee was assayed for the induction of somatic cell (wing imaginal disc) mutation and mitotic recombination. Treatment of cultured human lymphocytes with decaffeinated coffee induced gaps, breaks and total chromosomal aberrations. Sister chromatid exchange and endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells (Tucker *et al.*, 1989).

Coffee in combination with known mutagens: Brewed coffee, instant coffee and decaffeinated coffee suppressed SOS induction by ultra-violet light, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 4-nitroquinoline-*N*-oxide and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in *S. typhimurium* TA1535/pSK1002 (Obana *et al.*, 1986). Instant, decaffeinated and brewed coffee inhibited mutagenesis resulting from the nitrosation of methylurea in *S. typhimurium* TA1535 (Stich *et al.*, 1982).

In mouse bone-marrow micronucleus tests, positive responses to mitomycin C, cyclophosphamide and procarbazine (but not adriamycin) were significantly reduced by administration of instant coffee 2 h before the clastogens. Similar effects were observed with decaffeinated and brewed coffee on the micronucleating effect of mitomycin C, and with brewed coffee on the effect of procarbazine (Abraham, 1989). In contrast, it has been reported that instant coffee caused no significant alteration in the incidence of micronuclei induced by *N*-nitroso-dimethylamine (Shimizu & Yano, 1987).

Table 29. Genetic and related effects of brewed, instant and decaffeinated coffee

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Brewed coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
PRB, λ Prophage induction in E. coli, strain GY5022	–	0	21400.0000	Kosugi et al. (1983)
SAF, Salmonella typhimurium BA13, forward mutation to AraR	+	0	1000.0000	Dorado et al., (1987)
SAF, Salmonella typhimurium BA13, forward mutation to AraR	+	0	500.0000	Ariza et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	7000.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	12500.0000	Aeschbacher & Wurznèr (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	0	6000.0000	Kosugi et al. (1983)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	50000.0000	Kam (1980)
SA2, Salmonella typhimurium TA102, reverse mutation	+	(+)	2500.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA5, Salmonella typhimurium TA1535, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA7, Salmonella typhimurium TA1537, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA8, Salmonella typhimurium TA1538, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	+	–	50000.0000	Kam (1980)
ECR, E. coli WP2 uvrA/pKM101, reverse mutation	+	0	7500.0000	Kosugi et al. (1983)
DMN, Drosophila melanogaster, sex chromosome losses	–	0	30000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, somatic mutation (larval feeding)	(+)	0	30000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	(+)	0	30000.0000	Graf & Wurgler (1986)
DMX, Drosophila melanogaster, sex-linked recessive lethal mutation	–	0	30000.0000	Graf & Wurgler (1986)
DML, Drosophila melanogaster, dominant lethal test	–	0	30000.0000	Graf & Wurgler (1986)
SIC, Chinese hamster ovary AUXB1, sister chromatid exchange	+	0	200.0000	Tucker et al. (1989)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	2500.0000	Aeschbacher et al. (1985)
SHL, Human peripheral lymphocytes, sister chromatid exchange, in vitro	+	0	300.0000	Tucker et al. (1989)
MVH, Micronuclei, human (splenectomised) erythrocytes/reticulocytes in vivo	+	0	0.0000	Smith et al. (1990)

Table 29 (contd)

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Instant coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
PRB, SOS repair	–	0	9000.0000	Obana et al. (1986)
PRB, λ Prophage induction in E. coli GY5022	–	0	21400.0000	Kosugi et al. (1983)
SAF, Salmonella typhimurium BA13, forward mutation	+	0	500.0000	Dorado et al., (1987)
SAF, Salmonella typhimurium BA13, forward mutation	+	0	500.0000	Ariza et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	1500.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	17500.0000	Aeschbacher & Wurzner (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	12500.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	0	5000.0000	Aeschbacher et al. (1989)
SA2, Salmonella typhimurium TA102, reverse mutation	+	0	10000.0000	Aeschbacher et al. (1989)
SA2, Salmonella typhimurium TA102, reverse mutation	+	+	5000.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	+	10000.0000	Shane et al. (1988)
SA5, Salmonella typhimurium TA1535, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA7, Salmonella typhimurium TA1537, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA8, Salmonella typhimurium TA1538, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
DMN, Drosophila melanogaster, sex chromosome losses	–	0	40000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, somatic mutation	(+)	0	40000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	(+)	0	40000.0000	Graf & Wurgler (1986)
DMX, Drosophila melanogaster, sex-linked recessive lethal mutation	–	0	40000.0000	Graf & Wurgler (1986)
DML, Drosophila melanogaster, dominant lethal test	–	0	40000.0000	Graf & Wurgler (1986)
GCL, Chinese hamster lung (CHL) cells, diphtheria toxin resistance	+	0	4000.0000	Nakasato et al. (1984)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	25000.0000	Aeschbacher et al. (1985)
HMM, Host mediated assay, Salmonella typhimurium TA1530 in Swiss mice	–	0	6000.0000	Aeschbacher & Wurzner (1980)
HMM, Intrasanguinous test, E. coli , Swiss mice	–	0	6000.0000	Aeschbacher & Wurzner (1980)
SIC, Chinese hamster ovary AUXB1, sister chromatid exchange	+	0	200.0000	Tucker et al. (1989)
SVA, Sister chromatid exchange, Chinese hamsters in vivo	–	0	2500.0000	Aeschbacher et al. (1984b)
MVM, Micronucleus test, Swiss mice in vivo	–	0	3000.0000	Aeschbacher et al. (1984b)
MVM, Micronucleus test, ddy mice in vivo	–	0	2500.0000	Shimizu & Yano (1987)
MVM, Micronucleus test, ddy mice in vivo	–	0	1000.0000	Shimizu & Yano (1987)

Table 29 (contd)

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Decaffeinated coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	1500.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	2500.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	50000.0000	Kam (1980)
SA2, Salmonella typhimurium TA102, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	+	–	50000.0000	Kam (1980)
DMM, Drosophila melanogaster, somatic mutation	–	0	200000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	–	0	200000.0000	Graf & Wurgler (1986)
SIC, Chinese hamster ovary AUXB1 cells, sister chromatid exchange	+	0	300.0000	Tucker et al. (1989)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	2500.0000	Aeschbacher et al. (1985)

[a]Expressed as dry weight of extract

(*b*) *Humans*

(i) *Toxic effects*

Coffee drinking has been associated with a number of adverse effects (Goldman, 1984; Spiller, 1984c; Stone, 1987). Many of the undesirable effects of coffee have been ascribed to caffeine, and they are dealt with in the respective monograph; at least some of the effects of coffee on plasma cholesterol and lipids, however, can be attributed to ingredients other than caffeine.

A weak association was seen between coffee drinking and total mortality among men in a 25-year follow-up from the Netherlands. No cause-specific mortality was reported (Vandenbroucke *et al.*, 1986).

Plasma cholesterol and lipoproteins: A series of epidemiological studies have investigated possible associations between coffee drinking and serum cholesterol levels; these have been reviewed (Thelle *et al.*, 1987). Many of the studies found that coffee consumption was positively associated, to variable degrees, with levels of total serum cholesterol in people of each sex (Thelle *et al.*, 1983; Kark *et al.*, 1985; Klatsky *et al.*, 1985; Tuomilehto *et al.*, 1987; Aro *et al.*, 1989). Other investigators found some association in men or women (Nichols *et al.*, 1976; Shirlow & Mathers, 1984; Mathias *et al.*, 1985; Curb *et al.*, 1986; Pietinen *et al.*, 1988) or in only some segments of the general population, e.g., individuals with coronary heart disease (Little *et al.*, 1966) or hypertension (Davis *et al.*, 1988). There are also a number of studies in which no association was observed (Phillips *et al.*, 1981; Hofman *et al.*, 1983; Kovar *et al.*, 1983; Aro *et al.*, 1985; Donahue *et al.*, 1987; Paoletti *et al.*, 1989).

Only a few scientists have investigated the relationship between coffee consumption and the concentration of individual serum lipoproteins. A positive association was observed between the level of low-density lipoproteins and coffee intake, whereas no such relation was seen with high-density lipoproteins or triglycerides (Førde *et al.*, 1985; Aro *et al.*, 1987; Bak & Grobbee, 1989; Paoletti *et al.*, 1989).

The conflicting data on the effects of coffee on serum cholesterol may be due to the use of different methods in the preparation of coffee. Thus, boiled coffee, but not filtered coffee, raised serum cholesterol (0.5-1.0 mmol/l) in three separate clinical trials conducted in Norway, Finland and the Netherlands (Førde *et al.*, 1985; Aro *et al.*, 1987; Bak & Grobbee, 1989). Epidemiological observations agree with the results of these clinical trials (Stensvold *et al.*, 1989; Pietinen *et al.*, 1990). Zock *et al.* (1990) suggest that a nonsaponifiable lipid fraction, isolated from boiled coffee by ultracentrifugation, raised serum cholesterol in healthy volunteers.

Coronary heart disease: The results of the Boston Collaborative Drug Surveillance Program (1972) suggest that consumption of more than five cups of coffee per day doubles the risk for myocardial infarction, as compared to no consumption at all. Similar results were reported by other investigators (Jick *et al.*, 1973; Mann & Thorogood, 1975; LaCroix *et al.*, 1986; LeGrady *et al.*, 1987; Rosenberg *et al.*, 1988). Some established only a modest association between myocardial infarction and heavy coffee consumption and for only some segments of the population (Rosenberg *et al.*, 1980, 1987; La Vecchia *et al.*, 1989a). Several other epidemiological studies found no association (Klatsky *et al.*, 1973; Dawber *et al.*, 1974; Hennekens *et al.*, 1976).

In some studies, the apparent association between coffee drinking and ischaemic heart disease can be accounted for by cigarette smoking (Hennekens *et al.*, 1976; Wilhelmsen *et al.*, 1977; La Vecchia *et al.*, 1989a).

[The Working Group was not aware of any longitudinal study on the association between coffee intake and the risk of coronary heart disease from populations with high consumption of boiled coffee.]

(ii) *Effects on reproduction and prenatal toxicity*

The reproductive effects of coffee on humans have been reviewed (Ernster, 1984; Leviton, 1984; James & Paull, 1985; Pieters, 1985; Heller, 1987; Schneider, 1987; Leviton, 1988). Most epidemiological studies have been affected by a number of methodological issues, including (i) inadequate measurement of intake: almost all studies relied on reported intakes; some studies were limited to coffee consumption and ignored other sources of caffeine; and most studies ignored distinctions between different types of preparation and different strengths of coffee; (ii) inadequate control for the possible confounding effects of variables such as smoking, alcohol consumption, age, nutrition and life-style factors in some studies; (iii) low response rates in several studies; (iv) biased selection of adequate controls because of self-selection into groups of drinkers and nondrinkers of coffee; (v) recall bias in retrospective studies, particularly those of malformations; and (vi) insufficient statistical power in some of the studies. Despite these limitations, epidemiological studies are the single source of information on human reproductive effects of coffee.

Malformations: Borlée *et al.* (1978) identified 202 infants with congenital malformations of any type among 17 970 births in eight Belgian hospitals between 1972 and 1974. A group of 175 control infants was also selected. The parents of cases and controls were interviewed about consumption of coffee and other possible risk factors. Compared to women who did not drink coffee, the relative risks (RR) were calculated by the Working Group to be [0.7] for women drinking one to four cups per day, [0.8] for those drinking five to seven cups and [1.5] for

those drinking eight or more cups. In a chi-square test, the linear trend was barely significant [(p = 0.05)]. No significant association was found between coffee drinking and smoking or use of medicines. [The Working Group noted that no information was given on refusals or other losses, that the possibility of recall bias was not considered, and that there was no proper control of confounding variables.]

Jacobson *et al.* (1981) reported three cases of infants with ectrodactyly born to women who drank eight to 25 cups of percolated coffee per day. The women were selected from among those who contacted the authors after reading press accounts of the relationship between coffee drinking and malformations. [The Working Group noted that this letter to the Editor constitutes only anecdotal information.]

Linn *et al.* (1982) studied the association between coffee consumption and several outcomes of pregnancy in 12 205 women in Boston, MA, USA, in 1977-80, who represented 71% of women giving birth in one hospital. Women were interviewed one to two days after delivery about their previous medical and obstetric history and habits, including coffee and tea consumption during the first trimester. Diabetic and asthmatic women and those with multiple pregnancies were excluded. The analysis was controlled for a number of confounding factors. No association was found between coffee drinking and the frequency of malformations.

The association between drinking caffeine-containing beverages and six types of malformation (inguinal hernia, oral clefts, cardiac defects, pyloric stenosis and neural tube defects) was studied in a case-control study of 2030 children from a number of hospitals in Boston, MA, Philadelphia, PA, and Toronto, Canada, between 1976 and 1980 (Rosenberg *et al.*, 1982). Controls were 712 children with other malformations, mainly of the gastrointestinal, musculoskeletal and central nervous systems. Mothers were interviewed in their homes within six months of delivery about consumption of a number of caffeine-containing beverages, including coffee, tea and cola. Consumption of coffee was 0, occasional, 1-2 or >3 cups per day. No association was found between coffee consumption and any of the six malformations [all RRs, $\leq$1.4]. Adjustment for a large number of potentially confounding variables — but not for alcohol consumption — in the analysis did not change these estimates. [The Working Group noted that the use of malformed infants as controls helps reduce recall bias, but it might be inadequate if caffeine were a teratogen that affects many sites.]

A monitoring system identified 755 children with birth defects in Finland between 1980 and 1982 (Kurppa *et al.*, 1983) including 112 with central nervous system defects, 241 with orofacial clefts, 210 with musculoskeletal defects and 143 with cardiovascular malformations. Thirty-five pairs that included habitual tea drinkers and 14 pairs with incomplete data were excluded. One control infant matched to each case was an infant whose birth immediately preceded that of the

case in the same maternity district. Information on coffee drinking was collected through interviews; cola drinking was infrequent. No important difference was seen between mothers of cases and of controls regarding the consumption of coffee during pregnancy. After adjustment for maternal age, smoking and alcohol consumption, the RR for coffee drinkers relative to those who did not drink coffee was 1.1 (95% confidence interval [CI], 0.8-1.3). Separate analyses of the four diagnostic categories showed no significant association.

As reported in an abstract, a case-control study of risk factors for cleft palate was carried out in five areas of Japan from 1978 to 1981. One control was matched to each of 194 cases for residence, sex, birth order and maternal age. Questionnaires answered by mothers included information on dietary habits. Frequent intake of coffee was associated with a RR of 2.3 ($p < 0.05$) (Tohnai *et al.*, 1984).

Furuhashi *et al.* (1985) carried out a prospective study in Japan in which 9921 women at 24 weeks' gestation or more were interviewed about coffee and tea drinking. Women were divided into five consumption groups: those who drank neither tea nor coffee, drinkers of fewer than five cups of coffee per day, five or more cups of coffee per day, coffee (any quantity) plus green tea, and green tea only. The rates of congenital anomalies of any type were 3.7% among coffee and/or tea drinkers and 1.7% among women who drank neither beverage. [The Working Group calculated that this difference was highly significant ($p < 0.001$), although the authors stated the opposite.] The association with coffee drinking was particularly strong for multiple anomalies. [The Working Group noted that no data are given on how the women were selected, or on when and where the study was carried out. Data on refusals and losses to follow-up are not given. Confounding variables were not adjusted for. It was surprising that the excess risk was seen for a wide variety of congenital malformations, including those associated with chromosomal anomalies.]

Tikkanen and Heinonen (1988) carried out a case-control study of maternal exposure to organic solvents and cardiovascular malformations in Finland in 1982-84. The 569 cases were identified from a population-based registry of congenital malformations; all diagnoses were confirmed by a cardiologist with experience in teratology. Controls were selected randomly from 52 hospitals in the country, and of 1200 controls selected, 1052 (88%) were included in the study. Mothers were interviewed at maternity welfare centres concerning exposures during the first trimester of pregnancy. Coffee drinkers were equally distributed among cases and controls: 82.3% and 81.8%, respectively.

Low birthweight and/or preterm delivery: The three best-designed studies are summarized in Table 30.

Table 30. Summary of selected[a] studies that provide relative risks (RR) for low birthweight in relation to coffee or caffeine intake of mothers

Reference, location and design	No. of women	Coffee or caffeine consumption	RR (95% CI[b])	Comments
van den Berg (1977) California, USA Prospective	8 514	≤1 cup/day 2–6 cups/day ≥7 cups/day	1.0 [1.4][c] [2.2][c]	Coffee intake
		≤6 cups/day ≥7 cups/day	1.0 1.2	RR adjusted for smoking $p = 0.01$, calculated by Hogue (1981)
Linn *et al.* (1982) Boston, USA Cross-sectional	12 205	< 4 cups/day ≥4 cups/day	1.0 1.2 (0.9–1.6)	Adjusted for smoking and other confounding variables Coffee intake
Martin & Bracken (1987) New Haven, USA Prospective	3 891	Nondrinkers 1–150 mg/day 151–300 mg/day > 300 mg/day	1.0 1.4 (0.7–3.0) 2.3 (1.1–5.2) 4.6 (2.0–10.5)	Term deliveries only; RR adjusted for race, parity, smoking and gestational age Caffeine intake

[a] Selected on the basis of design and quality
[b] CI, confidence interval
[c] Crude RR calculated by the Working Group

Mau and Netter (1974) carried out a prospective study of over 5200 pregnant women from 20 maternity departments in the Federal Republic of Germany. The women were interviewed during the first trimester of pregnancy, but little information was provided on how coffee drinking was quantified. Compared to nondrinkers, women who occasionally drank coffee had a RR of [1.4]; frequent drinkers had a RR of [1.6] for delivering a low birthweight (<2500 g) baby [(p < 0.01)]. The risk among drinkers remained unchanged after stratification for smoking (as reanalysed by Hogue, 1981).

van den Berg (1977) studied the effect of coffee consumption on birthweight and preterm delivery in a prospective study carried out in California, USA, between 1960 and 1967. Approximately 15 000 pregnant women receiving antenatal care under a prepaid medical plan were enrolled. Data were obtained from their medical records as well as from interviews covering reproductive history, socioeconomic factors, smoking habits and beverage consumption. A dose-response effect of coffee drinking was seen on low birthweight (see Table 30). A similar effect was noted on prematurity (gestational age under 37 weeks at birth), with RRs of [1.3] for women drinking two to six cups per day and [1.8] for those drinking seven or more cups, compared to women drinking up to one cup per day. Hogue (1981) examined the data on low birthweight after adjustment for smoking and length of gestation: a smaller but still significant RR of 1.2 was found for women who drank seven or more cups per day as compared to women who drank fewer than seven cups per day.

Arnandova and Kaculov (1978) reported a study of the pregnancy outcomes of 600 women in the USSR in 1976. Coffee consumption was not associated with prematurity, but the mean birthweight of infants born to coffee drinkers (usually one to two cups per day) was 115 g less than that of babies of women who did not drink coffee. The authors commented that this difference was probably due to greater consumption of alcohol and tobacco among coffee drinkers.

Kuzma and Sokol (1982) carried out a study of pregnant women who gave birth at four hospitals in California, USA, in 1974-78. About three-quarters of the women receiving antenatal care in these hospitals answered a self-administered questionnaire on their first visit, which included information on demographic and socioeconomic variables and on the use of coffee, alcohol, tobacco and other substances. If a mother had not sought antenatal care or had been missed in the enrollment procedure, the same data were obtained shortly after delivery; 37% of the study sample was recruited in this way. No important difference was found between information collected prospectively and retrospectively. Complete data were available for 5093 mother-infant pairs. After adjustment for gestational age, pre-pregnancy weight, weight gain, ethnicity and smoking, caffeine use was significantly (p < 0.01) associated with lower birthweight. [The Working Group

noted that it is not clear what percentage of eligible women were included in the study and that no information was given on how caffeine intake was calculated, particularly as to whether sources other than coffee were accounted for.]

In the study of Linn *et al.* (1982), described on p. 105, coffee drinking during the first trimester was associated in the crude analysis with a greater proportion of low birthweight. After adjustment for smoking, with or without other confounding variables, no significant effect of coffee drinking was seen: the RR for women drinking four or more cups a day was 1.2 (95% CI, 0.9-1.6) (see Table 30). No dose-response effect was present, and the association between coffee drinking and duration of gestation was nonsignificant.

In a case-control study, Berkowitz *et al.* (1982) compared 175 preterm infants and 313 term infants delivered at a Connecticut, USA, hospital in 1977. Preterm infants (cases) were defined as those born before 37 weeks of gestation, as determined by the Dubowitz criteria, and controls were a random sample of term infants. Interviews were completed with the mothers of 86% of potential cases and 95% of potential controls and included data on alcohol, smoking and on the average daily number of cups of coffee or tea taken during each trimester. Cases were of lower socioeconomic status than controls. Coffee drinking was not associated with shortened gestation period.

Watkinson and Fried (1985) investigated the possible association between coffee consumption during pregnancy and perinatal outcomes among women in the Ottawa area, Canada. From 1978, 371 women were studied for a range of perinatal outcomes. Five years later, in 1983, those women whose offspring were at least one year of age by that date were mailed a questionnaire concerning their consumption of coffee, tea, cola and other sources of caffeine throughout their pregnancies; 284 women (77%) responded. Coffee and tea samples were collected from 53 mothers and were used to estimate the caffeine content of these drinks. Caffeine consumption was greater among smokers and among women of low educational level. Caffeine intake, expressed as a continuous variable, was not significantly associated with birthweight or gestational age; however, the mean weight of babies born to 12 heavy users (> 300 mg caffeine/day) was 3158 g, compared to 3537 g for the remaining sample ($p < 0.05$). This association was still significant after adjustment for nicotine use but not quite significant ($p = 0.06$) after controlling for maternal education. No association was found between heavy use and gestational age. [The Working Group noted that women had been asked to recall the intake of a number of caffeine-containing substances several years after a pregnancy. No dose-response effect was present.]

In the study of Furuhashi *et al* (1985), described on p. 106, no significant difference in mean birthweight was seen between the five categories. Infants born to 53 women who drank five or more cups of coffee per day, however, were on average

about 70 g lighter than the other infants. The incidence of infants who were small for gestational age was approximately three times greater [$p < 0.05$; Poisson test] in the women who drank more than five cups of coffee per day. [The Working Group noted that no information on smoking was available, and no definition was given of 'small for gestational age'.]

Martin and Bracken (1987) carried out a prospective study of 3891 pregnant women receiving antenatal care in greater New Haven, Connecticut, USA, between 1980 and 1982. A total of 6219 women were considered for the study but only 5331 agreed to be contacted. Of these, 4926 fulfilled the entry criteria, and 85% were interviewed at home within a few weeks of the first prenatal visit. Caffeine consumption during pregnancy was estimated from data on the consumption of coffee, tea, colas and drugs. Data on pregnancy outcomes were obtained from hospital records and were analysed using logistic regression. Caffeine consumption was associated with lower socioeconomic status, smoking and alcohol intake. The effect of caffeine on birthweight was restricted to term infants. After adjustment for gestational age, race, parity and smoking, intake of caffeine at >300 mg/day was associated with a RR of 4.6 (95% CI, 2.0-10.5) for low birthweight compared with that of women who did not consume caffeine-containing beverages or drugs. A dose-response pattern was present (see Table 30). No association was seen between caffeine intake and gestational age.

Brooke *et al.* (1989) studied the effects on birthweight of smoking, alcohol, caffeine, socioeconomic factors and psychosocial stress among 1860 white women in London, UK, of whom 1513 were included in the study and interviewed prenatally. Birthweight was corrected for gestational age, maternal height, parity and baby's sex (adjusted to a standard population). Smoking was found to be the most important single factor, inducing a 5% reduction in birthweight, which was statistically significant even when corrected for consumption of alcohol, tea, coffee or caffeine. Total caffeine consumption (milligrams per week) was calculated for the entire pregnancy and was found to be related to birthweight (adjusted to 40 weeks): with an intake of 0-200 mg/day, birth weight was 3664 g; with 200-400 mg/day, birthweight was 3609 g; and with a daily intake of more than 400 mg/day, the average birthweight was 3556 g. The corresponding birthweight ratios were 1.050, 1.034 and 1.019. In a crude analysis (not corrected for smoking), the difference across groups gives $p = 0.005$; however, when corrected for smoking, the adjusted birthweight ratios did not differ with caffeine consumption categories, being 1.051 (95% CI, 1.039-1.062) for 0-200 mg/day, 1.055 (95% CI, 1.043-1.068) for 200-400 mg/day and 1.054 (95% CI, 1.033-1.075) for >400 mg/day. The authors concluded that smoking was the main environmental cause of variations in birthweight (corrected for gestational age). [The Working Group noted that the

study was not designed to detect a possible effect on birthweight mediated through prematurity.]

In Costa Rica, women of low socioeconomic status were contacted at an antenatal care service before they were six months' pregnant (Muñoz *et al.*, 1988). Of 378 women contacted, 301 fulfilled the entry criteria, which included being aged between 17 and 30 years, uncomplicated pregnancy and delivery, term delivery, avoidance of smoking and alcohol, and initiation of breastfeeding. The study was restricted to non-coffee drinkers and to women who drank 450 ml or more coffee per day. Of 110 eligible women, 62 (56%) dropped out, so that the study was limited to 22 coffee drinkers and 26 who did not drink coffee. Dropouts had had less education and higher parity than the women studied. Birthweight was 121 g lower for the children of coffee drinkers than those of non-coffee drinkers ($p < 0.001$). This difference was still significant after adjustment for potential confounding factors through multiple linear regression. Iron deficiency anaemia was found in 23% of the coffee consumers and in none of the non-consumers. The haematocrit levels of infants of coffee-drinking mothers at one week and one month of age were lower than those of the controls. This association persisted after adjustment for confounding factors. [The Working Group noted the high rate of dropouts.]

The effect of first-trimester maternal caffeine consumption on birthweight was examined in a case-control study of 131 cases and 136 controls (Caan & Goldhaber, 1989). Heavy consumption of caffeine (300 mg/day or three servings) from coffee, tea or cola drinks was associated with a high prevalence of low birthweight. For women who had drunk three or more cups of coffee per day, the crude odds ratio was 2.1; when adjusted for ethnicity, alcohol, cigarettes, pre-pregnancy weight, weight gain and parity, the odds ratio increased to 2.8 (95% CI; 0.89-8.7).

Spontaneous abortions and stillbirths: In the study of Arnandova and Kaculov (1978), described on p. 108, no difference was reported in the rates of spontaneous abortions and stillbirths in relation to coffee drinking.

In the study of Furuhashi *et al.* (1985), described on p. 106, 2% of pregnant women who had drunk coffee and 1.2% of controls had spontaneous abortions ($p < 0.001$). [Reservations regarding this study are given on p. 106. The Working Group noted further that most abortions are likely to have been missed in this study, since women were recruited at 24 weeks' gestation or more. It is unclear whether stillbirths were included among abortions since there was no mention of stillbirths in the report. No confounding variable was adjusted for.]

Srisuphan and Bracken (1986) carried out a prospective study of 3135 pregnant women who had sought antenatal care in the New Haven, Connecticut, area, USA, between 1980 and 1982. Details of the study design are given on p. 110 in the description of the study by Martin and Bracken (1987). The abortion rates were 1.8% for non-caffeine users, 1.8% for light users (1-150 mg/day) and 3.1% for

moderate-to-heavy users (> 150 mg/day) (trend not significant). Comparing moderate-to-heavy users with the remainder, the RR was 1.7 (95% CI, 1.0-2.7; p = 0.03). This estimate was unchanged (RR, 1.7; p = 0.03) after adjustment for maternal age, gestational age, Jewish religion, prior gynaecological surgery and previous spontaneous abortions. Women who received caffeine only from coffee appeared to have a higher risk of miscarriage (RR, 2) than those who drank only tea (1.1) or colas (1.3), but the numbers were small and the differences not significant.

Kršnjavi and Mimica (1987) studied 308 pregnant women in Zagreb, Yugoslavia, in 1982-83, of whom 246 (80%) responded to a questionnaire on alcohol, tobacco and coffee consumption. No association was found between coffee drinking and the frequency of spontaneous abortions.

Effects on fertility: Information on caffeine consumption before trying to conceive was obtained for 221 women. The adjusted mean fecundability ratio for higher caffeine users compared to non-users was 0.80 (Wilcox *et al.*, 1988). An association between reduced fertility and caffeine intake received further support from data presented in a letter to the Editor of *The Lancet* (Christianson *et al.*, 1989). In a further study, however, no association was found between time to conceive and coffee consumption among 2817 women who had recently had a liveborn child, while there was a suggested effect of tea and also of age and tobacco smoking (Joesoef *et al.*, 1990).

(iii) *Genetic and related effects*

The nonpolar fractions of urine from humans who had ingested 12 g of instant coffee per day for four days or 12 g within 2 h were not mutagenic to *S. typhimurium* TA98 or TA100 in the presence or absence of an exogenous metabolic system, with or without β-glucuronidase treatment of the urine (Aeschbacher & Chappuis, 1981).

Organic fractions isolated from the urine of drinkers of at least five cups of coffee per day induced chromosomal aberrations in cultured Chinese hamster ovary cells. This clastogenic effect was abolished in two of the organic fractions by the addition of either catalase or superoxide dismutase to the cell system, suggesting that active oxygen species are involved (Dunn & Curtis, 1985).

In a population of 30 smokers and 30 nonsmokers, a positive, statistically significant linear relationship between the square-root transformed frequency of sister chromatid exchange in cultured peripheral blood lymphocytes and coffee consumption was reported (Reidy *et al.*, 1988). In the same population, a positive linear relationship was observed between the average number of cups of coffee consumed per day and the proportion of low-folate cultured blood lymphocytes with chromosomal aberrations. Only about 5% of the variance was attributable to

coffee consumption. In comparison, smoking contributed about 10% and the use of two different slide scorers contributed about 15% (Chen *et al.*, 1989). [The Working Group noted that this study of smokers and nonsmokers was not designed to evaluate coffee consumption.]

In a study on 44 otherwise healthy splenectomized persons, drinking coffee (and occasionally tea) was associated with a significant, dose-dependent increase in the frequency of micronuclei in both reticulocytes and mature erythrocytes (Smith *et al.*, 1990).

3.3 Epidemiological studies of carcinogenicity to humans[1]

(*a*) *Descriptive epidemiology*

These studies are of four main types. Ecological studies examining geographic variation in coffee consumption and either cancer incidence or mortality rates (Takahashi, 1964; Stocks, 1970; Shennan, 1973; Armstrong & Doll, 1975; Binstock *et al.*, 1983; Decarli & La Vecchia, 1986; Phelps & Phelps, 1988) are the most common. A second type of study examines time trends in cancer rates and coffee consumption within a given country or countries (Morrison, 1978; Pannelli *et al.*, 1989). A hybrid design combines an examination of time trends (Cuckle & Kinlen, 1981; Benarde & Weiss, 1982) and geographic differences among countries. The final type of descriptive studies examines cancer rates among special population groups such as Mormons, a cultural group one of whose practices is abstension from tea and coffee drinking (Enstrom, 1975; Lyon *et al.*, 1976; Enstrom, 1978, 1980; Lyon *et al.*, 1980), in which incidence and mortality rates for different cancer sites were compared either with the general population or with non-practising Mormons. It is not possible in these studies, however, to distinguish between the effect of reduced coffee and tea consumption, reduced cigarette smoking and alcohol drinking and the other prohibited behaviours of this sect; they do not contribute to our knowledge of the association between coffee drinking and cancer risk and are not discussed further in this monograph.

(i) *Bladder cancer*

In an examination of time trends in incidence rates and per-caput coffee imports in the USA and Denmark, coffee consumption was adjusted for cigarette consumption. No association was noted between changes in bladder cancer rates

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[1]The Working Group was aware of a large multicentre case-control study on pancreatic cancer which has been completed, but the results were not available.

and coffee imports in Denmark or among women in the USA; a weak positive association was noted for US men (Morrison, 1978). Cohort and period variation in bladder cancer mortality in Italy between 1950-54 and 1980-81 was compared with changes in coffee, cocoa, tea and cigarette consumption. The authors stated that changes in coffee intake do not explain the cohort changes (Pannelli *et al.*, 1989). No association was noted in the study of either Armstrong and Doll (1975) or Stocks (1970).

(ii) *Breast cancer*

Weak positive correlations were reported between incidence ($r = 0.42$) and mortality ($r = 0.37$) from breast cancer and coffee consumption in a geographical study (Armstrong & Doll, 1975). Phelps and Phelps (1988) conducted an ecological study, which did not distinguish between tea and coffee consumption, and reported a correlation of 0.004 with breast cancer mortality ratios after adjusting for dietary fat intake.

(iii) *Endometrial cancer*

A positive correlation was reported between the incidence of corpus uterine cancer ($r = 0.43$) and international variation in coffee consumption (Armstrong & Doll, 1975).

(iv) *Kidney cancer*

The correlation between age-adjusted mortality rates from kidney cancer in 1964 and per-caput coffee consumption was 0.79 ($p < 0.001$) (Shennan, 1973). A reported correlation between coffee consumption and the incidence of kidney cancer (men, 0.62; women, 0.40) was explained by the stronger association with consumption of animal protein (Armstrong & Doll, 1975), which is also correlated with coffee consumption.

(v) *Leukaemia*

A positive correlation was reported between mean, age-adjusted mortality rates for leukaemia in 1964-65 and annual coffee consumption (males, $p = 0.001$; females, $p = 0.03$) (Stocks, 1970).

(vi) *Ovarian cancer*

A positive correlation was reported between mean, age-adjusted mortality rates in 1964-65 and annual coffee consumption ($p = 0.006$) (Stocks, 1970). A weak correlation was reported between incidence ($r = 0.50$) and mortality ($r = 0.50$) and coffee consumption in the study of Armstrong and Doll (1975).

(vii) *Pancreatic cancer*

An association was reported between mean, age-adjusted death rates for males in 1964-65 and annual coffee consumption ($p = 0.008$) (Stocks, 1970). An

examination of international time trends in mortality rates and coffee consumption, in which adjustment was made for changes in lung cancer mortality as a proxy for smoking, showed correlations of 0.58 (males) and 0.66 (females) (Cuckle & Kinlen, 1981). An additional correlation study in the USA, which used lag periods to examine trends in mortality ratios and coffee consumption, reported correlation coefficients ranging from 0.39 to 0.68 over the period of the study (Benarde & Weiss, 1982). A simple correlation coefficient of 0.59 ($p = 0.001$) between coffee consumption in 1957-65 and mortality in 1971-74 was found to be significant after controlling for confounding variables (Binstock *et al.*, 1983). Positive but nonsignificant correlation coefficients have been reported between age-standardized, sex-specific mortality rates and per-caput coffee consumption in 20 regions of Italy (Decarli & La Vecchia, 1986).

(viii) *Prostatic cancer*

The correlation between age-adjusted mortality ratios for 1956-59 and per-caput coffee consumption for 1955-59 was 0.7 ($p < 0.001$) (Takahashi, 1964). This association was confirmed using mortality data for 1964-65 ($p < 0.001$) (Stocks, 1970).

(*b*) *Cohort studies*

The association between coffee consumption and subsequent cancer incidence or mortality has been investigated in a number of prospective studies. In the following text, the most recent publication on cancer outcomes has been summarized when a number of papers have been generated from a single cohort study. The studies are summarized in Table 31 on p. 119.

(i) *All sites combined*

Heyden *et al.* (1979) conducted a nine-year follow-up of 2530 US men and women interviewed about their daily coffee consumption in 1967-69. Seventy-four cancer deaths with biopsy or hospital data were analysed. Two sets of controls consisted of age-, race- and sex-matched deaths from cardiovascular disease and live study participants. Coffee consumption was more common among each set of controls than among the cancer cases (odds ratio, 0.67; $p > 0.05$). The matched-pairs odds ratios were based on 6:9 discordant pairs for each set of controls.

The association between coffee consumption and mortality from all causes, coronary heart disease and noncoronary causes over 19 years was examined among 1910 white men, aged 40-56 at the time of the baseline examination, who took part in a study of the Chicago Western Electric Company (LeGrady *et al.*, 1987). Intake was measured in terms of 6-oz (178-ml) cups over 28 days. Since only 97 men consumed

two or more cups of decaffeinated coffee per day, intake of caffeinated and decaffeinated coffee was combined. The Cox proportional hazards model was used to analyse the association between coffee intake and mortality after adjustment for age, diastolic blood pressure, serum cholesterol and smoking. The adjusted RR for cancers at all sites comparing none to one cup per day with all other levels of intake was 1.6 (95% CI, 0.95-2.6). [The Working Group noted that no analysis of site-specific cancer risks was undertaken.]

(ii) *Site-specific analyses*

A case-control analysis of a cohort study investigated pancreatic cancer mortality in a 16-50-year follow up of 50 000 male former college students (Whittemore *et al.*, 1983). There were 126 deaths from pancreatic cancer. Data on coffee and tea consumption and other variables had been collected during a physical examination at college. No significant association was noted with coffee consumption.

A series of letters to the Editor of *The Lancet* (Nomura *et al.*, 1981; Kinlen *et al.*, 1984; Nomura *et al.*, 1984) report pancreatic cancer incidence in cohort studies. Since Nomura *et al.* (1986) reported on pancreatic cancer and coffee consumption in the same cohort, no additional data from these letters are reported here. Kinlen *et al.* (1984) carried out a cohort study of 14 085 men in London, UK. There were 47 deaths from pancreatic cancer, identified from death certificates, in the 13 years of follow-up to 1982. The mean daily consumption of coffee, adjusted for age and smoking, was 0.83 cup for cases and 1.00 cup for controls.

In a Hawaiian cohort study of the association between cancer incidence and coffee consumption, 7355 Japanese men were followed for a minimum of 14 years from the time of collection of 24-h consumption data in 1965-68 (Nomura *et al.*, 1986). There were 672 incident cancers in the cohort as of July 1983. Incidence rates were adjusted for age or both age and smoking, using the entire cohort as the standard population. The reference category for all analyses included the 1173 men who reported drinking no coffee. Coffee intake was analysed according to none, one to two, three to four and five or more cups per day. No significant association was reported between coffee drinking and age- and smoking-adjusted RRs for pancreatic cancer (p for trend, 0.41), lung cancer (p for trend, 0.19) or bladder cancer (p for trend, 0.25). No association was noted with colon cancer risk. [The Working Group noted that dietary information was based on a single 24-h recall.]

A series of papers has examined the association between coffee intake and 21-year mortality among Seventh-day Adventists in the USA (Phillips & Snowdon, 1983; Snowdon & Phillips, 1984; Phillips & Snowdon, 1985).

The final analysis in the series was based on a cohort of 25 493 subjects (Phillips & Snowdon, 1985). Univariate analyses indicated a consistent positive

relationship between colon and rectal cancer death rates and increased coffee consumption for both men and women. Drinking two or more cups of coffee per day was associated with a crude RR for colon cancer of 2.0 (95% CI, 1.1-3.6) for men and 1.5 (0.8-2.6) for women. Different multivariate analyses were completed for the first 10 and the last 11 years of follow-up since the association between coffee drinking and colorectal cancer varied across this period. The excess risk associated with drinking two or more cups of coffee per day in the latter follow-up period was 3.0 ($p > 0.05$) for men following adjustment for age, egg consumption, excess weight and meat consumption. The equivalent adjusted risk for women was 2.4 ($p < 0.05$). [The Working Group noted that the distribution of coffee drinking in this population is unusual because there are few heavy coffee drinkers: 17-18% of the population drank two or more cups per day. There may be residual confounding by other factors associated with non-adherence to dietary restrictions.]

Two papers have been published from a prospective study conducted in Norway examining the relationship between coffee drinking and cancer incidence and mortality among approximately 16 000 men and women (Heuch *et al.*, 1983; Jacobsen *et al.*, 1986). Site-specific incidence and mortality were determined among three groups of people: a probability sample of adult males selected from the 1960 census, Norwegian brothers of migrants to the USA, and spouses and siblings of people interviewed for a case-control study of gastrointestinal cancer. Average daily coffee consumption was determined by questionnaire in 1967-69. No data are presented on the completeness of the 11.5-year follow-up, during which time there were 602 cancer deaths and 1498 incident cancers (including 207 nonmelanomatous skin cancers). Incidence data that were presented for approximately 20 cancer sites were adjusted for sex, age and residence; some additional analyses among males were also adjusted for smoking. In the calculation of RRs, comparisons were made between the consumption of two or fewer and seven or more cups per day. The RR for mortality from cancers at all sites was 1.3 (p for trend = 0.09). Raised RRs were reported for the incidence of cervical (10.6; p for trend = 0.07) and lung cancer (1.8; p for trend = 0.02); the smoking-adjusted RR for lung cancer incidence among males was 1.1 (p for trend = 0.84). Heavy coffee drinking was associated with reduced risks for the incidence of colon (RR, 0.6; p for trend = 0.10) and kidney cancer (RR, 0.3; p for trend = 0.01). The RR for the incidence of pancreatic cancer was 0.7 (p for trend = 0.37) and that for bladder cancer was 0.99 (p for trend = 0.99). [The Working Group noted that odds ratios were in fact calculated and presented as RRs.]

A cohort study investigated a six-year follow-up of pancreatic cancer incidence among 122 894 men and women who had completed a questionnaire collecting data on coffee, tea, smoking and alcohol use in 1978-84 (Hiatt *et al.*, 1988). There were 49 cases of pancreatic cancer. A multivariate analysis (adjusting for age, sex, ethnicity,

blood glucose level, smoking, alcohol and diabetes) identified no increased risk associated with increasing coffee consumption.

A cohort study (Mills *et al.*, 1988) of approximately 34 000 non-Hispanic, white Californian Seventh-day Adventists followed participants for six years after their completion of a questionnaire determining their exposures in 1976. Forty deaths from pancreatic cancer were reported. In the analyses of age- and sex-adjusted RRs for pancreatic cancer, current consumption of coffee at least once a day relative to no consumption was associated with a RR of 2.0 (95% CI, 0.9-4.4). Past consumption showed an inconsistent, nonsignificant protective relationship with mortality from pancreatic cancer. Multivariate analyses, using the Cox proportional hazards model, give a RR for current coffee consumption, adjusted for age, sex and smoking of 2.2 (95% CI, 0.6-8.0).

A cohort study of colorectal cancer incidence in a retirement community (Wu *et al.*, 1987) identified 58 male and 68 female cases among 11 888 people in a 4.5-year follow up. Questionnaires were completed between 1981 and 1982 by 62% of community members. In an analysis that adjusted only for age, there was no effect of increased coffee intake on cancer risk in women and a nonsignificant increase in men.

Paffenbarger *et al.* (1978) examined the association between coffee drinking and mortality from six cancers in a nested case-control analysis of a cohort study in the USA of 50 000 male former college students (the same population as used by Whittemore *et al.*, 1983, p. 116). Each case was matched with four controls chosen randomly from among classmates born in the same year and known to have survived the decedent. Information on risk factors was obtained from medical records completed at the time of college entry. Coffee drinking at that time was associated with a two- to three-fold higher risk for Hodgkin's disease, lymphatic and myeloid leukaemia, but no significant association was found with non-Hodgkin's lymphoma, with malignant melanoma or with other and unspecified leukaemias.

(c) *Case-control studies*

(i) *Bladder and urinary tract*

Bladder cancer: More than two dozen case-control studies have been published on the association between coffee and bladder cancer. Their main results are summarized in Tables 32 (users *versus* non-users) and 33 (dose-response relationships and significance of the linear trend in risk) on pp. 129 and 132. Whenever possible, combined RRs are derived from data presented in strata of sex, age, race and other possible covariates.

Cole (1971) reported a population-based case-control study of 445 cases of cancer of the lower urinary tract (renal pelvis, ureter, bladder (90% of cases) and

Table 31. Summary of results of cohort studies on cancer and coffee consumption

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Heyden *et al.* (1979) USA All sites	2530 men and women	74	<5 ≥5	1.0 0.7	$p > 0.05$; same RR with each control group
LeGrady *et al.* (1987) USA All sites	1910 white men	117	0–1 ≥2	1.0 1.6 (0.95–2.6)	Adjusted for age, diastolic blood pressure, serum cholesterol and smoking
Whittemore *et al.* (1983) USA Pancreas	50 000 men	126	0 Any	1.0 1.1 (0.7–1.9)	Past coffee consumption Adjusted for age, college and class year
Kinlen *et al.* (1984) UK Pancreas	14 085 men	47	Mean: cases, 0.83 controls, 1.00		Adjusted for age and smoking
Nomura *et al.* (1986) Hawaii	7355 Japanese men				
Pancreas		21	0 1–2 3–4 ≥5	1.0 [1.2] [2.1] [1.6]	$p = 0.41$, adjusted for age and smoking
Lung		110	0 1–2 3–4 ≥5	1.0 1.1 1.1 1.4	$p = 0.19$, adjusted for age and smoking
Bladder		39	0 1–2 3–4 ≥5	1.0 1.0 1.4 1.6	$p = 0.25$, adjusted for age and smoking

Table 31 (contd)

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Phillips & Snowdon (1985) USA Colon	Seventh-day Adventists 9 175 men	53	< 1 1 ≥2	1 1.3 (0.5–3.4) 2.0 (1.1–3.6)	p = 0.04, adjusted for age
	16 336 women	83	< 1 1 ≥2	1 1.2 (0.6–2.4) 1.5 (0.8–2.6)	p = 0.20, adjusted for age
Rectum	25 493 men and women	28	< 1 1 ≥2	1.0 1.4 (0.6–3.1)	p = 0.38, adjusted for age and sex
Wu *et al.* (1987) USA Colon and rectum	11 888 men and women	58 men	0–1 2–3 ≥4	1.0 1.3 (0.7–2.5) 1.5 (0.6–3.7)	Adjusted for age
		68 women	0–1 2–3 ≥4	1.0 1.5 (0.8–2.7) 1.2 (0.4–3.1)	
Hiatt *et al.* (1988) USA Pancreas	122 894 men and women	49	0 < 1 1–3 ≥4	1.0 0.8 (0.3–2.6) 0.9 (0.4–2.1) 0.7 (0.2–1.9)	Adjusted for age, sex, ethnic group, blood glucose, smoking, alcohol and diabetes
Mills *et al.* (1988) USA Pancreas	34 198 white male and female Seventh-day Adventists	40	Current use Never < Daily Daily	 1.0 1.4 (0.6–3.6) 2.0 (0.9–4.4)	p for trend = 0.087, adjusted for age and sex

Table 31 (contd)

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Mills *et al.* (1988) USA Pancreas (contd)			Past use Never < Daily Daily	 1.0 0.7 (0.2–1.9) 0.7 (0.3–1.5)	$p = 0.254$, adjusted for age and sex
Paffenbarger *et al.* (1978) USA	50 000 men				
Hodgkin's disease		45	Never Ever	1.0 2.5	$p = 0.07$; RR based on matched analysis
Non-Hodgkin's lymphoma		89	Never Ever	1.0 1.6	Nonsignificant
Malignant melanoma		45	Never Ever	1.0 1.3	Nonsignificant
Lymphatic leukaemia		27	Never Ever	1.0 2.7	$p = 0.06$
Myeloid leukaemia		41	Never Ever	1.0 3.2	$p = 0.02$
Other/unspecified leukaemias		30	Never Ever	1.0 0.8	Nonsignificant

urethra) and 451 controls from Massachusetts, USA. The study, in which 90% of cases and controls participated, found a RR of 1.2 for men and 2.6 for women among coffee drinkers *versus* non-coffee drinkers, after adjustment for age and smoking at three levels (non-smokers, $\leq$1/2 pack, > 1/2 pack per day). The RR was significant for women, and was 1.6 for one, 3.8 for two to three and 2.2 for four or more cups per day. The association was apparently stronger among the 90 cases who neither smoked nor had a high-risk occupation.

In a study conducted in Louisiana, USA, Dunham *et al.* (1968) obtained information on 493 patients with bladder cancer and 527 controls admitted to hospital for a wide spectrum of other conditions. The data were stratified for type of coffee, sex and race, and reanalysed by Fraumeni *et al.* (1971), in a study reported as a letter to the Editor of *The Lancet*. Some association was found for blacks (significant in females) but not for whites. After adjustment for age and smoking, the overall RR was 1.5 (nonsignificant). There was no consistent dose-response relationship.

In a Canadian case-control study of 158 men and 74 women with bladder cancer and similar numbers of controls with benign prostatic hypertrophy (men) or stress incontinence (women), data were collected using a postal questionnaire on previous health, employment, beverage and artificial sweetener intake (Morgan & Jain, 1974). The overall response rate was 69% among the cases and 57% among the controls, but the numbers of subjects included in the final analysis were further reduced by matching for age. The mean number of cups of coffee drunk per day was 1.8 for cases and 2.0 for controls among females, and 2.1 for both cases and controls among males. The RR (calculated by the Working Group) for coffee drinkers *versus* non-drinkers was [0.7] for males and [1.3] for females. None of these estimates, nor the corresponding trends in risk with dose was significant.

A study by Simon *et al.* (1975) was based on 216 white female cases of cancer of the lower urinary tract (renal pelvis, ureter, bladder (95% of cases) and urethra) identified at 10 hospitals in urban areas in Massachussets, USA. Among them, 40 had died and 41 did not respond. The remaining 135 cases were compared with 390 respondent controls out of a total of 648 selected from the discharge lists of the same hospitals. Postal questionnaires were used for data collection. Ninety-three percent of cases drank coffee *versus* 85% of the controls, with an unadjusted RR of 2.1 (95% CI, 1.1-4.3). The unadjusted RRs were 2.2 for one or two cups per day, 1.9 for three to four and 2.3 for five or more. [Adjustment for smoking by the Working Group was possible according to two categories only (nonsmokers and light smokers *versus* moderate to heavy smokers); the RR declined to [1.9] and was no longer significant.]

Wynder and Goldsmith (1977) utilized data collected between 1969 and 1974 on patients interviewed in 17 hospitals in six areas of the USA (46% from Memorial

Hospital in New York City). A total of 574 male and 158 female bladder cancer patients and equal numbers of hospital controls were considered. The refusal or nonparticipation rate was less than 4%. The RRs for whether coffee was ever drunk or not, adjusted for smoking at four levels, were above unity [RR, 1.5 for males, 1.3 for females]. Trends in risk with dose were not significant.

Miller *et al.* (1978) published data from a study originally planned to consider the possible association between isonicotinic acid hydrazide, a drug used in the treatment and prophylaxis of tuberculosis, and bladder cancer. Patients admitted to a hospital in Ottawa for bladder cancer (255 cases) and other urological conditions (510 controls) completed a questionnaire including, among other items, information on coffee and tea consumption. In relation to coffee, a matched, unadjusted analysis provided a RR of 1.3 for males and of 1.6 for females. [The Working Group noted that no information was provided on the confounding or modifying effect of covariates, including smoking.]

Mettlin and Graham (1979) studied the role of dietary factors in the risk for bladder cancer using data from the Roswell Park Memorial Institute, NY, USA, collected between 1957 and 1965 (Bross & Tidings, 1973). A total of 429 white male and 140 white female patients with primary bladder cancer were compared with 1025 controls admitted for non-neoplastic conditions. After adjustment for smoking in two categories (less than half a pack *versus* half a pack or more per day), the RR for five subsequent levels of coffee drinking was around unity in women, but above unity in men, in the absence, however, of any trend in risk (RRs, 1 (referent), 1.4, 1.2, 2.1 and 1.6). Consequently, in the two sexes combined, there was a small, inconsistent increase in smoking-adjusted RRs for bladder cancer risk with increasing coffee consumption: 1 (referent), [1.2, 1.1, 1.8 and 1.3].

Howe *et al.* (1980) reconsidered the relation between coffee and bladder cancer in a Canadian population-based case-control study of 480 male and 152 female case-control pairs (Miller, 1977). The overall response rate was 77% for the cases and 86% for the controls. For users *versus* non-users of any coffee preparation, the RR was 1.4 for men and 1.0 for women, neither estimate being significant. The unadjusted RRs were 1.5 (95% CI, 1.0-2.2) for men consuming brewed coffee and 1.5 (1.1-2.0) for those drinking instant coffee, and 1.4 (0.8-2.6) for women consuming instant coffee, but no dose-response relationship was found.

Cartwright *et al.* (1981) conducted a case-control study of bladder cancer in West Yorkshire, UK, a high incidence area for the disease. The study population included 841 cases (631 male, 210 female; 622 prevalent, 219 incident) and 1060 hospital patients of similar age and same sex. In this preliminary report, no information was given on participation rate. Questions were asked on coffee drinking habits and various types of coffee, besides other known and potential bladder cancer risk factors (smoking, saccharin use, occupational history, past

medical history). No relation was found between any type of coffee consumption and bladder cancer risk after adjustment for smoking. The RRs for drinking all types of coffee, adjusted for age, type of case (incident/prevalent) and cigarette smoking, were 1.1 for males and 0.8 for females (corresponding estimates not adjusted for smoking were 1.3 and 1.1, respectively). Similarly, no heterogeneity in risk was observed between instant and ground coffee. The authors concluded that the correlation between cigarette and coffee consumption can explain the moderate association observed in the unadjusted analysis.

Morrison *et al.* (1982) published data from a population-based case-control study from Boston, MA, USA (587 cases, 528 controls), Manchester, UK (541 cases, 725 controls) and Nagoya, Japan (289 cases, 586 controls). A further report of a section of this study was made by Ohno *et al.* (1985). Controls were selected from electoral rolls or other population registries. Participation rates in various centres were over 80% for both cases and controls. The overall RR for coffee drinkers *versus* non-drinkers, adjusted for age, sex, centre and smoking was 1.0 (95% CI, 0.8-1.2), and in none of the centres was there consistent evidence of a dose-response relationship.

Najem *et al.* (1982) considered several risk factors for bladder carcinogenesis in a case-control study in New Jersey, USA, of 75 histologically confirmed cases among white people and 142 matched controls derived from the same clinic and hospital populations from which bladder cancer cases were obtained. Only five cases and 16 controls did not consume coffee. The RR (not adjusted) was 1.8, with a very wide 95% CI (0.1-10.0). [The Working Group noted the small number of cases and the limited information provided.]

Sullivan (1982) analysed 82 bladder cancer cases (out of 101 diagnosed) and 169 controls selected through random digit dialling in the area of greater New Orleans, LA, USA. In relation to coffee drinking, a number of inconsistent relationships was observed. White male cases, for instance, reported significantly greater consumption of brewed ground coffee than controls, and white women consumed more decaffeinated ground coffee than controls. No relationship was found with duration of use. [The Working Group noted that no RR was given, and there was no indication that adjustment was made for covariates.]

The largest case-control study on bladder cancer was that published by Hartge *et al.* (1983), based on 2982 cases and 5782 general population controls interviewed in a collaborative, population-based study conducted in ten geographical areas of the USA. A report of part of this study was made by Marrett *et al.* (1983). Participation was 73% for the cases and 82% for the controls. The RRs for ever *versus* never coffee drinking were 1.6 (95% CI, 1.2-2.2) for men, 1.2 (0.8-1.7) for women and 1.4 (1.1-1.8) for men and women combined, after simultaneous allowance for sex (when appropriate), age, race, geographical area and tobacco

consumption. When various levels of coffee consumption were considered, the RR was significantly above unity (1.5; 1.1-1.9) only for men drinking over 63 cups of coffee per week, but no dose-response relationship was evident for either men or women. Similarly, there was no association with duration of coffee drinking. No interaction was observed with geographical area, race, occupation, artificial sweetener use or history of urinary infections. The authors noted that adjustment for smoking reduced the RR for ever/never coffee drinking from 1.8 to 1.4, and that residual confounding by tobacco (or possibly other correlates of coffee drinking) may explain the persistent but inconsistent relation between bladder cancer and coffee. Men who drank only decaffeinated coffee (ground or instant) had an estimated RR of 1.2 (0.8-1.9) compared to men who never drank coffee. The corresponding estimate for women was 1.5 (0.9-2.6). Kantor *et al.* (1988), examining the same data set by three separate histological types (squamous-cell, adeno- and transitional-cell carcinomas), found a significant trend in risk for adenocarcinomas in men and women combined, although the number was extremely low (32 cases) and none of the point estimates was significant. [The Working Group noted that the lack of significance may be the result of less precise adjustment for smoking than in the study by Hartge *et al.* (1983).]

In a population-based study carried out using the Connecticut (USA) Tumor Registry during 1978-79, Marrett *et al.* (1983) investigated the relationship between coffee consumption and bladder cancer. Data were available on 412 cases aged 21-84 (80% of those identified) and 493 controls (81% of those selected). After adjustment for age and smoking, the RR for one cup per week or more was 1.3 for males and 1.1 for females; for more than seven cups per week the RR was 1.5 for males and [1.0] for females. In males, there was some evidence of a dose-response relationship: for over 21 cups per week, the RR was 2.0. No trend in risk with dose was evident in females, nor with duration in people of either sex. The authors noted that among male and female nonsmokers combined, the RR for more than seven cups per week was 1.9 (95% CI, 1.0-3.6). There was no significant effect of the consumption of decaffeinated coffee. [The Working Group noted that there may be some overlap between this study and that of Hartge *et al.* (1983).]

In a case-control study in Aarhus, Denmark, Mommsen *et al.* (1983a,b) collected information from cases admitted to hospital and (through mailed questionnaires) from population controls (response rate of first selected controls, 85%). The overall report, based on 165 male and 47 female cases, found no association with coffee drinking, but an elevated risk was observed (RR, 2.6) among women, although the estimate was not significant and only one case and five controls were not coffee drinkers. Dose-response relationships were not analysed. [The Working Group noted the small number of cases and the limited information provided.]

In a study in Greece, Rebelakos *et al.* (1985) compared 300 cases of histologically confirmed bladder cancer (250 male, 50 female) admitted to the major cancer hospital in Athens with an equal number of age- and sex-matched orthopaedic controls. The refusal rate was only approximately 1%. The RR, adjusted for smoking, was not elevated in drinkers of one cup per day compared with non-coffee users; however, a significant RR of 1.7 was found when drinkers of two or more cups were compared with those drinking fewer than two cups per day. For male and female cases combined, the point estimates for five levels of coffee consumption were 1 (referent), 1.2, 1.7, 2.7 and 0.7, and the trend in risk was significant ($p = 0.02$).

Gonzáles *et al.* (1985) reported a hospital-based case-control study in Spain based on 58 cases; two age-matched controls were available for each case — one with non-urinary tract cancer (excluding lung cancer) and one with non-neoplastic conditions. They found a RR of [0.6] (not significant) for 'habitual coffee consumers'. [The Working Group noted the small number of cases, the limited information provided and that no allowance was made for potential confounders.]

Jensen *et al.* (1986) conducted a population-based case-control study in 1979-81 in Copenhagen, Denmark, of 371 (280 male, 91 female) bladder cancer cases (including papillomas) and 771 controls. The participation rate, as given in a previous paper (Jensen *et al.*, 1983), was 94% among the cases and 75% among the controls. The RR for coffee users *versus* non-users, adjusted for age, sex, smoking (never/ever, plus a measure of pack years) was [approximately 1.4] in men and women combined, and the trend in risk with dose was not significant. The RRs were 1 (referent), 1.4, 1.2, 1.4 and 1.8 for subsequent levels of coffee use. The point estimates tended to be above unity for female coffee drinkers, but they were not dose-related.

Claude *et al.* (1986) conducted a case-control study of lower urinary tract cancer (90% were bladder tumours) in the Federal Republic of Germany. A total of 431 cases (340 male, 91 female) were matched for age and sex with 431 controls, who were primarily patients in hospitals for urological diseases (79%) and in homes for the elderly (21%). Only about 2% of cases refused to participate. The results were presented for each sex separately after allowance for smoking (never/ever and lifetime consumption in packs). In people of each sex, the RRs were above unity for coffee drinkers; the point estimates for more than four cups per day were 2.3 in males and 2.2 in females, and the trend in risk was significant for males. The RRs associated with coffee drinking were similar in smokers and nonsmokers. In this study, a positive association was found with total daily fluid intake, with a particularly high RR in males. The RR for drinking decaffeinated coffee *versus* that for non-users was 1.6 in males and 1.0 in females.

Piper *et al.* (1986) described a population-based case-control study of bladder cancer in women (aged 20-49) conducted in New York State in 1975-80. Information was available through telephone interviews on a total of 173 age-matched pairs, for a participation rate of 68% among cases and 71% among community controls. The crude RR for drinking brewed coffee was 1.6. The RR increased with dose, but the trend was not statistically significant.

In a study in Spain, based on 353 male and 53 female cases of bladder cancer compared with equal numbers of hospital controls without malignant or urological conditions (Bravo *et al.*, 1986, 1987), a positive association emerged among males for drinking 'espresso' coffee, with RRs of 1.9 for fewer than three cups and 2.6 for three or more cups per day. For women, the RR for daily use of coffee was [2.3], of borderline statistical significance. [The Working Group noted that details of the response rate were not given, and no allowance was made for any covariate, including smoking.]

Kabat *et al.* (1986) studied bladder cancer in nonsmokers among 76 male and 76 female cases and 238 male and 254 female hospital controls matched for sex, race, hospital and year of interview; the male controls consisted of 67% cancers not related to tobacco smoking and 33% non-neoplastic conditions; the female controls consisted of 59% and 41%, respectively. No association with brewed coffee was observed in either sex [overall RR adjusted for sex, 1.1; 95% CI, 0.8-1.5], and all subsequent risk estimates with dose were close to unity. Similarly, no association was evident with decaffeinated coffee use.

The RR for coffee drinking was significantly above unity (2.4; 95% CI, 1.4-4.4) in a study of 99 male cases of histologically confirmed bladder cancer and two groups each of 99 controls (one hospital, one neighbourhood) in La Plata, Argentina (Iscovich *et al.*, 1987). A positive trend in risk with dose was found, which persisted after allowance for smoking. The refusal rate was negligible (less than 3% of cases and 5% of controls). [The Working Group noted the limited size of the study and that an unstated number of re-interviews were undertaken to obtain missing information or to correct inconsistencies.]

In a population-based case-control study in Utah, USA, Slattery *et al.* (1988) obtained data on a total of 419 cases of bladder cancer and 889 controls (participation rate, 76% among cases and 82% among controls). A substantial proportion of the Utah population belongs to the Mormon church, which proscribes the use of coffee and tea, besides alcohol and tobacco. The RR for coffee consumption, adjusted for age, sex, diabetes, bladder infections and cigarette smoking was [approximately 1.2]. No consistent dose-response was evident, since the RR was 1.2 for up to 20 servings per week, 1.1 for 21-40 and 1.6 for over 40. Similarly, no association emerged in relation to drinking decaffeinated coffee (RR, 1.0).

In a study in Italy, Ciccone and Vineis (1988) studied coffee drinking among cases of bladder cancer (512 men, 55 women) from the main hospital of Turin; controls were 596 men and 202 women with urological or surgical conditions. The overall participation rate was 82% for cases (although there were only 2% refusals) and 98% for controls. With current coffee use, the overall RR, adjusted for smoking (never, ex- or current smoker) was [1.0] for men and [0.9] for women. There was no evidence of an increase in risk with increasing intake: in both men and women, the adjusted RR for four cups per day or more was 0.8. Similarly, no association was evident for either sex for past use (10 years before interview). The authors noted that the only subgroup with an elevated risk and a dose-response relationship was male nonsmokers.

Risch *et al.* (1988) analysed the association between drinking of coffee, tea and other beverages in a population-based case-control study on dietary factors and bladder cancer based on 826 cases of histologically confirmed bladder cancer and 792 controls in Canada. The participation rate was 67% for cases and 53% for controls. For total coffee consumption, the RR was 0.9 in males and 1.9 in females. Adjustment was made for history of diabetes and cigarette use in terms of cumulated pack-years. There was no association in either sex with frequency of use, and the RRs for the highest intake level (over six cups per day) were 0.9 for males and 1.1 for females. [The Working Group noted that the participation rates were lower than in other case-control studies.]

La Vecchia *et al.* (1989b) provided information on the coffee consumption of 163 patients with histologically confirmed bladder cancer (136 male, 27 female), from a network of hospitals in northern Italy, and of 181 controls with acute, nonneoplastic or urological conditions. The participation rate was over 98%. Compared with non- or moderate coffee drinkers, the RRs adjusted for age, sex, area of residence, social class and smoking were 2.0 for intermediate and 1.6 for heavy drinkers; the trend was not significant.

Renal pelvis and ureter. The etiology and pathogenesis of transitional-cell cancer of the renal pelvis and ureter are in several aspects similar to those of bladder cancer, although the frequency of cancer at these sites is much lower and, hence, the studies are based on small data sets.

One study in the USA (Schmauz & Cole, 1974), based on 43 cases of cancer of the renal pelvis and ureter and 451 population controls, showed a positive association with high levels of coffee consumption among men (RR for over seven cups per day, 14.9; 95% CI, 2.4-94.3).

Table 32. Summary of results of case–control studies of bladder cancer and coffee consumption: users *versus* nonusers[a]

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Cole (1971) USA	Men (345, 351)	1.2 (0.8–1.9)	NS	Adjusted for age and smoking (nonsmokers/ <½pack/≥½ pack per day). Similar relation among nonsmokers non-occupationally exposed to carcinogens
	Women (100, 100)	2.6 (1.3–5.1)	Significant	
Dunham *et al.* (1968); Fraumeni *et al.* (1971) USA	Men and women (493, 527)	1.5	NS; significant in black women	Adjusted for age and cigarette smoking
Morgan & Jain (1974) Canada	Men (158, 158)	[0.7]	NS	Unadjusted; mailed questionnaire
	Women (74, 74)	[1.3]	NS	
Simon *et al.* (1975) USA	Women (135, 390)	2.1 (1.1–4.3)	Significant	[RR, 1.9] (NS) after adjustment for smoking in two categories
Wynder & Goldsmith (1977) USA	Men (574, 574)	[1.5]	NS	Adjusted for smoking (four levels)
	Women (158, 158)	[1.3]	NS	
Miller *et al.* (1978) Canada	Men (183, 366)	1.3	NS	
	Women (72, 144)	1.6 [1.0–2.9]	NS	
Mettlin & Graham (1979) USA	Men and women (569, 1025)	[1.5 (0.9–2.5)]	NS	Adjusted for smoking (two levels) from published data
Howe *et al.* (1980) Canada	Men (480, 480)	1.4 (0.9–2.0)	NS	Unadjusted estimates from matched analysis
	Women (152, 152)	1.0 (0.5–2.1)	NS	
Cartwright *et al.* (1981) UK	Men (631, 789)	1.1 (0.9–1.4)	NS	Adjusted for age, type of case (incident/prevalent) and smoking; no heterogeneity according to type of coffee (instant/ground)
	Women (210, 271)	0.8 (0.6–1.2)	NS	

Table 32 (contd)

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Morrison *et al.* (1982) USA, UK and Japan	Men and women (1417, 1839)	1.0 (0.8–1.2)	NS	Adjusted for age, sex, study area and smoking
Najem *et al.* (1982) USA	Men and women (75, 142)	1.8 (0.1–10.0)	NS	Unadjusted estimates; low power
Sullivan (1982) USA	Men and women (82, 169)	Not given	Significant difference in average mean intake of ground coffee in white men, decaffeinated ground in white women	No relation with duration; unadjusted covariates
Hartge *et al.* (1983) USA	Men and women (2982, 5782)	1.4 (1.1–1.8)	Significant	Adjusted for sex, age, race, geographical area and tobacco history
Marrett *et al.* (1983)[c] USA	Men Women (412, 493)	1.3 [1.1–1.6] 1.1 [0.8–1.4]	Significant NS	Adjusted for age and smoking
Mommsen *et al.* (1983a,b) Denmark	Men (165, 165) Women (47, 94)	No association 2.6 (0.4–18.8)	 NS	Details not given for men; only one female case and five controls non-coffee drinkers
Rebelakos *et al.* (1985) Greece	Men and women (300, 300)	1.7 (1.2–2.3)	Significant	$\geq$2 *versus* < 2 cups per day; adjusted for age, sex and smoking
Gonzáles *et al.* (1985) Spain	Men and women (58, 116)	[0.6]	NS	'Habitual consumers'
Jensen *et al.* (1986) Denmark	Men and women (371, 771)	[~1.4]	NS	Including papillomas; adjusted for age, sex, smoking (never/current; lifetime pack years), tea and soft drinks
Claude *et al.* (1986) Federal Republic of Germany	Men (340, 340) Women (91, 91)	1.8 1.1	NS NS	Adjusted for smoking (never/ever; lifetime pack years). Significant trend in men

Table 32 (contd)

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Piper *et al.* (1986) USA	Women (173, 173)	1.6 (0.8–3.3)	NS	Aged 20–49; unadjusted
Bravo *et al.* (1986) Spain	Men (353, 353)	1.9 (1.4–2.6)	Significant	Matched for age and area of residence; unadjusted
	Women (53, 53)	[2.3 (1.1–5.1)]	Significant	
Kabat *et al.* (1986) USA	Men (76, 238) Women (76, 254)	[1.1 (0.8–1.5)]	NS	Nonsmokers only; adjusted for sex
Iscovich *et al.* (1987) Argentina	Men (99, 198)	2.4 (1.4–4.4)	Significant	Adjusted for smoking
Slattery *et al.* (1988) USA	Men and women (419, 889)	[~1.2]	NS	Adjusted for age, sex, diabetes, bladder infections and smoking
Ciccone & Vineis (1988) Italy	Men	[1.0]	NS	Adjusted for smoking (never, ex-, current)
	Women (567, 798)	[0.9]		
Risch *et al.* (1988) Canada	Men	0.9 (0.6–1.3)	NS	Adjusted for smoking (cumulated pack years) and history of diabetes
	Women (826, 792)	1.9 (1.0–3.4)	Significant	
La Vecchia *et al.* (1989b) Italy	Men and women (163, 181)	[1.8]	Significant	Adjusted for age, sex, area of residence, social class, smoking

[a] In square brackets, calculated by the Working Group

[b] NS, not significant

[c] Some overlap with the study of Hartge *et al.* (1983)

Table 33. Summary of results of case–control studies of bladder cancer and coffee consumption: dose–response relationships

Reference and location	Sex	Relative risk for level of coffee consumption[a]							Significance (trend; p)
		I Lowest	II	III	IV	V	VI	VII Highest	
Cole (1971)	Men	1	1.3	1.2	1.3	–	–	–	Not given
USA	Women	1	1.6	3.8	2.2	–	–	–	
Fraumeni *et al.* (1971)	Men, white	1	1.4	2.0	1.7	–	–	–	Not given
	Men, black	1	2.1	2.9	2.1	–	–	–	
USA	Women, white	1	0.7	0.5	0.3	–	–	–	
	Women, black	1	10.0	4.6	2.2	–	–	–	
Morgan & Jain (1974)[b]	Men and women	[1	0.6	0.9	0.8	1.1]	–	–	Nonsignificant
Canada									
Simon *et al.* (1975)[b]	Women	1	2.2	1.9	2.3	–	–	–	0.28
USA									
Wynder &	Men	1	1.4	1.9	2.0	–	–	–	Nonsignificant
Goldsmith (1977)	Women	1	1.0	1.9	1.3	–	–	–	Nonsignificant
USA									
Mettlin & Graham (1979)	Men and women	1	[1.2	1.1	1.8	1.3]	–	–	Nonsignificant
USA									
Howe *et al.* (1980)[b]	Men	1	[1.6	1.3	1.5]	–	–	–	Nonsignificant
Canada	Women	1	[0.7	1.7	1.3]	–	–	–	Nonsignificant
Morrison *et al.* (1982)									
USA	Men	1	0.8	0.7	0.9	0.8	0.8	1.5	Nonsignificant
	Women	1	0.8	0.6	1.7	0.9	0.7	1.0	Nonsignificant
UK	Men	1	1.1	0.9	0.9	0.8	–	–	Nonsignificant
	Women	1	1.4	0.4	1.2	1.0	–	–	Nonsignificant
Japan	Men	1	1.0	1.2	1.3	1.9	–	–	Nonsignificant
	Women	1	0.7	–	0.7	–	–	–	Nonsignificant
Hartge *et al.* (1983)	Men	1	0.9	1.0	1.1	1.0	1.2	1.5	Nonsignificant
USA	Women	1	0.9	0.8	0.9	0.7	0.9	0.8	Nonsignificant
Marrett *et al.* (1983)[c]	Men	1	1.6	2.0	2.0	–	–	–	Significant
USA	Women	1	[1.3	1.2	1.0]	–	–	–	Nonsignificant

Table 33 (contd)

Reference and location	Sex	Relative risk for level of coffee consumption[a]							Significance (trend; p)
		I Lowest	II	III	IV	V	VI	VII Highest	
Rebelakos *et al.* (1985) Greece	Men and women	1	1.2	1.7	2.7	0.7	–	–	0.02
Jensen *et al.* (1986) Denmark	Men and women	1	1.4	1.2	1.4	1.8	–	–	0.12
Claude *et al.* (1986)	Men	1	1.4	1.4	2.3	–	–	–	< 0.05
Federal Republic of Germany	Women	1	1.3	1.9	2.2	–	–	–	Nonsignificant
Piper *et al.* (1986)[d] USA	Women	1	0.9	1.9	2.1	–	–	–	Nonsignificant
Bravo *et al.* (1986, 1987)[b] Spain	Men	1	1.9	2.6	–	–	–	–	< 0.01
Kabat *et al.* (1986)[b]	Men	1	0.9	1.4	1.4	0.5	–	–	Nonsignificant
USA	Women	1	1.5	0.8	0.7	2.4	–	–	Nonsignificant
Iscovich *et al.* (1987) Argentina	Men and women	1	1.1	4.5	12.0	–	–	–	< 0.01
Slattery *et al.* (1988) USA	Men and women	1	1.2	1.1	1.6	–	–	–	Nonsignificant
Ciccone & Vineis (1988)	Men	1	0.8	1.0	1.2	0.8	–	–	Nonsignificant
	Women	1	1.4	1.0	0.7	0.8	–	–	Nonsignificant
Italy									
Risch *et al.* (1988)	Men	1	1.0	1.2	0.9	–	–	–	Nonsignificant
Canada	Women	1	1.0	1.9	1.1	–	–	–	Nonsignificant
La Vecchia *et al.* (1989b) Italy	Men and women	1	2.0	1.6	–	–	–	–	Nonsignificant

[a] The levels relate to different quantities in each study; therefore, they offer information for analyses within each study but not for comparisons between studies. 1, lowest (referent) level; 7, highest level

[b] Crude risks

[c] Some overlap with the study of Hartge *et al.* (1983)

[d] Adjusted risks, but not stated whether smoking included

A matched hospital-based study of 33 cases of cancer of the renal pelvis and 33 controls in the UK (Amstrong *et al.*, 1976) found no positive association with coffee [RR, 0.2; $p < 0.01$]. Indeed, there was a significant excess of cases who had never consumed coffee regularly.

A population-based case-control study of 74 cases and 697 controls in the USA (McLaughlin *et al.*, 1983) showed no consistent association between cancer of the renal pelvis and coffee drinking in people of either sex after adjustment for smoking (RR, 1.6 for men, 0.5 for women).

The largest study on cancer at this site (187 case-control pairs) was conducted in Los Angeles County, USA, using telephone interviews for cases and neighbourhood controls (Ross *et al.*, 1989). Heavy coffee drinkers had an apparently elevated risk for cancer of the renal pelvis and ureter (RR for seven cups or more per day, adjusted for cigarette smoking, 1.8), but the trend in risk with dose was not significant.

Kidney: The causes of renal-cell cancer (adenocarcinoma of the kidney) are less well defined but are certainly, at least in part, different from those of cancer of the urinary tract.

In a case-control study conducted in several areas of the USA between 1965 and 1973 on 202 patients with adenocarcinoma of the kidney and 394 hospital controls, Wynder *et al.* (1974) found no significant difference in daily coffee consumption within each smoking category: [RR, 0.6, 0.9 and 1.1 for 1-2, 3-4 and $\geq$5 cups per day).

Armstrong *et al.* (1976) conducted a case-control study of 106 cases of adenocarcinoma of the renal parenchyma and 106 controls in Oxford, UK, and found neither an association with coffee use [RR, 1.1] nor a dose-response relationship.

McLaughlin *et al.* (1984) conducted a population-based case-control study on 495 cases of renal-cell carcinoma and 697 controls from the Minneapolis-St Paul seven-county metropolitan area (USA). The RR for ever having drunk coffee was 1.0 (95% CI, 0.6-1.8) in men and 1.4 (0.7-2.9) in women. In neither was a dose-response relationship observed.

Goodman *et al.* (1986) conducted a hospital-based case-control study of renal-cell carcinoma among 189 men and 78 women from various areas of the USA. For coffee drinking, the RRs (for the two sexes combined) were 0.7 for one to two cups per day and 0.8 for three or more compared with non-coffee drinkers. The RR for ever having drunk decaffeinated coffee was 1.9 (95% CI, 1.0-3.6), but people drinking one to two cups per day had a RR of 2.0 while those drinking three cups or more had a RR of 1.3.

In a study of 166 incident cases of renal-cell carcinoma and an equal number of age-, sex- and race-matched neighbourhood controls, Yu *et al.* (1986) found an association in women for daily coffee consumption (RR, 2.3; $p = 0.06$) in the absence of a direct dose-response relationship. No significant association was observed in men.

A study from Australia (McCredie *et al.*, 1988) based on 360 cases of cancer of the renal parenchyma and 985 population controls found no association with coffee consumption, but no precise information is given in the text.

(ii) *Pancreas*

Twenty-one case-control studies have reported on the relationship between coffee consumption and pancreatic cancer; these data are summarized in Table 34 on p. 140.

As part of a study of cancer at 13 sites, Lin and Kessler (1981) reported on 109 histologically confirmed cases (67 male, 42 female) of pancreatic cancer (94 adenocarcinomas and 15 islet-cell tumours) identified in 1972-75 in more than 115 hospitals in the USA. Equal numbers of hospital controls were matched for age, sex, race, hospital and year of admission. Most of the cases and controls were interviewed while in hospital by a person who was unaware of the diagnosis of the patient. Overall 86% of eligible subjects were interviewed. It was reported in a letter that an association was found with drinking decaffeinated coffee but not with total coffee consumption: 91% of the cases drank coffee compared to 93% of controls, but 41% of cases drank decaffeinated coffee compared to only 25% of controls ($p < 0.01$) (Kessler, 1981).

MacMahon *et al.* (1981a,b; the latter study was reported in a letter) reported on 367 histologically confirmed cases (216 male, 151 female) of pancreatic cancer (excluding islet-cell tumours) out of 578 patients under 80 years of age identified in 11 hospitals in Boston and Rhode Island, USA. There were 643 hospital controls, out of 1118 eligible patients, who had been at hospital at the same time as the cases; 254 had diseases other than cancer at sites other than the gastrointestinal tract, 157 had cancers other than in the gastrointestinal tract, 117 had diseases of the gastrointestinal tract other than cancer, and 115 had gastrointestinal cancer. Each case and control pair was interviewed personally by the same physician. The main reasons for failure to participate were death (20 cases, 9 controls), early discharge (35, 131), illness (78, 179), language difficulties (14, 26) and refusal (26, 73). An increased risk was found for both men and women. The RR of coffee drinkers *versus* non-coffee drinkers was 2.6 for men and 2.3 for women. No dose-response was observed in men, but a significant trend with consumption was found in women, rising to a risk of 3.1 for women who drank five or more cups per day. These risks persisted after adjustment for cigarette smoking.

Several generally smaller studies (Elinder *et al.*, 1981; Jick & Dinan, 1981; Goldstein, 1982; Severson *et al.*, 1982) reported essentially negative results. The study of Jick and Dinan (1981), published as a letter, which gave few details, was based on 83 cases and 161 hospital controls aged < 80 years in several countries matched 2:1 for age, sex, hospital and year of admission and used a standard personal hospital interview. Elinder *et al.* (1981) conducted two studies: In one, they used information from certificates of deaths in 1961-74 in two small Swedish parishes; the study was based on 21 male cases and 51 deceased male controls obtained from a random sample of deaths in the same parish and matched for age. Next-of-kin, usually wives, were interviewed. The second study was based on 41 twin pairs, born 1886-1925, both of whom were alive in 1961 and one of whom developed pancreatic cancer. Information was obtained from postal questionnaires. The study of Goldstein (1982) was based on 91 histologically verified cases of pancreatic cancer diagnosed in 1973-80 in San Diego, CA, USA; controls were patients with cancer of the prostate (45) and breast (48). Routine hospital interview data were used. Severson *et al.* (1982) based their study on 22 cases aged 40-79 from a registry that was part of the SEER (Surveillance, Epidemiology and End Results) Program in Seattle, WA, USA, 1977-80, and on a random population sample of controls. Next-of-kin were interviewed for most of the cases (20), whereas personal interviews were obtained for controls. The last two studies were also published as letters, which contained few details.

A large study of 275 histologically verified cases (153 men, 122 women) aged 20-80 interviewed in 1977-81 and of 7994 hospital controls also gave negative results, with risk ratios very near to unity after adjustment for smoking (Wynder *et al.*, 1983). This was part of a large study of tobacco-related cancers in six US cities; controls were patients with non-tobacco-related diseases: 42% had other cancers, 10% had benign neoplasms and 7% had trauma. Personal interviews were carried out within six months of diagnosis. During the last year of interviewing, 45% of potential cases and 35% of potential controls completed interviews. The main reasons for not interviewing cases were death, early discharge, illness and personal or physician refusal. The main reason for not interviewing controls was that their initial diagnosis had been made more than six months before interview.

Kinlen and McPherson (1984) re-evaluated data from the case-control study of Stocks (partly reported by Stocks, 1957) on data collected in north-west England and north Wales in 1952-54 on 216 cases (109 men, 107 women) aged > 40 years. These were compared with 432 controls, who were patients with other cancers in the original study, matched 2:1 for age, sex and area of residence; cancers of the lung, bladder, mouth, pharynx, oesophagus, gastrointestinal tract and ovary were excluded, and controls were thus patients with breast cancer (38%), prostatic cancer (19%), leukaemia or lymphoma (19%), renal cancer (7%) and other cancers

(17%). No relation with coffee consumption was found either before or after adjustment for smoking.

Subsequent studies by Gold *et al.* (1985), Mack *et al.* (1986) and Norell *et al.* (1986) all provided some evidence of an association. In the study of Gold *et al.* (1985), 201 cases (94 men, 107 women) were interviewed and included in a matched analysis out of a total of 392 patients with pancreatic cancer from 16 hospitals in Baltimore, MD, USA, in 1977-80. Seventy-two patients refused to be interviewed, physician consent was not obtained for 36, and 10 patients could not be traced or had died and no relative could be found. Of the 201, 25% had a personal interview; for 35% the spouse was interviewed and for 40%, another relative. Two control groups were used: a matched hospital series (for age, race, sex, hospital, date of admission) in which patients with other cancers were excluded (30% had heart or other circulatory disease and 13% had digestive disease) and a population-based group that was chosen by random-digit dialling, matched by age, race, sex and telephone exchange and interviewed by telephone. Participation was about 50% of 'eligible' individuals in both control series; a total of 20 706 telephone numbers and 37 033 calls were made to find eligible controls. A nonsignificant relationship was found among women only, but this was less apparent when smoking was adjusted for.

Mack *et al.* (1986) conducted a study of 490 histologically confirmed cases (282 male, 208 female) of adenocarcinoma of the exocrine pancreas in patients aged <65 years, comprising all those registered in Los Angeles county, and an equal number of neighbourhood controls matched for age, sex, race and neighbourhood in Los Angeles, CA, USA. Home interviews were conducted; for cases, about 25% of the interviews were with the case, 53% with the spouse and 19% with a first-degree relative. Cases were selected from 736 eligible cases; losses were due to failure to locate the case (77), physician refusal (43), patient refusal (86), language problems (10) and failure to find a matched control (17). Final medical review eliminated another 13 cases. Results for coffee drinking showed a significant relationship, which persisted after adjustment for smoking.

Norell *et al.* (1986) conducted a study in Stockholm and Uppsala, Sweden, in 1982-84, based on 99 cases (55 male, 44 female) aged 40-79 out of 120 that were eligible, 138 population controls (a sample from the same parish matched for age and sex) out of 162 that were eligible and 163 hospital controls who were a random sample of patients with inguinal hernia, of whom 179 were eligible. Of the cases, 61% were verified by resection or autopsy, 33% by radiology and biopsy, and 6% by clinical examination and radiology. Cases and hospital controls were given a questionnaire at the time of diagnosis, whereas population controls were sent a postal questionnaire followed by a telephone call when necessary. The results were positive when hospital controls were used and disappeared when population

controls were the basis of comparison. Results adjusted for smoking were not presented.

Wynder *et al.* (1986) undertook a study of 238 patients (127 men, 111 women) and 696 controls in 18 hospitals in six US cities, 1981-84, in which both coffee and decaffeinated coffee were examined. Controls were selected from among patients with non-tobacco-related diseases matched for age, sex, race, hospital and year of interview; 62% had other cancers. A hospital interview was used. Neither exposure was related to pancreatic cancer either before or after adjustment for smoking.

A study (reported in a letter to the Editor of *The New England Journal of Medicine*) of 172 patients (85 men, 87 women) aged < 80 years with histologically verified pancreatic cancer and 267 controls was conducted in 1981-84 in Boston and Rhode Island, MA, USA, on the basis of hospital interviews (Hsieh *et al.*, 1986). Controls had the same physician, and the main diagnoses were cancer of the breast, colon, stomach or uterus, benign tumours, hernia, colitis, enteritis and bowel obstruction. An elevated risk, of borderline significance, was found only in patients who had drunk more than five cups of coffee per day, the RR being 2.4 in men and 2.2 in women. Similar results were found for coffee and for decaffeinated coffee.

A study was carried out in northern Italy of 150 histologically verified cases aged < 75 (99 men, 51 women) and 605 hospital controls with acute conditions except cancer, digestive-tract disorders or conditions related to coffee, alcohol or tobacco consumption (33% trauma, 12% other orthopaedic, 42% general surgery) (La Vecchia *et al.*, 1987). More than 98% of eligible patients (cases and controls) agreed to participate and were given a hospital interview. Some evidence of risk was seen, but there was no dose-response relationship and the highest risk was found among people who drank one to two cups per day. Only 16 cases did not drink coffee. No relationship with decaffeinated coffee was found.

Studies by Raymond *et al.* (1987), based on 88 cases (43 male, 45 female), 67% of which were verified histologically, and 336 population controls, and by Falk *et al.* (1988), based on 363 cases (203 male, 160 female) out of 427 incident cases and 1234 hospital controls, gave negative results. In the first study, personal interviews were obtained from cases identified through the Geneva, Switzerland, registry in 1976-81 and from controls who were contacted by letter. The study by Falk *et al.* (1988) was carried out in Louisiana, USA; 82% of cases were confirmed histologically and the remainder by X-ray, ultrasound or clinical examination. Controls were matched for hospital, age, sex and race and excluded patients with cancer, diabetes, circulatory disorders and digestive or respiratory diseases. Direct interviews were carried out with 50% of cases, and 50% were with next of kin.

A small study by Gorham *et al.* (1988) of 30 cases (out of 51 eligible) and 47 controls (out of 58 eligible) was based only on death certificates in Imperial County, CA, USA, in 1978-84. Controls were matched for age, sex, race and year of death;

cancer patients were excluded, and 47% had died from heart disease, 17% from cerebrovascular disease, 4% from pneumonia and 4% from chronic obstructive pulmonary disease. The estimated RR for three or more cups of coffee a day was [2.7] compared to less than three cups, which dropped to [1.9] and was nonsignificant after adjustment for smoking. [The Working Group noted that only 30 of 51 deaths from pancreatic cancer were included; hospital records were not examined.]

Clavel *et al.* (1989) conducted a hospital interview study in Paris, France, with 161 cases (98 male, 63 female), 63% of which were histologically verified (28% by surgery and 9% by clinical examination) in 1982-85. There were 268 hospital controls: 129 had other cancers, excluding biliary, liver, stomach, oesophagus, respiratory and bladder cancers, and 139 had non-neoplastic disease. All were matched to cases for age, sex and hospital interviewer. None of the cases and about 5% of controls refused to participate. After adjustment for education, alcohol and smoking, a nonsignificant trend was found for males, giving a RR of 2.1 for four or more cups/day. In females, a significant trend was observed, and the observed risk for more than four cups per day was 9.6. Unusually high risks were seen in women and in persons who had never drunk alcohol.

A study of 216 cases (123 male, 93 female) and 279 controls was carried out in the UK for 1983-86 (Cuzick & Babiker, 1989), based on personal interview. Of the cases, 30% were verified histologically, 23% by surgery and 47% by clinical examination or imaging. The controls included 212 hospital controls without other cancers or other chronic medical conditions: 27% had fractures, 23%, hernia, 15%, varicose veins and haemorrhoids and 11%, genitourinary diseases; the remaining 67 were population controls. The study gave essentially negative results, although a slightly elevated risk was seen in cases whose current consumption was more than five cups per day (RR, 1.4). This trend disappeared when consumption approximately 10 years previously was examined.

A case-control study in the USA involved 212 cases (140 of which were confirmed pathologically) identified from death certificates, out of 262 that were eligible, and 250 population-based controls contacted by random telephone dialling and matched to cases by age within five years (Olsen *et al.*, 1989). Family members (usually widow or spouse) were interviewed on the case's use of cigarettes, alcohol, coffee and other dietary factors two years prior to death of the patient or prior to interview. Coffee was not a risk factor (odds ratio for seven cups or more per day, 0.6; 95% CI, 0.3-1.3).

Table 34. Summary of results of case-control studies of coffee drinking and pancreatic cancer

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Lin & Kessler (1981); Kessler (1981) USA	Men and women (109, 109)			91% cases *vs* 93% controls drank coffee 41% cases *vs* 25% controls drank decaffeinated coffee ($p < 0.01$)
MacMahon *et al.* (1981a,b) USA	Men (216, 307)	0 1–2 3–4 ≥5	1.0 2.6 2.3 2.6	χ^2 trend = 1.5
	Women (151, 336)	0 1–2 3–4 ≥5	1.0 1.6 3.3 3.1	χ^2 trend = 13.7
	Men and women	0 1–2 ≥3	1.0 1.8 2.7	Adjusted for smoking; χ^2 trend = 10.6
Jick & Dinan (1981) Several countries	Men and women (83, 166)	0 1–5 ≥6	1.0 0.7 0.5	
Elinder *et al.* (1981) Sweden	Men (21, 51) Cases Controls	 5.3 ± 2.1 (SD) 6.1 ± 2.4		95% CI for difference: –2.9–0.2
	Men and women (twins; 41, 41)	3.8 3.6		95% CI for difference –0.33–0.77
Goldstein (1982) USA	Men and women (91, 93)	0 1–2 3–4 ≥5	1.0 1.8 1.0 1.6	Crude odds ratio; χ^2 for trend nonsignificant
Severson *et al.* (1982) USA	Men and women (22, 485)	Current	1.0 (0.2–4.5)	Adjusted for age, sex, smoking
Wynder *et al.* (1983) USA	Men (153, 5469)	0 1–2 3–4 ≥5	1.0 [1.1] 1.0 1.4	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Wynder *et al.* (1983) (contd)	Women (122, 2525)	0 1–2 3–4 ≥5	1.0 [1.0] 1.0 1.2	
	Men	0 1–2 3–4 ≥5	1.0 [1.0] 1.0 1.0	Adjusted for smoking
	Women	0 1–2 3–4 ≥5	1.0 0.9 0.9 1.0	Adjusted for smoking
Kinlen & McPherson (1984) UK	Men (109, 218)	Never Weekly Daily	1.0 0.9 0.9	
	Women (107, 214)	Never Weekly Daily	1.0 1.3 0.9	Adjusted for tea and smoking
Gold *et al.* (1985) USA	Men (94, 96/96)	0 1–2 3–4 ≥5	1.0 1.6/1.5 1.5/1.0 1.0/1.3	Adjusted for age; hospital random-digit dialling controls; χ^2 for trend, [0.02/0.4]
	Women (103, 103/104)	0 1–2 3–4 ≥5	1.0 0.8/1.2 2.0/1.6 2.1/2.9	χ^2 for trend, [3.8/2.7]
Mack *et al.* (1986) USA	Men and women (490, 490)	0 1–4 ≥5	1.0 1.6 2.0	Crude odds ratio
	Men and women	0 1–4 ≥5	1.0 [1.4] [1.6]	Adjusted for smoking
Norell *et al.* (1986) Sweden	Men and women (99, 163/138)	0–1 2–4 ≥5	1.0 1.7/1.6 (0.7–3.9/0.8–3.2) 1.9/1.0 (0.8–4.9/0.4–2.6)	Hospital/population controls; 90% CI

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Wynder *et al.* (1986) USA	Men (127, 371)	0	1.0	
		1–2	[1.1]	
		≥3	[1.5]	
	Women (111, 325)	0	1.0	
		1–2	[0.7]	
		≥3	[1.0]	
	Men	0	1.0	Decaffeinated
		1–2	0.8	
		≥3	0.7	
	Women	0	1.0	
		1–2	1.6	
		≥3	0.9	
Hsieh *et al.* (1986) USA	Men (85, 129)	0	1.0	Consumption ~10 years previously; χ^2 for trend, [2.8]
		1–2	1.1	
		3–4	1.0	
		≥5	2.4	
	Women (87, 138)	0	1.0	χ^2 for trend, [1.3]
		1–2	1.3	
		3–4	1.0	
		≥5	2.2	
	Men and women (170, 265)	0	1.0	Total consumption of coffee; χ^2 for trend, [3.3]
		< 20.000	1.0	
		20–39 000	1.3	
		40–59 000	1.8	
		≥60 000	1.4	
	Men and women (170, 265)	0	1.0	Total consumption of decaffeinated coffee; χ^2 for trend, [2.1]
		< 20.000	1.0	
		20–39 000	1.0	
		40–59 000	1.5	
		≥60 000	1.6	
	Men and women (170, 266)	0	1.0	Total consumption of both types of coffee; χ^2 for trend, [2.4]
		< 20.000	1.4	
		20–39 000	1.2	
		40–59 000	2.0	
		≥60 000	1.5	
La Vecchia *et al.* (1987) Italy	Men and women (150, 605)	0	1.0	
		1–2	1.8	
		3–4	1.5	
		≥5	1.4	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
La Vecchia *et al.* (1987) (contd)	Men and women	0	1.0	Adjusted for smoking, alcohol, occupation
		1–2	1.7	
		3–4	1.4	
		≥5	1.1	
	Men and women	0	1.0	Decaffeinated coffee
		3–4	0.8	
	Men and women	0	1.0	Decaffeinated coffee; adjusted for smoking, alcohol, occupation
		3–4	0.9	
Raymond *et al.* (1987) Switzerland	Men and women (88, 336)	0	1.0	90% CI
		< 1.4 l/week	0.9 (0.5–1.8)	
		≥1.4 l/week	1.3 (0.7–2.3)	
	Men and women	0	1.0	Instant coffee; 90% CI
		Any	1.4 (0.8–2.4)	
Falk *et al.* (1988) USA	Men (203, 890)	0	1.0	Adjusted for smoking, alcohol, fruit consumption, income
		1–2	0.7	
		3–4	0.5	
		5–7	0.7	
		≥8	1.4	
	Women (160, 344)	0	1.0	Adjusted as above
		1–2	0.7	
		3–4	0.7	
		5–7	1.0	
		≥8	0.9	
Gorham *et al.* (1988) USA	Men and women (30, 47)	0	1.0	
		1–2	[0.5]	
		3–4	[1.2]	
		≥5	[2.3]	
Clavel *et al.* (1989) France	Men (98, 161)	0	1.0	χ^2 for trend, [1.2]
		1	1.1	
		2–3	1.5	
		≥4	2.1	
	Women (63, 107)	0	1.0	χ^2 for trend, [6.4]
		1	3.9	
		2–3	6.7	
		≥4	9.6	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Cuzick & Babiker (1989) UK	Men and women (216, 279)	0 1–2 3–4 ≥5	1.0 0.9 0.6 1.4	Adjusted for smoking; χ^2 for trend, 0.23
	Men and women	0 1–2 3–4 ≥5	1.0 0.9 0.6 1.4	Coffee consumption ~10 years previously; χ^2 for trend, 0.43
Olsen *et al.* (1989) USA	Men and women (212, 220)	<1 1–3 4–6 ≥7	1.0 0.5 0.7 0.6	Odds ratio, adjusted for smoking, diet

(iii) *Breast cancer*

Case-control studies of breast cancer and coffee, instant coffee and decaffeinated coffee are summarized in Table 35 (p. 147).

Lawson *et al.* (1981) analysed data obtained from the Boston Collaborative Drug Surveillance Program and from a collaborative study conducted in the USA, Scotland and New Zealand. Cases were 241 women discharged with a diagnosis of breast cancer. Three controls were matched to each case for age, smoking habit, study and country. Coffee and tea drinking were grouped as 'hot beverage consumption'. Compared to those who did not drink coffee or tea, RRs for those who drank one to three, four to six and seven or more cups per day were 1.3, 1.5 and 1.1 (90% CI, 0.6-1.8 for the last category), respectively.

Lubin *et al.* (1981) reported the results of a study conducted in northern Alberta, Canada, during 1976-77. Interview was completed for 577 cases and 826 population controls. The response rate was 95% for cases and 72% for controls. Information on consumption of tea or coffee was obtained along with demographic, reproductive and medical histories and data on several food items. Tea and coffee consumption was analysed together: the age-adjusted RR when comparing more than five cups per day to five or fewer was 1.2 (95% CI, 0.9-1.5).

Mansel *et al.* (1982) in an abstract reported the results from an analysis of a computer data base of 20 000 hospital in-patients with a diagnosis of breast disease. These patients were compared with a matched non-breast disease group. As compared with non-coffee drinkers, coffee drinkers had an increased risk for breast cancer (RR, 1.3; 95% CI, 0.99-1.6). [It was not clear who was included in the control

group, what variables were matched on, whether matched analyses were carried out, and thus, what confounders had been controlled. Although information was collected on several doses levels, information on any dose-effect relation was not available.]

Lubin *et al.* (1984, 1985) conducted a hospital-based case-control study in Israel. Cases were histologically confirmed breast cancer cases in the greater Tel Aviv metropolitan area diagnosed between 1975 and 1979. Two control series, surgical and neighbourhood, were used; each was matched individually to a case by age (± five years), country of origin and length of residence in Israel. Neighbourhood controls were drawn from the national voting list and lived in the same voting district as the cases. Information was sought on the frequency of consumption of 250 food and beverage items as well as on selected hormonal, medical and demographic characteristics. Response rates among the eligible subjects were 96% for cases and surgical controls and 72% for neighbourhood controls. A total of 818 cases, 743 surgical controls and 813 neighbourhood controls were included in the analysis. Breast cancer cases were found to consume less coffee than both control series.

Rosenberg *et al.* (1984, 1985) analysed data obtained in a case-control programme for the surveillance of drug effects. Cases were 2651 in-patients in hospitals located in eastern USA who were interviewed between 1975 and 1982. There were two control groups: one consisted of 1501 women admitted for acute nonmalignant conditions (trauma or infections); the other comprised 385 women with malignancies (malignant melanoma, lymphoma and leukaemia). With either control group, RRs were close to 1.0 and there was no trend of increasing risk with increasing daily intake of coffee. Coffee drinking was not associated with breast cancer risk among subgroups of women stratified by age and reproductive history, history of fibrocystic breast disease, family history of breast cancer, or body mass index. Among a subset of subjects who did not drink caffeine-containing coffee, age-adjusted RRs were close to 1.0.

In a study in France, described by Lê *et al.* (1984) and reported in a letter by Lê (1985), 500 cases and 945 surgical controls with nonmalignant disease were studied. The risk for breast cancer was found to be inversely associated with reported current daily coffee consumption. Results were similar for women with and without a history of benign breast disease.

La Vecchia *et al.* (1986) conducted a hospital-based case-control study of breast cancer in Italy, beginning in 1980. There were 616 pairs of cases and controls. Adjusted RRs for coffee drinking were 1.0 for none, 1.6 (95% CI, 1.1-2.4) for less than two, 1.4 (1.0-2.0) for two to three and 1.1 (0.7-1.7) for four or more cups per day. There was no tendency for the risk of breast cancer to increase with increasing quantity or duration of coffee drinking.

Katsouyanni *et al.* (1986) conducted a hospital-based case-control study in Greece over a 12-month period in 1983-84. The study included 120 cases from two teaching hospitals in the Greater Athens area and 120 controls admitted for accidents and orthopaedic disorders in a third teaching hospital. Subjects were asked to indicate average frequency of consumption of 120 food or beverage items in the period preceding the onset of disease, along with information on demographic, socioeconomic, reproductive and medical variables. A test for a linear trend was not significant for coffee consumption.

Schairer *et al.* (1987) conducted a case-control study on participants in the Breast Cancer Detection Demonstration Project in the USA, a five-year screening programme begun in 1973. Cases were diagnosed from June 1977 to November 1980. Control subjects were women who had not been recommended for, and had not undergone, surgical evaluation during screening participation and were similar to breast cancer cases with regard to screening centre, age, ethnic origin, time of entry into the screening programme and length of participation in the programme. The number of daily servings of brewed, instant or decaffeinated coffee was not associated with increased risk for breast cancer.

Pozner *et al.* (1986) examined caffeine and coffee intake in women with breast cancer to determine whether it influences cell differentiation in tumours. Dietary history was obtained by interview with 106 women who had undergone mastectomy and axillary dissection for breast cancer at the Mount Sinai Medical Center in New York, USA. Information on tumour differentiation was missing for five women, leaving 101 with complete data. Tumours categorized as well or moderately differentiated were grouped (70 subjects) and compared to poorly differentiated tumours (31 subjects). Women with moderately to well differentiated tumours had had a higher intake of coffee (2.65 ± 2.23 cups per day) than women with poorly differentiated tumours (1.71 ± 1.43); the same trend was seen for caffeine and for all coffee, decaffeinated coffee, cola and tea. Stepwise logistic regression, with tumour differentiation as the dependent variable and coffee, both caffeinated and decaffeinated, tea, cola, cocoa, caffeine (mg/day), caffeine (mg per kg body weight per day), vitamin A, age and Quetelet's index as candidate independent variables, indicated that high coffee consumption is associated with moderately and well differentiated tumours; after accounting for differences in coffee intake, no other variable in the model emerged as significant. When logistic regression was performed including smoking, oral-contraceptive use, parity, number of children, age at first pregnancy, age at menarche, total calories, protein, total fat and other nutrients, however, no variable appeared to be significantly associated with degree of tumour differentiation. [The Working Group noted that this study is difficult to group with other studies of etiology. Also, factors that historically have been linked to breast cancer did not appear to influence tumour differentiation in this study.]

Mabuchi *et al.* (1985a) studied risk factors for male breast cancer as part of a larger case-control investigation of various rare cancers conducted over 1972-75 in a large number of hospitals in five US metropolitan areas. Cases were identified through continuous monitoring of documents in the hospital pathology and medical records departments. Controls were hospital patients free of cancer and matched to the cases for age (± three years), sex, race and marital status. Of the 64 eligible male breast cancer patients identified, 52 were interviewed, along with an equal number of controls. Matched analysis showed no difference in coffee or decaffeinated coffee consumption.

Table 35. Summary of results of case–control studies of breast cancer and coffee consumption

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Lawson *et al.* (1981) USA, Scotland, New Zealand	Women (241, 723)	0 1–3 4–6 ≥7	1.0 1.3 1.5 1.1 (0.6–1.8)	Coffee and tea; 90% CI
Lubin *et al.* (1981) Canada	Women (577, 826)	≤5 >5	1.0 1.2 (0.9–1.5)	Coffee and tea
Lubin *et al.* (1984, 1985) Israel	Women (738, 738) surgical controls	0 1 2–3 ≥4	1.0 0.7 (0.4–1.1) 0.7 (0.4–1.0) 0.7 (0.4–1.1)	Matched by age, country of origin, length of residence in Israel. Cases in the two comparisons involved the same series of subjects.
	(807, 807) neighbourhood controls	0 1 2–3 ≥4	1.0 0.5 (0.3–0.9) 0.5 (0.2–0.9) 0.6 (0.2–0.9)	
Rosenberg *et al.* (1984, 1985) USA	Women (2651, 1501) controls with non-malignant conditions	0 1–2 3–4 ≥5	1.0 1.2 (1.0–1.5) 1.2 (1.0–1.6) 1.2 (0.9–1.6)	Extensive adjustment made for known or suspected breast cancer risk factors
	(2651, 385) controls with cancers at other sites	0 1–2 3–4 ≥5	1.0 1.0 (0.7–1.4) 0.9 (0.7–1.3) 1.1 (0.7–1.6)	

Table 35 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Rosenberg *et al.* (1984, 1985) (contd)	(916, 584) controls with non-malignant conditions	0 1–2 3–4 ≥5	1.0 1.2 (0.9–1.5) 1.4 (0.9–1.8) 0.6 (0.3–1.1)	Decaffeinated coffee; adjusted for age
	(916, 138) controls with cancers at other sites	0 1–2 3–4 ≥5	1.0 1.1 (0.7–1.7) 1.1 (0.6–2.0) 1.0 (0.4–2.8)	Decaffeinated coffee; adjusted for age
Lê (1985) France	Women (500, 945)	Never 1–2 ≥3	1.0 0.8 0.6	Test for trend, p = 0.003; adjusted for known risk factors
La Vecchia *et al.* (1986) Italy	Women (616, 616)	0 <2 2–3 ≥4	1.0 1.6 (1.1–2.4) 1.4 (1.0–2.0) 1.1 (0.7–1.7)	Adjusted for known risk factors
Katsouyanni *et al.* (1986) Greece	Women (120, 120)	Frequency of use Tertile 1 2 3		Adjusted for age, interviewer, and length of schooling; nonsignificant inverse trend
Schairer *et al.* (1987) USA	Women (1510, 1882)	0 <1 2 3 4 ≥5	1.0 1.0 (0.8–1.3) 1.0 (0.7–1.2) 0.9 (0.7–1.2) 0.9 (0.7–1.3) 1.0 (0.8–1.3)	Crude, unmatched analysis; adjustment for other risk factors and types of caffeine-containing beverage did not change the results.
		0 <1 2 3 4 ≥5	1.0 0.9 (0.8–1.1) 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.9 (0.5–1.7) 0.7 (0.3–1.3)	Instant coffee

Table 35 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Schairer *et al.* (1987) (contd)		0	1.0	Decaffeinated coffee
		<1	1.0 (0.9–1.2)	
		2	1.0 (0.8–1.4)	
		3	0.7 (0.4–1.1)	
		4	0.9 (0.5–1.7)	
		≥5	1.1 (0.6–2.2)	
Mabuchi *et al.* (1985a) USA	Men (52, 52)	<1	(81% *versus* 83%, NS)	Matched on age, sex, race, marital status
		≥1		
		<1	(38% *versus* 31%, NS)	Decaffeinated coffee
		≥1		

(iv) *Ovary*

Case-control studies of ovarian cancer and coffee or decaffeinated coffee are summarized in Table 36 (p. 153).

Trichopoulos *et al.* (1981) reported data from a relatively small case-control study in Athens, Greece, showing a suggestive positive association between coffee consumption and risk of ovarian cancer of common epithelial types. The association was significant (two-tailed $p \sim 0.03$) when dose trends (cups of coffee per day, lifetime consumption of cups of coffee) were taken into account. [The Working Group noted that this study is not considered separately, since the relevant data are part of a larger subsequent study (Trichopoulos *et al.*, 1984; Tzonou *et al.*, 1984).]

Subsequently, Hartge *et al.* (1982) reported in a letter to the Editor of *The International Journal of Cancer* data on coffee and ovarian cancer collected as part of a case-control study of ovarian cancer (McGowan *et al.*, 1979). Cases were 158 women with pathologically confirmed primary ovarian cancer of the epithelial type treated in participating hospitals in the Washington DC area. Controls were 187 women frequency-matched to cases for age, race and hospital, treated at the same hospitals for conditions other than gynaecological, psychiatric or malignant diseases or pregnancy. Ten women had been excluded from the control series because they were hospitalized for conditions that might necessitate alterations in the diet. Women who regularly drank any amount of coffee had a nonsignificant increased risk for ovarian cancer compared to non-coffee drinkers (adjusted RR, 1.3; 95% CI, 0.8-2.2), but there was no statistically significant dose-response. [The

Working Group noted that there was no apparent confounding by the controlled variables in this study. The crude estimate of RR for drinkers of any amount of coffee was [1.3], i.e., identical to the reported adjusted figure.]

In a multicentre, hospital-based case-control study, Miller *et al.* (1984, 1987) collected data on 290 women, 20-69 years old, with epithelial ovarian cancer diagnosed within six months of the index hospital admission. Two control groups were used: women with benign conditions hospitalized more or less acutely (580) and women with malignancies (476) presumed to be unrelated to coffee (thus excluding women with pancreatic or bladder cancer) and to other factors that are considered to be predictive of ovarian cancer (thus excluding women with endometrial cancer). Women with benign conditions were *a priori* considered to be heavier consumers of coffee than the other control group (Miller *et al.*, 1984). There was no evidence of a positive association between ovarian cancer and drinking decaffeinated coffee. With respect to brewed coffee, there was evidence of a positive association with overall consumption when comparison was made with noncancer controls, but there was no such evidence when ovarian cancer cases were compared with the 'other cancers' control group. In no instance was there a clear indication of a dose-dependent trend. [The Working Group noted that, since the results with respect to the two control groups are contrary to what was predicted, it is legitimate to combine the two control groups, the results of which are given in Table 36. The crude estimate of RR for drinkers of any amount of coffee was [1.2]; from the crude and adjusted data, there seems to be no evidence of confounding.]

Byers *et al.* (1983) conducted a case-control study of dietary and nondietary factors in ovarian cancer. Cases were 274 white women, 30-79 years old, admitted to the Roswell Park Memorial Institute, Buffalo, NY, USA, between 1957-65 for ovarian cancer. Nineteen additional cases with ovarian tumours of nonepithelial origin and 36 additional cases with ovarian cancer diagnosed more than two years prior to the admission date were excluded. Controls were 1034 women, 30-79 years old [probably white only] admitted during the same period to the Institute for conditions that were found to be nonmalignant. An additional 499 women with diagnoses related to the reproductive system and 408 with conditions of the gastrointestinal system (401) or diabetes (seven) were excluded. There was no statistically significant association with any consumption category or dose trend with respect to coffee consumption. [The Working Group calculated that the age-adjusted RR for drinkers of any amount of coffee, with adjustment to age distribution of the control group by the direct method, was [1.2] (nonsignificant).]

In the Greek case-control study (Tzonou *et al.*, 1984), coffee consumption was compared between 150 women with epithelial ovarian cancer admitted to any of ten large hospitals in Athens between 1980 and 1981, and 250 control women hospitalized during the same period for fractures or orthopaedic disorders in the

Athens Hospital for Orthopaedic Disorders. In the final results, after adjustment for age, parity, menopausal status, age at menopause, use of exogenous oestrogens, tobacco smoking and consumption of alcoholic beverages, the χ^2 for trend in coffee consumption was 1.15 ($p \sim 0.27$); at no level of coffee consumption did the RR differ significantly from the value of 1.0. [The Working Group noted that the crude estimate of RR for drinkers of any amount of coffee was 1.2; comparison of crude and adjusted RR estimates indicates that there was little confounding, and that which existed was slightly 'negative'.]

Cramer *et al.* (1984) conducted a case-control study in the Boston, MA (USA), area between 1978 and 1981. Cases were 215 white women with newly diagnosed epithelial ovarian cancer admitted to 12 participating hospitals, whereas controls were 215 white women randomly selected from lists of Massachusetts residents, matched for age and precinct of residence. There was no evidence of an association between ovarian cancer and any of the combinations of coffee drinking, alcohol drinking or tobacco smoking. The crude RR was 1.2 for coffee drinkers. In the combinations that included coffee drinking, the RRs of coffee users *versus* nonusers of either coffee, alcohol or tobacco were between 1.2 and 1.8. [The Working Group noted that there was no evidence of overt confounding with respect to the results for coffee.]

La Vecchia *et al.* (1984) conducted a case-control study of ovarian cancer in Milan between 1979 and 1983. Cases were 247 women, 19-74 years of age, with epithelial ovarian cancer admitted to the university hospital and the National Cancer Institute of Milan. Controls were 494 women below the age of 75 years admitted to the university or general hospitals of the Milan area, suffering from diseases judged to be unrelated to coffee consumption or to any of the established or suspected risk factors of ovarian cancer. In the logistic regression analyses, there were statistically significant linear trends with daily consumption of coffee ($p = 0.003$) and with years of regular coffee consumption ($p = 0.02$). [The Working Group noted that comparison of crude [1.4] and adjusted RR indicates that there is some degree of confounding that incorrectly reduces the association between coffee consumption and risk of ovarian cancer ('negative' confounding).]

In a case-control study in the San Francisco Bay area, CA, USA, between 1983 and 1985, Whittemore *et al.* (1988) compared the exposure histories of 188 women with primary epithelial ovarian cancer admitted to one of seven participating hospitals with the exposure histories of women in two control groups. The first control group consisted of women hospitalized in one of the hospitals to which cases were admitted, whereas the second group was selected from the general population using random-digit dialling. When both control groups were combined, there was a statistically significant positive association between coffee drinking and the risk for ovarian cancer. [The Working Group noted that there may be an error, in that the

risk relative to the two control groups combined is higher (2.0) than that relative to either control group (1.9 for hospital controls and 1.5 for population controls).] RRs were elevated in 23 of the 24 categories of coffee drinking by quantity (cups per day), duration (years) or by product when hospital and population controls were considered separately; they were significantly elevated ($p < 0.05$) in 11 out of 12 such categories when hospital and population controls were combined. However, no clear trend was seen with daily quantity of coffee consumed.

Overall, in all seven case-control studies of coffee use and risk for ovarian cancer, users of any amount of coffee had an increased risk, although the elevation was significant in only two. In most of the studies, the increase was small or minimal: the overall crude RR estimates were between 1.1 and 1.3 in five studies, 1.4 in a recent study and 1.9 in the last one. Use of crude estimates is legitimate, since confounding of the association between coffee drinking and ovarian cancer in these sets was either absent or negative. In only one study was there a statistically significant dose-response relationship. A Mantel-Haenszel meta-analysis by the Working Group of the crude data from these seven studies (an acceptable, although slightly conservative procedure, for the reasons indicated above) gave a significant ($p < 0.01$) pooled estimated RR of [1.3 (95% CI, 1.1-1.5)] for coffee users *versus* nonusers.

(v) *Cancers of the digestive tract*

Case-control studies of cancers of the digestive tract and coffee consumption are summarized in Tables 37-39 (pp. 158, 162, 164).

Large bowel: Higginson (1966) studied 340 cases of colorectal cancer (196 male, 144 female) from seven hospitals in the Kansas City area, USA, from 1959 to the early 1960s. Three controls per case were selected from the same hospitals. Cases had histologically confirmed diagnoses, and controls excluded patients with gastrointestinal disease or with recent dietary abnormalities. Cases and controls were matched for age, sex and race. The socioeconomic status of cases and controls were similar. No significant association was found between coffee consumption and colorectal cancer: the RR for subjects who drank one or more cups of coffee a day was [0.8 (95% CI, 0.7-1.0)]. [The Working Group noted that no adjustment was made for confounding variables other than age, sex and race.]

Haenszel *et al.* (1973) studied 179 Japanese patients (101 male, 78 female) with colorectal cancer and 357 age- and sex-matched controls from the three largest general hospital in Honolulu, Hawaii, between 1966 and 1970. All but one of the cases had been confirmed histologically. Controls did not include patients with gastric or duodenal ulcers, gastrointestinal cancer or other diseases of the large bowel; their most frequent diagnoses were circulatory diseases, external causes and genito-urinary diseases. Patients were interviewed on dietary history, habits and

Table 36. Case–control studies of ovarian cancer (common epithelial tumours) and brewed coffee intake

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)			Comments
Hartge *et al.* (1982) USA	158, 187	0	1.0			Adjusted for age, gravity and smoking
		< 2	1.0 (0.5–2.2)			
		2–3	1.8 (0.9–3.6)			
		≥4	1.4 (0.6–3.0)			
Byers *et al.* (1983) USA	274, 1034	0	1.0			No significant association with any consumption category or trend
		< 3	[1.3]			
		≥3	[1.0]			
Miller *et al.* (1984, 1987) Several cities in the USA and Canada	287, 569/470		Noncancer controls	Cancer controls	All controls	Multivariate analysis
		0	1.0	1.0	1.0	
		1	1.6 (0.9–2.7)	1.0 (0.5–1.7)	[1.3]	
		2	1.5 (0.9–2.6)	0.9 (0.6–1.6)	[1.2]	
		3	1.6 (0.9–2.7)	0.9 (0.6–1.6)	[1.3]	
		4	1.7 (0.9–3.3)	1.6 (0.8–3.1)	[1.7]	
		≥5	1.1 (0.6–2.0)	1.0 (0.5–1.8)	[1.1]	
	289, 572/473	0	1.0	1.0	1.0	Decaffeinated coffee
		1–2	1.4 (0.9–2.2)	1.0 (0.6–1.4)	[1.2]	
		3–4	0.8 (0.4–1.6)	0.9 (0.5–1.6)	[0.9]	
		≥5	0.7 (0.2–2.1)	0.7 (0.2–3.3)	[0.7]	
Trichopoulos *et al.* (1981, 1984); Tzonou *et al.* (1984) Greece	149, 250	0	1.0			
		0.5–1	0.9			
		1.5–2	1.6			
		2.5–3	0.9			
		≥3.5	1.5			
Cramer *et al.* (1984) USA	215, 215	0	1.0			Adjusted for smoking
		Any	1.1			

Table 36 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption	Relative risk (95% CI)			Comments
La Vecchia *et al.* (1984) Italy	247, 494	0	1.0			Multivariate analysis
		≤1	1.5 (0.9–2.5)			
		2–3	1.9 (1.2–3.0)			
		≥4	2.2 (1.2–3.9)			
Whittemore *et al.* (1988) USA	188, 280/259		Hospital controls	Population controls	All controls	Adjusted for smoking
		0	1.0	1.0	1.0	
		1	2.2	1.9	2.4 (1.2–5.1)	
		2–3	2.1	1.6	2.3 (1.1–4.7)	
		≥4	2.0	1.6	2.1 (1.0–4.4)	
		0	1.0	1.0	1.0	
		1–14 years	1.6	0.7	1.5 (0.6–3.6)	
		15–24 years	1.8	1.7	2.2 (1.0–4.8)	
		25–39 years	2.4	1.7	2.3 (1.1–4.9)	
		≥40 years	3.5	2.5	3.4 (1.5–8.0)	

socioeconomic status. Coffee drinking was associated with a RR of 0.7, which was not statistically significant.

A significant negative association between coffee consumption and colon cancer was reported from case-control studies in Norway and the USA (Bjelke, 1973).

Graham *et al.* (1978) carried out a case-control study of white male patients with histologically confirmed cancer of the colon (256 patients) or rectum (330 patients) and 1222 controls seen at the Roswell Park Memorial Institute in Buffalo, NY, USA, during 1959-65. Controls were non-cancer, non-gastrointestinal patients who were selected so as to have a similar distribution as the cases, but no individual matching was carried out. Patients attending the hospital where the study was carried out were similar to the population of the neighouring areas in terms of socioeconomic and marital status, religion and smoking habits. The interview included demographic, socioeconomic and dietary variables. Frequent drinking of coffee was associated with a 'significant but small excess risk' for cancer of the colon but not of the rectum, as was 'drinking coffee very hot'. [The Working Group noted that no figures were given, that, other than for age, there was no adjustment for possible confounding variables and that no RRs or CIs are given.]

Dales *et al.* (1979) carried out a study of black patients with colorectal cancer and matched controls from hospitals and clinics in the San Francisco Bay area, CA, USA. Cases were identified from a cancer registry covering the period September 1973 to August 1976, but 60% could not be interviewed, mostly due to death or severe illness, leaving 99 cases. Similarly, only 50% (280) of the controls who were identified were successfully interviewed. The questionnaire was answered at the patients' homes and included demographic and socioeconomic data, as well as information on dietary habits three years prior to the interview. No association between coffee drinking and colorectal cancer was found. [The Working Group noted that the low rates of participation make this study difficult to interpret and that RRs associated with coffee consumption are not given.]

Watanabe *et al.* (1984) studied 65 cases of cancer of the rectum (39 male, 26 female) and 138 cases of colon cancer (71 male, 67 female) in Kyoto, Japan. For each case, one control was selected; the sex and age distribution of cases and controls were similar. Data were collected on a number of dietary items including coffee and tea consumption. No significant association was found between coffee drinking and cancer of the rectum or of the colon, although both risks were reduced by 20-30% among coffee drinkers.

Tajima and Tominaga (1985) compared the characteristics of 42 incident cases of colon cancer (27 male, 15 female) and 51 cases of rectal cancer (25 male, 26 female) with those of 186 controls admitted to a specialized hospital in Nagoya, Japan, between 1981 and 1983. The diagnoses of the cases were confirmed

histologically. There was no significant association between coffee drinking and either colon or rectal cancer (RRs for daily drinkers, 1.1 and 1.0, respectively). [The Working Group noted that almost half of the controls had gastrointestinal conditions.]

Macquart-Moulin *et al.* (1986) reported a case-control study from Marseille, France, based on 399 histologically confirmed cases of colorectal cancer and the same number of controls which was conducted between 1979 and 1984. After adjustment for age, sex, calories and weight, the risk in increasing quartiles of coffee consumption was 1.0, 0.6, 0.7 and 0.6. The test for trend was not significant.

Tuyns (1986) and Tuyns *et al.* (1988) presented the results of a study which covered approximately one-half of the cases of colorectal cancer in two Belgian provinces, Oost-Vlaanderen and Liège, in 1978-82. A total of 453 cases of colon cancer, 365 of rectal cancer and 2851 population controls were included. The response rate for controls was approximately 70%. The analyses were adjusted for age, sex and residence. 'Heavy consumers' of coffee and/or tea had crude RRs of 0.7 (95% CI, 0.6-0.9) for colon cancer and 0.8 for rectal cancer (0.6-0.9), relative to 'light consumers' (Tuyns, 1986). Separate results are not given for coffee and tea drinking, but the latter was reported to be rare.

In Yugoslavia, Jarebinski *et al.* (1989) compared 98 patients (56 male, 42 female) with histologically confirmed rectal cancer admitted to one of five hospitals in Belgrade in 1984-86 to two control groups: Hospital controls were patients admitted due to non-cancer conditions — mainly fractures and other injuries, cardiovascular diseases and hernias; a second control group consisted of neighbours of the cases. Controls were matched to cases by age, sex, place of residence and interviewer. The RRs associated with any coffee consumption were 1.7 when compared with hospital controls and 0.8 when compared with neighbourhood controls. The corresponding RRs for consumption of three or more cups per day were 1.1 and 0.8, and for having consumed coffee for 30 or more years, 1.2 and 1.2. None of these differences approached statistical significance. [The Working Group noted that no data are given on the proportions of potential cases or controls who could not be contacted.]

La Vecchia *et al.* (1988, 1989c) studied 455 histologically confirmed cases of colon cancer (221 male, 234 female), 295 cases of rectal cancer (170 male, 125 female) and 1944 hospital controls recruited from a network of teaching and general hospitals in greater Milan, Italy, between 1985 and 1988. Controls did not include patients with malignant tumours, digestive diseases or any condition related to use of coffee, alcohol or tobacco or which may have resulted in long-term dietary modification. RRs were calculated through logistic regression after adjustment for sex, age, social class, education, marital status, smoking and alcohol consumption. Compared to subjects consuming no to one cup per day, those consuming two cups

per day had a RR of 0.9 for colon cancer, and those consuming three or more cups had a RR of 0.6 (p for trend, < 0.01). The corresponding figures for rectal cancer were 1.0 and 0.7 (p for trend, < 0.05). The RRs were also examined after stratification for sex, age, marital status, education, social class, smoking and alcohol consumption. The overall pattern of protection afforded by coffee against colon cancer was evident in all strata but appeared to be restricted to males.

In another case-control study, carried out among Singapore Chinese, Lee *et al.* (1989) studied 203 (121 male, 82 female) consecutive incident cases (132 cases of colon cancer, 71 of rectal cancer) admitted to a general hospital in 1985-87. All cases had histologically confirmed colorectal cancer. A total of 426 controls were selected among 489 patients who were free of any gastrointestinal disease, cancer or diabetes; approximately two controls were selected for each case, matched for age group and sex. The response rates for cases and controls were above 80%. Coffee intake of one or more cups per day was associated with a nonsignificant 30-40% reduction in the risk for cancer at each site. When both sites were pooled, the association was close to significance ($0.1 > p > 0.05$). The effect of coffee remained virtually unchanged after adjustment for other food items for which a significant result was found. However, there was no evidence of a dose-response relationship.

Data on coffee consumption was collected as part of a multicentre, multiorgan case-control study in the USA (Rosenberg *et al.*, 1989). In 1978-82, data were obtained on coffee consumption one month before interview, whereas during 1983-86 the data on consumption were for one and three years before hospital admission. Cases were 717 patients with cancer of colon and 538 with rectal cancer, aged 30-69 years. A non-cancer control group consisted of 2128 trauma and 369 appendicitis patients, and a second, cancer control group was composed of 892 patients with malignant melanoma and 494 with lymphoma and bone cancer. Multiple logistic regression analyses, adjusting for age, sex, geographic area, year of interview, cigarette smoking, alcohol consumption, education, religion and race, were employed, using persons who consumed one cup of coffee per day as the referent category. For colon cancer, the adjusted RRs for drinking less than one, two and three to four cups of coffee per day compared to one cup per day were all close to one, but the risk associated with drinking five or more cups per day was significantly reduced (0.6; 95% CI, 0.4-0.8). This risk pattern was similar for men and women and when recent or past consumption was evaluated. For rectal cancer, the risks were close to unity for present or past consumption at all dose levels. The risk pattern was somewhat different for males and females: with the exception of a significantly elevated risk for drinking three to four cups per day (1.7; 95% CI, 1.0-2.8), men had nonsignificantly increased risks for all other dose categories; however, women had nonsignificantly reduced risks.

Benito *et al.* (1990) reported a case-control study of 286 incident cases of histologically confirmed colorectal cancer, 295 population controls and 203 hospital controls in Majorca, Spain. Coffee consumption was presented in quartiles. Risk in the lowest intake category was 1.0 and that in increasing quartiles of intake was 0.7, 0.5 and 0.8. The trend statistic was not significant.

Table 37. Summary of results of case–control studies on colorectal cancer and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Higginson (1966) USA Colon and rectum	Men and women (340, 1020)	0/irregular < 1 < 2 ≥3	1.0 [0.4] [0.7] [0.6]	Crude RR; nonsignificant
Haenszel *et al.* (1973) USA Colon and rectum	Men and women (179, 357)	0 Any	1.0 0.7	Crude RR; nonsignificant
Watanabe *et al.* (1984) Japan				
Rectum	Men and women (65, 65)	0 Any	1.0 0.7 (0.3–1.6)	
Colon	Men and women (138, 138)	0 Any	1.0 0.8 (0.5–1.3)	
Tajima & Tominaga (1985) Japan				
Rectum	Men and women (51, 186)	0 Sometimes Daily	1.0 1.3 1.0	Nonsignificant; adjusted for age, sex
Colon	Men and women (42, 186)	0 Sometimes Daily	1.0 1.2 1.1	Nonsignificant; adjusted for age, sex
Macquart-Moulin *et al.* (1986) France Colon and rectum	Men and women (399, 399)	Quartiles Low 2nd 3rd High	 1.0 0.6 0.7 0.6	Nonsignificant; adjusted for age, sex, calories, weight

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Tuyns *et al.* (1988) Belgium				
Rectum	Men and women (365, 2851)	Quartiles		Coffee and tea, but latter said to be uncommon; adjusted for age, sex, province; significant trend
		Low	1.0	
		2nd	0.9	
		3rd	0.9	
		High	0.7	
Colon	Men and women (453, 2851)	Quartiles		
		Low	1.0	
		2nd	0.9	
		3rd	1.0	
		High	0.6	
Jarebinski *et al.* (1989) Yugoslavia	Men and women (98, 98)	0	1.0	Nonsignificant; hospital controls
Rectum		Any	1.7	
		<3	1.0	Nonsignificant
		≥ 3	1.1	
		<30 years	1.0	Nonsignificant
		≥ 30 years	1.2	
		0	1.0	Nonsignificant; neighbourhood controls
		Any	0.8	
		<3	1.0	Nonsignificant
		≥ 3 cups/day	0.8	
		<30 years	1.0	Nonsignificant
		≥ 30 years	1.2	
La Vecchia *et al.* (1989c) Italy				
Rectum	Men (170, 1334)	0–1	1.0	$p < 0.01$ for men; nonsignificant for women; adjusted for age, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; p levels based on chi-squared test for linear trend
		2	0.8	
		≥ 3	0.5	
	Women (125, 610)	0–1	1.0	
		2	1.2	
		≥ 3	0.9	

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
La Vecchia *et al.* (1989c) (contd)				
Colon	Men (221, 1334)	0–1	1.0	$p < 0.05$
		2	0.8	
		≥3	0.6	
	Women (234, 610)	0–1	1.0	$p < 0.05$
		2	0.9	
		≥3	0.6	
Lee *et al.* (1989) Singapore				
Colon	Men and women (132, 426)	Tertiles		
		Low	1.0	
		Intermediate	0.7 (0.4–1.1)	Nonsignificant
		High	0.7 (0.4–1.2)	
Rectum	(71, 426)	Low	1.0	
		Intermediate	0.6 (0.3–1.1)	Nonsignificant
		High	0.7 (0.4–1.4)	
Colon and rectum	(203, 426)	Low	1.0	$0.1 > p > 0.05$; logistic analysis
		Intermediate	0.7 (0.4–1.0)	
		High	0.7 (0.5–1.1)	
Colon and rectum		Low	1.0	Nonsignificant; combined analysis; adjusted for cruciferous vegetables, total vegetables, meat/vegetable ratio, cholecystectomy history
		Intermediate	0.7 (0.4–1.0)	
		High	0.7 (0.5–1.2)	
Rosenberg *et al.* (1989) USA				Adjusted for age, sex, cigarette smoking, alcohol consumption,
Colon	Men and women (717, 3883)	< 1	1.1 (0.8–1.4)	several other potential confounding factors
		1	1.0	
		2	1.0 (0.8–1.3)	
		3–4	0.9 (0.7–1.2)	
		≥5	0.6 (0.4–0.8)	

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Rosenberg *et al.* (1989) (contd)				
Rectum	(538, 3883)	< 1	1.2 (0.9–1.6)	
		1	1.0	
		2	1.1 (0.8–1.5)	
		3–4	1.1 (0.8–1.5)	
		≥5	1.2 (0.8–1.8)	
Benito *et al.* (1990)	Men and women	0	1.0	Nonsignificant; adjusted for age, sex, weight
Spain	(286, 498)	1–30/month	0.7	
Colon and rectum		31–60/month	0.5	
		≥60/month	0.8	

Stomach: In the study of Higginson (1966), described on p. 152, 93 cases of histologically confirmed stomach cancer and 279 age-, sex- and race-matched controls were studied. No significant association was found between coffee drinking and stomach cancer.

Graham *et al.* (1967) compared 276 cases (188 male, 88 female) of gastric cancer and 2221 controls (800 male, 1421 female) with non-neoplastic, non-digestive conditions seen at the Roswell Park Memorial Institute in Buffalo, NY, USA, between 1957 and 1965. Interviews on dietary habits prior to the onset of symptoms were carried out at admission. Separate analyses were made for each sex and for four age groups. The authors infer that the frequency of drinking coffee was not significantly associated with the risk for gastric cancer, but no figures were given.

Tajima and Tominaga (1985), in the study described above (p. 155), reported on 93 cases of histologically confirmed stomach cancer and 186 controls admitted to a specialized hospital in Nagoya, Japan. There was no significant association between coffee drinking and cancer of the stomach. [The Working Group noted that almost half of the controls had gastrointestinal conditions.]

Trichopoulos *et al.* (1985) studied 110 consecutive incident cases (57 male, 53 female) of histologically confirmed adenocarcinoma of the stomach admitted to two hospitals in Piraeus, Greece, between 1981 and 1984. Controls were 100 patients admitted to a nearby hospital due to accidents, fractures and orthopaedic disorders. Age, sex and years of schooling were controlled for in the statistical analysis. The association between the consumption of coffee and tea and the risk for stomach cancer was not statistically significant.

La Vecchia *et al.* (1989c) studied 397 histologically confirmed cases of stomach cancer (243 male, 154 female) and 1944 hospital controls from greater Milan, Italy. No association between coffee drinking and stomach cancer was found after adjustment for sex and age. The lack of association remained when the data were also adjusted for social class, education, marital status, smoking and alcohol consumption.

Table 38. Summary of results of case–control studies on stomach cancer and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Higginson (1966) USA	Men and women (93, 279)	0/irregular <1 <2 ≥3	1.0 [0.7] [1.3] [1.3]	Crude RR; nonsignificant
Graham *et al.* (1967) USA	Men and women (276, 2221)			No association
Tajima & Tominaga (1985) Japan	Men and women (93, 186)	0 Not daily Daily	1.0 0.8 1.0	Nonsignificant; adjusted for age, sex
Trichopoulos *et al.* (1985) Greece	Men and women (110, 100)	1 (low) 2 3 4 5 (high)	1.0 [1.7] [1.8] [2.7] [3.2]	Nonsignificant after adjustment for age, sex, years of schooling; *p* values based on chi-squared test for linear trend; coffee and tea
La Vecchia *et al.* (1989c) Italy	Men and women (397, 1944)	0–1 2 ≥3	1.0 0.9 1.3	Nonsignificant; adjusted for age, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; *p* values based on chi-squared test for linear trend

Upper digestive tract: Martinez (1969) studied 400 cases of cancer of the oesophagus (179 cases; 120 male, 59 female), mouth (153 cases; 115 male, 38 female) and pharynx (68 cases; 55 male, 13 female), comprising all histologically confirmed cases reported to the Puerto Rico cancer registry in 1966. For each case, three age- and sex-matched controls were selected: one non-cancer patient from the same hospital and two community controls. The results were presented for cancer of the mouth, pharynx and oesophagus taken together. For men, there was a significant association between drinking hot coffee and cancer at these three sites; there was a

similar, but nonsignificant trend for women. There was no association between drinking coffee with milk and the occurrence of cancer.

de Jong *et al.* (1974) carried out a hospital-based case-control study of oesophageal cancer among Singapore Chinese in 1970-72. For each case, four age- and sex-matched control patients were selected: two non-cancer patients from the same ward and two orthopaedic controls from a general hospital. Neither in the unadjusted analysis nor after adjustment for dialect group was there an association between coffee drinking and oesophageal cancer. Reported drinking of 'burning hot' coffee, however, was associated with a five- to six-fold higher crude risk of cancer. [The Working Group noted that the control groups included a large number of patients with digestive disorders.]

Yen *et al.* (1987) studied 67 patients with cancer of the extrahepatic bile ducts (40 men, 27 women) who had originally been recruited as controls in a case-control study of pancreatic cancer carried out in 11 large hospitals in Massachusetts and Rhode Island, USA, in 1975-79. The cases were obtained from a group of 104 patients with histologically confirmed cancer of the extrahepatic bile ducts, 37 of whom could not be interviewed. A control group was selected comprising 275 patients with other cancers not known to be related to tobacco or alcohol consumption — mainly of the breast (65 patients) and colon (60 patients). The analysis was stratified by age and sex. No association was found betweeen cancer occurrence and coffee drinking. [The Working Group noted that the study was not designed to study extrahepatic bile duct cancer, and a large proportion of the potential cases could not be interviewed.]

Victora *et al.* (1987), in a study described in detail in the monograph on mate, compared 171 cases of oesophageal cancer in southern Brazil with 342 hospital controls matched for age and sex. They found no effect of coffee drinking. [The Working Group noted that data are not given.]

In the study of La Vecchia *et al.* (1989c), described on p. 156, the association between coffee drinking and oesophageal cancer was examined by comparing 209 histologically confirmed cases (162 male, 47 female) with 1944 controls. The data were initially adjusted for age and sex, and later also for a number of confounding variables. Neither analysis showed any association. These authors also studied 50 cases of cancer of the mouth and pharynx (43 male, seven female) and 151 cases of liver cancer (115 male, 36 female). No association was found between coffee drinking and cancer of the mouth or pharynx, either in the analysis adjusted for sex and age or after adjustment for a number of confounding variables. In the first type of analysis, the RR for liver cancer for those drinking two cups per day was 0.7, and that for people drinking more than three cups per day, 0.6. This trend was less marked and no longer significant after adjustment for other confounding variables, when the corresponding RRs were 0.8 and 0.8.

Franco *et al.* (1989) carried out a case-control study of cancer of the mouth in three Brazilian cities. A total of 232 incident cases (201 male, 31 female) of histologically confirmed cancer of the tongue, gum, floor of the mouth and other parts of the oral cavity were recruited in three head-and-neck surgery services. Two hospital controls matched for age, sex, hospital and time of admission were selected for each case. Patients with cancer or with mental disorders were not included as controls. The crude analysis showed a clear trend of increasing risk with greater frequency of coffee drinking ($p = 0.01$). After adjustment for tobacco and alcohol consumption, however, this association was no longer significant. There was no indication that the temperature at which coffee was drunk affected the risk. [The Working Group noted that approximately one-third of the controls had digestive conditions.]

Table 39. Summary of results of case–control studies on other digestive cancers and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Martinez (1969) Puerto Rico Oesophagus, mouth and pharynx	Men (290, 870)	0 Cold or warm Hot	1.0 [1.3] [2.7]	Black coffee; $p < 0.01$
		0 Cold or warm Hot	1.0 [0.8] [1.2]	With milk; non-significant
	Women (110, 330)	0 Cold or warm Hot	1.0 [1.6] [3.4]	Black coffee; non-significant
		0 Cold or warm Hot	1.0 [1.0] [1.6]	With milk; nonsignificant
de Jong *et al.* (1974) Singapore Oesophagus	Men (95, 465)	Not daily Daily Burning hot	1.0 0.9 5.1 crude RR 4.2 adjusted RR	Nonsignificant $p < 0.01$ for both
	Women (36, 200)	Not daily Daily Burning hot	1.0 1.4 6.6 crude RR 4.1 adjusted RR	Nonsignificant $p < 0.01$ for both; RR crude and adjusted for dialect group

Table 39 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Yen *et al.* (1987) USA Extrahepatic bile ducts	Men and women (67, 275)	0 Any 1–2 3–4 ≥5	1.0 0.8 (0.3–2.0) 0.8 (0.3–2.0) 1.0 (0.4–2.8) 0.6 (0.2–1.9)	Adjusted for age, sex
Victora *et al.* (1987) Brazil Oesophagus	Men and women (171, 342)			No association
La Vecchia *et al.* (1989c)				Nonsignificant; adjusted for age, sex, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; *p* values based on chi-squared test for linear trend
Oesophagus	Men and women (209, 1944)	0–1 2 ≥3	1.0 0.9 1.0	
Mouth and pharynx	Men and women (50, 1944)	0–1 2 ≥3	1.0 0.9 0.8	
Liver	(151, 1944)	0–1 2 ≥3	1.0 0.8 0.8	
Franco *et al.* (1989) Brazil Oral cavity	Men and women (232, 464)	0–1 2–5 ≥6	1.0 1.3 (0.8–1.9) 1.9 (1.2–3.2)	$p = 0.01$; crude matched analysis; *p* value based on test for linear trend
		0–1 2–5 ≥6	1.0 1.1 (0.7–1.8) 1.5 (0.9–2.6)	Nonsignificant; adjusted for tobacco, alcohol consumption

(vi) *Cancers at other sites*

These studies are summarized in Table 40 (p. 166).

Henderson *et al.* (1976) studied 156 (105 male, 51 female) patients with *nasopharyngeal* squamous-cell *carcinoma* from three cancer registries and 267 controls in California, USA. From the main registry included in the study, 41% of the cases could not be interviewed. Controls were selected from inpatient and outpatient facilities and were matched to the cases for age, sex, race and socioeconomic status. No association was found between coffee drinking and nasopharyngeal carcinoma. [The Working Group noted that the description of the

selection of cases and controls is confusing, as several different sources were used, and that a high proportion of cases could not be interviewed.]

Mabuchi *et al.* (1985b) studied 149 patients with histologically confirmed *carcinoma of the vulva* from five metropolitan areas in the USA between 1972 and 1975. Cases were identified from more than 115 hospitals. One non-cancer patient was matched to each case according to age, race, marital status and hospital. Drinking one or more cups of coffee daily was associated with a doubling of the RR for cancer of the vulva, but this was not significant. The risk was significantly higher, however, among women drinking three or more cups per day. There was no dose-response relationship.

Mettlin (1989) reported a case-control study of 569 cases of histologically diagnosed *lung cancer* and the same number of controls who had no diagnosis or history of malignant or benign neoplasms, selected from patients seen at Roswell Park Memorial Institute in Buffalo, NY, USA. After adjustment for sex, smoking history, beta-carotene intake and education level relative to the risk in people who had never drunk coffee (1.0), the risk in increasing categories of coffee consumption was 1.0 (0.7-1.5) for less than one cup per day, 1.0 (0.7-1.4) for two to three cups per day and 1.3 (0.9-1.8) for four or more cups per day. The study also presented data regarding intake of decaffeinated coffee, and for the same categories of consumption the RRs were 1.0, 0.7 (0.5-0.9), 0.5 (0.3-0.7) and 0.8 (0.5-1.3).

In a case-control study of 208 cases of *non-Hodgkin's lymphoma* and 401 hospital controls in northeastern Italy, Franceschi *et al.* (1989) found a direct trend in risk, of borderline statistical significance, for coffee drinking in a multivariate analysis (RR for the upper tertile, 1.6). Only total methylxanthine-containing beverage consumption was correlated in multivariate analysis, which seemed to flatten out the relationship moderately.

Table 40. Summary of results of case–control studies on other cancers and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk	Comments
Henderson *et al.* (1976) USA Nasopharynx	Men and women (156, 267)	0 Any	1.0 1.1	Nonsignificant; adjusted for sex, race, socioeconomic status, place of residence
Paffenbarger *et al.* (1978) USA				Case–control analysis of cohort study described on p. 118
Hodgkin's disease	Men (45, 180)	0 Any	1.0 2.5	Nonsignificant; matched analysis

Table 40 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Paffenbarger *et al.* (1978) (contd)				
Non-Hodgkin's lymphoma	Men (89, 356)	0 Any	1.0 1.6	Nonsignificant
Malignant melanoma	Men (45, 180)	0 Any	1.0 1.3	Nonsignificant
Lymphatic leukaemia	Men (27, 108)	0 Any	1.0 2.7	Nonsignificant
Myeloid leukaemia	Men (41, 164)	0 Any	1.0 3.2	$p = 0.02$
Other/unspecified leukaemias	Men (30, 120)	0 Any	1.0 0.8	Nonsignificant
Mabuchi *et al.* (1985b) USA Vulva	Women (149, 149)	< 1 1–2 3–4 ≥ 5	1.0 1.5 3.0 2.4	Unmatched analysis Nonsignificant $p < 0.05$ $p < 0.05$
Franceschi *et al.* (1989) Italy Non-Hodgkin's lymphoma	Men and women (208, 401)	Low Intermediate High	1.0 1.2 1.6	Borderline significance