SHORT COMMUNICATION

BJC

British Journal of Cancer (2013) 109, 1908–1913 | doi: 10.1038/bjc.2013.540

Keywords: coffee; endometrial cancer; decaffeinated coffee; caffeine; tea; methylxanthines; cola

Intake of coffee, caffeine and other methylxanthines and risk of Type I *vs* Type II endometrial cancer

S Uccella[1], A Mariani[1], A H Wang[2], R A Vierkant[2], W A Cliby[1], K Robien[3], K E Anderson[3] and J R Cerhan*[,4]

[1]*Department of Obstetrics and Gynecology, Division of Gynecologic Surgery, Rochester, MN 55901, USA;* [2]*Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, MN 55901, USA;* [3]*Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55455, USA and* [4]*Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic College of Medicine, 200 First Street Southwest, Rochester, MN 55901, USA*

Background: Coffee and other sources of methylxanthines and risk of Type I *vs* Type II endometrial cancer (EC) have not been evaluated previously.

Methods: Prospective cohort of 23 356 postmenopausal women with 471 Type I and 71 Type II EC cases.

Results: Type I EC was statistically significantly associated with caffeinated (relative risk (RR) = 0.65 for 4+ cups per day *vs* ⩽1 cup per month: 95% confidence interval (CI): 0.47–0.89) but not decaffeinated (RR = 0.76; 95% CI: 0.50–1.15) coffee intake; there were no associations with tea, cola or chocolate, or for Type II EC. The inverse association with caffeinated coffee intake was specific to women with a body mass index 30+ kg m^{-2} (RR = 0.56; 95% CI: 0.36–0.89).

Conclusion: Coffee may protect against Type I EC in obese postmenopausal women.

Following water and tea, coffee is the third most consumed beverage in the world (Bushman, 1998; La Vecchia and Tavani, 2007). A recent meta-analysis reported an inverse association of coffee intake with endometrial cancer (EC) risk (Je and Giovannucci, 2011). The presence of antioxidants and other chemopreventive compounds in coffee may explain its anticarcinogenic effect (Vivani, 1993; Cavin *et al*, 2002). However, it is not clear whether coffee *per se*, caffeine or other methylxanthines (e.g., theophylline and theobromine) are most relevant. Also unexplored is whether there is heterogeneity by Type I *vs* Type II EC, which may have different aetiologies (Bokhman, 1983; Doll *et al*, 2008; Mendivil *et al*, 2009). The aim of the present study was to evaluate the association of coffee consumption (with and without caffeine) and other sources of methylxanthines with risk of Type I *vs* Type II EC, overall and stratified on body mass index (BMI), smoking history and hormone therapy (HT) use.

MATERIALS AND METHODS

Details regarding the Iowa Women's Health Study (IWHS) have been published (Folsom *et al*, 1990). In brief, 41 836 women aged 55–69 years completed a self-administered survey at enrolment in 1986. The baseline survey included a 126-item semiquantitative food-frequency questionnaire (FFQ) (Willett *et al*, 1988), which included the average intake in the past year of the following items: caffeinated coffee; decaffeinated coffee; tea (excluding herbal teas); regular and sugar-free carbonated beverages with caffeine; chocolate; chocolate bars; and brownies. The FFQ was reliable and valid in this population (Munger *et al*, 1992).

Incident EC cases were identified through 2005 via annual linkage with the Iowa Cancer Registry. Cancer data were coded according to the International Classification of Diseases for Oncology (Fritz *et al*, 2000). Type I or Type II were classified

*Correspondence: Dr JR Cerhan; E-mail: cerhan.james@mayo.edu

Received 16 April 2013; revised 25 July 2013; accepted 13 August 2013; published online 10 September 2013

Table 1. Association of coffee and sources of caffeine and methylxanthines with risk of Type I and Type II endometrial cancer[a], Iowa Women's Health Study, 1986–2005

		Type I (*N* = 471)					Type II (*N* = 71)					
Intake[b]	Person-years	Cases	Age-and energy-adjusted RR	*P*-trend	Multivariable-adjusted RR (95% CI)[c]	*P*-trend	Cases	Age- and energy-adjusted RR	*P*-trend	Multivariable-adjusted RR (95% CI)[c]	*P*-trend	*P*-heterogeneity
Total coffee intake (cups)												
Never or ⩽once per month	37 203	64	1.00	0.00021	1.00 (reference)	0.11	7	1.00	0.63	1.00 (reference)	0.64	0.90
<1 cup per week	41 565	64	0.89		0.95 (0.66, 1.36)		8	0.98		0.98 (0.36, 2.72)		
1 cup per day	48 627	55	0.65		0.75 (0.52, 1.09)		13	1.39		1.31 (0.51, 3.35)		
2–3 cups per day	136 795	188	0.80		0.95 (0.71, 1.28)		26	1.02		1.01 (0.43, 2.36)		
4+ cups per day	109 730	100	0.54		0.71 (0.51, 0.99)		17	0.87		0.84 (0.33, 2.12)		
Caffeinated coffee (cups)												
Never or ⩽once per month	106 367	168	1.00	0.00023	1.00 (reference)	0.033	18	1.00	0.66	1.00 (reference)	0.58	0.79
<1 cup per week	68 439	86	0.80		0.83 (0.63, 1.08)		19	1.66		1.56 (0.81, 3.01)		
1 cup per day	35 148	37	0.67		0.70 (0.48, 1.02)		7	1.19		1.08 (0.43, 2.74)		
2–3 cups per day	91 456	121	0.84		0.92 (0.72, 1.18)		16	1.07		1.08 (0.55, 2.13)		
4+ cups per day	72 510	59	0.52		0.65 (0.47, 0.89)		11	0.97		0.85 (0.37, 1.93)		
Decaffeinated coffee (cups)												
Never or ⩽once per month	163 125	224	1.00	0.19	1.00 (reference)	0.53	31	1.00	0.86	1.00 (reference)	0.93	0.76
<1 cup per week	80 239	90	0.81		0.85 (0.66, 1.09)		16	1.04		1.15 (0.62, 2.14)		
1 cup per day	36 994	42	0.82		0.82 (0.58, 1.15)		7	0.97		1.05 (0.46, 2.41)		
2–3 cups per day	63 125	87	1.00		1.06 (0.82, 1.36)		12	1.00		1.01 (0.50, 2.04)		
4+ cups per day	30 436	28	0.68		0.76 (0.50, 1.15)		5	0.89		1.08 (0.41, 2.80)		
Joint intake of caffeinated and decaffeinated coffee intake (cups)												
Never or ⩽once per month	83 259	132	1.00	N/A	1.00 (reference)	N/A						
Decaffeinated only, 1–3 cups per day	67 797	97	0.90		1.02 (0.78, 1.33)							
Decaffeinated only, 4+ cups per day	23 749	25	0.67		0.81 (0.52, 1.27)							
Caffeinated only, 1–3 cups per day	95 043	125	0.83		0.95 (0.73, 1.22)							
Caffeinated only, 4+ cups per day	65 062	57	0.56		0.73 (0.52, 1.02)							
Caffeinated 1+ cups per day and decaffeinated 1+ cups per day	39 009	35	0.57		0.69 (0.47, 1.01)							
Tea (cups), not herbal												
Never or <once per month	161 860	207	1.00	0.72	1.00 (reference)	0.55	27	1.00	0.32	1.00 (reference)	0.46	0.36
1–3 cups a month	62 881	70	0.87		0.87 (0.66, 1.15)		13	1.26		1.28 (0.65, 2.52)		
1–4 cups a week	75 012	95	0.99		0.89 (0.69, 1.15)		15	1.24		1.23 (0.65, 2.34)		
5+ cups a week	74 166	99	1.05		0.95 (0.74, 1.22)		16	1.35		1.26 (0.65, 2.43)		
Cola, regular or low calorie (glass, bottle or can)												
Never or <once per month	234 311	295	1.00	0.52	1.00 (reference)	0.55	39	1.00	0.15	1.00 (reference)	0.16	0.28
1–3 cups a month	57 412	66	0.93		0.99 (0.75, 1.30)		15	1.68		1.65 (0.89, 3.07)		
1+ per week	82 196	110	1.10		1.08 (0.86, 1.36)		17	1.41		1.42 (0.79, 2.56)		

Table 1. (Continued)

	Type I (*N* = 471)						Type II (*N* = 71)					
Chocolate (bars or pieces)												
Never or <once per month	171 617	232	1.00	0.28	1.00 (reference)	0.47	30	1.00	0.071	1.00 (reference)	0.085	0.062
1–3 bars per pieces a month	122 065	143	0.87		0.87 (0.70, 1.09)		20	1.01		1.00 (0.55, 1.80)		
1+ per week	80 237	96	0.90		0.94 (0.73, 1.21)		21	1.80		1.79 (0.98, 3.26)		
Candy bars												
Never or <once per month	208 240	269	1.00	0.60	1.00 (reference)	0.76	33	1.00	0.044	1.00 (reference)	0.087	0.090
1–3 bars a month	113 664	141	0.97		0.98 (0.79, 1.21)		26	1.58		1.46 (0.85, 2.50)		
1+ per week	52 015	61	0.93		0.96 (0.71, 1.29)		12	1.80		1.71 (0.84, 3.48)		
Brownies (one)												
Never or <once per month	229 481	297	1.00	0.52	1.00 (reference)	1.00	43	1.00	0.71	1.00 (reference)	0.82	0.83
1–3 servings a month	110 854	135	0.95		1.02 (0.82, 1.26)		23	1.21		1.12 (0.65, 1.92)		
1+ per week	33 584	39	0.92		0.98 (0.68, 1.40)		5	0.97		1.00 (0.38, 2.58)		
Caffeine (mg per day)												
<29.7	92 717	138	1.00	0.0015	1.00 (reference)	0.059	13	1.00	0.76	1.00 (reference)	0.84	0.38
29.7–158.3	93 302	132	0.95		0.93 (0.72, 1.18)		22	1.74		1.65 (0.82, 3.29)		
158.4–385.0	93 896	107	0.77		0.80 (0.61, 1.04)		23	1.84		1.80 (0.90, 3.59)		
>385.0	94 004	94	0.68		0.80 (0.61, 1.05)		13	1.09		0.98 (0.43, 2.23)		

Abbreviations: CI = confidence interval; HT = hormone therapy; ICD = International Classification of Diseases; RR = relative risk.

[a]Type I defined as ICD-O codes 8000, 8010, 8041, 8140, 8210, 8262, 8263, 8380, 8480, 8560 and 8570, and Type II defined as ICD-O codes 8050, 8260, 8310, 8323, 8441, 8460, 8950, 8951 and 8980.

[b]Frequency of use ('never or less than once per month', '1–3 per month', '1 per week', '2–4 per week', '5–6 per week', '1 per day', '2–3 per day', 4–5 per day', '6 + per day') was asked for the following items: (1) caffeinated coffee (1 cup); (2) decaffeinated coffee (1 cup); (3) tea (1 cup), not herbal teas; (4) Coke, Pepsi or other cola with sugar; (5) caffeine-free Coke, Pepsi or other cola with sugar; (6) low calorie cola, for example, Tab with caffeine; (7) low calorie caffeine-free cola, for example, Pepsi free; (8) chocolate (bars or pieces), for example, Hershey's, M&M's; (9) candy bars, for example, Snickers, Milky Way, Reeses); and (10) brownies (1). Total coffee is the sum of caffeinated plus decaffeinated coffee intake.

[c]Adjusted for age, diabetes, duration of HT use, hypertension, age at menarche, age at menopause, quartiles of body mass index, waist-to-hip ratio, smoking status, pack years of smoking, total energy and alcohol use.

based on registry codes (see Table 1 footnote) as described previously (Uccella *et al*, 2011); there was no central pathology review. Deaths were ascertained by follow-up surveys, annual linkage with Iowa death certificates and linkage to the National Death Index.

Women with history of cancer before baseline, except non-melanoma skin cancer ($n=3830$); hysterectomy before baseline ($n=14\,350$); extreme dietary intake (<600 or >5000 kcal per day) or incomplete FFQ questionnaires ($\geqslant 30$ blank food items) ($n=3096$); or who were not postmenopausal at baseline ($n=569$) were excluded from the present analysis (not mutually exclusive), yielding a final sample size of 23 356 study participants.

Each woman accumulated person-years of follow-up from baseline to date of EC diagnosis, move from Iowa, death or administrative censoring on 31 December 2005. Relative risks (RR) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards regression, and modelling age was used as the time variable (Korn *et al*, 1997). All Cox model attributes included as covariates are listed in corresponding table footnotes, and were selected *a priori* based on their suspected or known associations with endometrial cancer. Separate analyses were carried out for Type I and Type II EC. Tests for trend were carried out by ordering the intake quartiles from lowest to highest and including the resulting variable as a 1 d.f. linear term in the Cox regression models.

We formally determined if risk ratios for the exposure variables differed by type of EC using a competing risk form of Cox proportional hazards regression (Lunn and McNeil, 1995). We also examined associations between exposure variables and subtype-specific EC risk within strata defined by BMI, smoking status and use of HT. All statistical tests were two-sided, and analyses were carried out using SAS (SAS Institute Inc., Cary, NC, USA) and R software systems.

RESULTS

At study baseline, there were 23 356 women in the at-risk cohort, of whom 5218 (22.3%) were obese (BMI $\geqslant 30\,\mathrm{kg\,m^{-2}}$) and 6843 (29.3%) drank 4+ cups per day of coffee (caffeinated or decaffeinated). The correlation of coffee intake with EC risk factors is shown in Table 2.

During the 20-year follow-up period, we identified a total of 542 incident cases of EC, 471 Type I and 71 Type II. The mean age at diagnosis of Type I EC was 71.8 years (range, 57.2–89.5 years) and Type II EC was 72.8 years (range, 60.2–89.3 years).

There was an inverse association of caffeinated coffee consumption with risk of Type I EC after multivariate adjustment (RR = 0.65 for 4+ cups per day compared with $\leqslant 1$ cup per month; P-trend = 0.033), but there were no statistically significant trends with intake of total coffee, decaffeinated coffee, tea, colas or other sources of methylxanthines, although the highest intake of total coffee and decaffeinated coffee did have RRs <0.8 (Table 1). Compared with women who did not drink either caffeinated or decaffeinated coffee, those who drank 4+ cups per day of caffeinated coffee only (RR = 0.73; 95% CI: 0.52–1.02) or 1+ cups per day of both types of coffee (RR = 0.69; 95% CI: 0.47–1.01) had lower EC risk, whereas the association was weaker and not statistically significant for women who drank 4+ cups per day of decaffeinated coffee only (RR = 0.81; 95% CI: 0.52–1.27). Caffeine intake showed a suggestive inverse associated with risk (RR = 0.80 for >385 mg per day compared with <29.7 mg per day; P-trend = 0.059). In contrast, coffee and other sources of methylxanthines were not associated with risk of Type II EC.

We next examined coffee intake with risk of Type I EC within strata defined by BMI (30+ *vs* $<30\,\mathrm{kg\,m^{-2}}$), smoking history (ever/never) and HT use (ever/never); the sample size was too small to conduct these analyses for risk of Type II EC. As shown in Table 3, the inverse associations for total and caffeinated coffee, caffeine and perhaps decaffeinated coffee were only observed among obese women and not among women with a BMI $<30\,\mathrm{kg\,m^{-2}}$. There was no striking or consistent heterogeneity in the associations for coffee or caffeine intake when stratified on smoking status (Supplementary Table 1) or HT use (Supplementary Table 2).

Table 2. Correlation of coffee intake with selected endometrial cancer risk factors, Iowa Women's Health Study (1986)

	Intake of coffee				
Variable	**Never or ⩽1 per month (*N* = 2340)**	**<1 cup per week (*N* = 2638)**	**1 cup per day (*N* = 3040)**	**2–3 cups per day (*N* = 8495)**	**4+ cups per day (*N* = 6843)**
Mean ± s.d.					
Age (years)	62.1 ± 4.2	62.7 ± 4.2	62.9 ± 4.2	62.3 ± 4.2	61.4 ± 4.1
Body mass index ($\mathrm{kg\,m^{-2}}$)	27.6 ± 5.6	27.3 ± 5.5	27.0 ± 5.0	26.8 ± 4.9	26.5 ± 5.0
Waist-to-hip ratio	0.843 ± 0.086	0.837 ± 0.082	0.838 ± 0.083	0.832 ± 0.081	0.828 ± 0.086
Total energy (kcal per day)	1785 ± 613	1718 ± 600	1785 ± 602	1804 ± 584	1871 ± 648
Pack years of smoking	5.7 ± 15.0	5.9 ± 14.4	5.6 ± 14.0	8.3 ± 16.4	15.7 ± 21.4
Percent distribution					
Adult-onset diabetes (ever)	7.1%	6.9%	6.3%	5.3%	4.8%
Hypertension (ever)	36.7%	38.5%	38.3%	34.9%	30.1%
Any alcohol use	22.9%	35.9%	39.6%	50.0%	54.9%
Age at menarche >12 years	55.8%	58.9%	60.7%	59.1%	57.9%
Age at menopause >50 years	63.2%	62.0%	64.3%	64.1%	59.7%
Never used HT	74.4%	73.9%	73.1%	73.1%	73.3%
Smoking history					
Current	7.6%	8.6%	8.0%	12.7%	27.7%
Former	12.8%	15.8%	15.8%	20.7%	22.8%
Never	79.6%	75.6%	76.3%	66.6%	49.4%

Abbreviation: HT = hormone therapy.

Table 3. Association of coffee and caffeine with risk of Type I endometrial cancer, stratified by BMI, Iowa Women's Health Study, 1986–2005

	BMI $<30\,kg\,m^{-2}$				BMI $30+\,kg\,m^{-2}$				
Level of intake	Person-years	Cases	Multivariable-adjusted RR[a] (95% CI)	*P*-trend	Person-years	Cases	Multivariable-adjusted RR[a] (95% CI)	*P*-trend	*P*-interaction
Total coffee intake									
Never or ⩽once per month	27 242	25	1.00 (reference)	0.75	9961	39	1.00 (reference)	0.010	0.054
<1 cup per week	31 426	28	1.09 (0.62, 1.94)		10 140	36	0.82 (0.52, 1.31)		
1 cup per day	37 451	29	1.00 (0.57, 1.77)		11 176	26	0.60 (0.36, 0.99)		
2–3 cups per day	108 294	110	1.33 (0.83, 2.14)		28 501	78	0.72 (0.49, 1.07)		
4+ cups per day	88 005	59	0.99 (0.59, 1.66)		21 725	41	0.53 (0.34, 0.84)		
Caffeinated coffee									
Never or ⩽once per month	80 699	74	1.00 (reference)	0.80	25 668	94	1.00 (reference)	0.0079	0.063
<1 cup per week	53 029	46	1.02 (0.70, 1.49)		15 410	40	0.66 (0.45, 0.97)		
1 cup per day	27 728	23	0.97 (0.59, 1.59)		7420	14	0.51 (0.28, 0.91)		
2–3 cups per day	72 716	75	1.21 (0.86, 1.69)		18 740	46	0.71 (0.50, 1.02)		
4+ cups per day	58 245	33	0.77 (0.50, 1.19)		14 264	26	0.56 (0.36, 0.89)		
Decaffeinated coffee									
Never or ⩽once per month	125 409	110	1.00 (reference)	0.95	37 716	114	1.00 (reference)	0.32	0.58
<1 cup per week	63 908	54	0.94 (0.67, 1.32)		16 331	36	0.73 (0.50, 1.08)		
1 cup per day	28 922	24	0.93 (0.59, 1.46)		8072	18	0.71 (0.43, 1.19)		
2–3 cups per day	49 781	45	1.06 (0.74, 1.51)		13 344	42	1.05 (0.73, 1.50)		
4+ cups per day	24 397	18	0.90 (0.53, 1.53)		6039	10	0.58 (0.30, 1.11)		
Caffeine (mg per day)									
<29.7	71 320	63	1.00 (reference)	0.66	21 397	75	1.00 (reference)	0.038	0.19
29.7–158.3	71 693	71	1.11 (0.78, 1.58)		21 609	61	0.80 (0.56, 1.12)		
158.4–385.0	74 716	64	1.00 (0.69, 1.44)		19 179	43	0.67 (0.46, 0.99)		
>385.0	74 687	53	0.94 (0.64, 1.38)		19 317	41	0.70 (0.47, 1.04)		

Abbreviations: BMI = body mass index; HT = hormone therapy.
[a]Adjusted for age, duration of HT use, diabetes, hypertension, age at menarche, age at menopause, BMI (continuous), waist-to-hip ratio, smoking status, pack years of smoking, total energy and alcohol use.

DISCUSSION

Coffee consumption was most strongly associated with a lower risk of Type I EC among obese postmenopausal women, and these associations were generally stronger and statistically significant for caffeinated relative to decaffeinated coffee intake. There were no statistically significant associations of coffee consumption with Type I EC among non-obese women or for Type II EC. Tea, cola and chocolate intake were not associated with risk of Type I or Type II EC.

A recently updated meta-analysis of 6 cohort and 10 case–control studies (Je and Giovannucci, 2011) reported a pooled RR of 0.71 (95% CI: 0.62–0.81) for the risk of EC for the highest *vs* lowest categories of coffee intake, with the strongest inverse association observed in Japanese studies (RR = 0.40; 95% CI: 0.25–0.63), intermediate for North American studies (RR = 0.69; 95% CI: 0.60–0.79) and weakest but still evident for European studies (RR = 0.79; 95% CI: 0.63–0.99). Consistent with our results, four recent studies found an inverse association of coffee with EC, particularly among women with BMI $\geqslant 30\,kg\,m^{-2}$ (Friberg *et al*, 2009; Giri *et al*, 2011; Gunter *et al*, 2011; Je *et al*, 2011). For the first time, we extend this association specifically to Type I EC and to coffee but not other common sources of methylxanthines, which were not addressed by these prior studies.

The exact mechanisms involved in any putative beneficial effect of coffee on EC remain largely unknown. Coffee is a major source of caffeine, and this methylxanthine may increase levels of circulating sex-hormone-binding globulin, thus reducing the concentrations of bioavailable sex-steroid hormones, in particular free oestradiol, and consequently modifying the hormonal milieu leading to downregulation of endometrial hyperproliferation (Ferrini and Barrett-Connor, 1996; Nagata *et al*, 1998). However, coffee, irrespective of caffeine content, also contains additional compounds with antioxidant activities. These compounds vary widely depending on the type of coffee, roasting and preparation, and many have been found to inhibit the proliferation of tumour cells *in vitro* (Vivani, 1993; Cavin *et al*, 2002).

An intriguing hypothesis suggests that coffee may be an insulin sensitiser (Wu *et al*, 2005; Huxley *et al*, 2009; Loopstra-Masters *et al*, 2011). Coffee (both caffeinated and decaffeinated) and caffeine intake were inversely associated with levels of circulating C-peptide, a marker of insulin secretion and resistance, and this association was much stronger in overweight and obese women (Wu *et al*, 2005).

An inverse association with coffee was not observed for Type II EC, although our analysis was limited by the relatively small number of Type II cases and by the absence of central pathology review. Type I and Type II EC may have different aetiologic pathways and distinct risk factors (Uccella *et al*, 2011). From a molecular point of view, Type II EC is often associated with p53 mutations, which commonly lead to DNA derangements, chromosomal instability and a more aggressive clinical behaviour (Doll *et al*, 2008). Conversely, alterations of p53 have been reported

in only a small proportion of Type I tumours and, when they occur, they are usually a late event (Doll *et al*, 2008). Apoptosis of rapidly growing cells induced by caffeine *in vitro* is dependent on the presence of a functional p53 product, so when p53 is mutated cellular growth is not inhibited by caffeine (He *et al*, 2003).

In conclusion, our results suggest that coffee consumption, perhaps in part related to caffeine, may be relevant for chemoprevention of Type I EC, particularly among obese women.

ACKNOWLEDGEMENTS

This study was supported by the National Institutes of Health (NIH) Grant R01 CA39742, and was approved by the IRB of the University of Minnesota.

REFERENCES

Bokhman JV (1983) Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* **15**(1): 10–17.

Bushman JL (1998) Green tea and cancer in humans: a review of the literature. *Nutr Cancer* **31**(3): 151–159.

Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B (2002) Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem Toxicol* **40**(8): 1155–1163.

Doll A, Abal M, Rigau M, Monge M, Gonzalez M, Demajo S, Colas E, Llaurado M, Alazzouzi H, Planaguma J, Lohmann MA, Garcia J, Castellvi S, Ramon y Cajal J, Gil-Moreno A, Xercavins J, Alameda F, Reventos J (2008) Novel molecular profiles of endometrial cancer – new light through old windows. *J Steroid Biochem Mol Biol* **108**(3–5): 221–229.

Ferrini RL, Barrett-Connor E (1996) Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. *Am J Epidemiol* **144**(7): 642–644.

Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB (1990) Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. *Am J Epidemiol* **131**(5): 794–803.

Friberg E, Orsini N, Mantzoros CS, Wolk A (2009) Coffee drinking and risk of endometrial cancer – a population-based cohort study. *Int J Cancer* **125**(10): 2413–2417.

Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (2000) *International Classification of Diseases for Oncology*. 3rd edn. World Health Organization: Geneva, Switzerland.

Giri A, Sturgeon SR, Luisi N, Bertone-Johnson E, Balasubramanian R, Reeves KW (2011) Caffeinated coffee, decaffeinated coffee and endometrial cancer risk: a prospective cohort study among US postmenopausal women. *Nutrients* **3**(11): 937–950.

Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE, Hollenbeck AR, Sinha R (2011) A prospective investigation of coffee drinking and endometrial cancer incidence. *Int J Cancer* **131**: E530–E536.

He Z, Ma WY, Hashimoto T, Bode AM, Yang CS, Dong Z (2003) Induction of apoptosis by caffeine is mediated by the p53, Bax, and caspase 3 pathways. *Cancer Res* **63**(15): 4396–4401.

Huxley R, Lee CM, Barzi F, Timmermeister L, Czernichow S, Perkovic V, Grobbee DE, Batty D, Woodward M (2009) Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus: a systematic review with meta-analysis. *Arch Intern Med* **169**(22): 2053–2063.

Je Y, Giovannucci E (2011) Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int J Cancer* **131**(7): 1700–1710.

Je Y, Hankinson SE, Tworoger SS, DeVivo I, Giovannucci E (2011) A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. *Cancer Epidemiol Biomarkers Prev* **20**: 2487–2495.

Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* **145**(1): 72–80.

La Vecchia C, Tavani A (2007) Coffee and cancer risk: an update. *Eur J Cancer Prev* **16**(5): 385–389.

Loopstra-Masters RC, Liese AD, Haffner SM, Wagenknecht LE, Hanley AJ (2011) Associations between the intake of caffeinated and decaffeinated coffee and measures of insulin sensitivity and beta cell function. *Diabetologia* **54**(2): 320–328.

Lunn M, McNeil D (1995) Applying Cox regression to competing risks. *Biometrics* **51**(2): 524–532.

Mendivil A, Schuler KM, Gehrig PA (2009) Non-endometrioid adenocarcinoma of the uterine corpus: a review of selected histological subtypes. *Cancer Control* **16**(1): 46–52.

Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA (1992) Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. *Am J Epidemiol* **136**(2): 192–200.

Nagata C, Kabuto M, Shimizu H (1998) Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. *Nutr Cancer* **30**(1): 21–24.

Uccella S, Mariani A, Wang AH, Vierkant RA, Robien K, Anderson KE, Cerhan JR (2011) Dietary and supplemental intake of one-carbon nutrients and the risk of type I and type II endometrial cancer: a prospective cohort study. *Ann Oncol* **22**(9): 2129–2136.

Vivani R (1993) The composition of coffee. In *Caffeine, Coffee and Health*, Garattini S (ed). pp 17–41. Rave Press Ltd: New York, NY, USA.

Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE (1988) The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol* **127**: 188–199.

Wu T, Willett WC, Hankinson SE, Giovannucci E (2005) Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. *Diabetes Care* **28**(6): 1390–1396.

Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)