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

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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 \textit{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 \textit{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 \textit{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 \textit{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 \textit{et al.}, 2000). Type I or Type II were classified

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| Intake of Coffee (cups) | Type I (N = 71) | Type II (N = 71) |
|------------------------|----------------|-----------------|
| Total coffee intake (cups) | | |
| Never or once per month | 39 | 82 |
| <1 cup per week | 41 | 86 |
| 1 cup per week | 37 | 83 |
| 2–3 cups per day | 46 | 83 |
| 4+ cups per day | 44 | 83 |
| Caffeinated coffee (cups) | | |
| Never or once per month | 61 | 110 |
| <1 cup per week | 65 | 110 |
| 1 cup per week | 60 | 109 |
| 2–3 cups per day | 64 | 109 |
| 4+ cups per day | 66 | 109 |
| Decaffeinated coffee (cups) | | |
| Never or once per month | 145 | 263 |
| <1 cup per week | 148 | 263 |
| 1 cup per week | 148 | 263 |
| 2–3 cups per day | 147 | 263 |
| 4+ cups per day | 149 | 263 |
| Joint intake of caffeinated and decaffeinated coffee intake (cups) | | |
| Never or once per month | 24 | 87 |
| Decaffeinated only, 1–3 cups per day | 63 | 109 |
| Decaffeinated only, 4+ cups per day | 22 | 44 |
| Caffeinated only, 1–3 cups per day | 87 | 132 |
| Caffeinated only, 4+ cups per day | 35 | 60 |
| Caffeinated 1+ cups per day and decaffeinated 1+ cups per day | 30 | 60 |
| Tea (cups), not herbal | | |
| Never or once per month | 161 | 314 |
| <1 cup per month | 162 | 314 |
| 1+ cups per month | 161 | 314 |
| Cola, regular or low calorie (glass, bottle or can) | | |
| Never or once per month | 234 | 466 |
| 1–3 cups per month | 57 | 109 |
| 4+ cups per month | 82 | 110 |
| Age- and energy-adjusted RR (95% CI) | | |
| Type I | | |
| Age and energy-adjusted RR | | |
| Type II | | |
| Age and energy-adjusted RR | | |
| P-trend | | |
| Multivariable-adjusted RR (95% CI) | | |
| P-trend | | |
| P-heterogeneity | | |

Table 1. Association of coffee and sources of caffeine and methylxanthines with risk of Type I and Type II endometrial cancer, Iowa Women’s Health Study, 1986–2005.
Table 1. (Continued)

| Chocolate (bars or pieces) | Type I (N = 471) | Type II (N = 71) |
|---------------------------|-----------------|-----------------|
| Never or < once per month | 171,617 | 232 | 1.00 | 1.00 (reference) | 0.47 | 30 | 1.00 | 1.00 (reference) | 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) | 21 | 1.80 | 1.79 (0.98, 3.26) |
| 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 | 1.00 (reference) | 0.76 | 33 | 1.00 | 1.00 (reference) | 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) | 12 | 1.80 | 1.71 (0.84, 3.48) |
| 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 | 1.00 (reference) | 1.00 | 43 | 1.00 | 1.00 (reference) | 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) | 5 | 0.97 | 1.00 (0.38, 2.58) |
| 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 | 1.00 (reference) | 0.0015 | 13 | 1.00 | 1.00 (reference) | 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) | 23 | 1.84 | 1.80 (0.90, 3.59) |
| 158.4–385.0 | 93,896 | 107 | 0.77 | 0.80 (0.61, 1.04) | 23 | 1.84 | 1.80 (0.90, 3.59) | 13 | 1.09 | 0.98 (0.43, 2.23) |
| >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.

*Type I defined as ICD-O codes 8000, 8010, 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 8990.

**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 tea; (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, Reese; and (10) brownies (1). Total coffee is the sum of caffeinated plus decaffeinated coffee intake.

*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 (≥ 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.

At study baseline, there were 23,356 women in the at-risk cohort, of whom 5218 (22.3%) were obese (BMI ≥ 30 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 ≤ 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 1–4 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 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 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).

RESULTS

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

| Intake of coffee                  | 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 (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%                       |
| 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

| Total coffee intake | Person-years | Cases | Multivariable-adjusted RR* | P-trend | Person-years | Cases | Multivariable-adjusted RR* |
|---------------------|--------------|-------|---------------------------|---------|--------------|-------|---------------------------|
| Never or < once per month | 27,242 | 25 | 1.00 (reference) | 0.75 | 9961 | 39 | 1.00 (reference) | 0.010 | 0.554 |
| <1 cup per week | 31,426 | 28 | 1.09 (0.62, 1.94) | 10,140 | 36 | 0.62 (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 | Person-years | Cases | Multivariable-adjusted RR* | P-trend | Person-years | Cases | Multivariable-adjusted RR* |
|--------------------|--------------|-------|---------------------------|---------|--------------|-------|---------------------------|
| Never or < once per month | 80,699 | 74 | 1.00 (reference) | 0.801 | 25,668 | 94 | 1.00 (reference) | 0.0079 | 0.63 |
| <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 | 27,278 | 23 | 0.97 (0.59, 1.59) | 7,420 | 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 | Person-years | Cases | Multivariable-adjusted RR* | P-trend | Person-years | Cases | Multivariable-adjusted RR* |
|----------------------|--------------|-------|---------------------------|---------|--------------|-------|---------------------------|
| 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, 0.98) | | |
| 1 cup per day | 28,922 | 24 | 0.93 (0.59, 1.46) | 8,072 | 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) | 6,039 | 10 | 0.58 (0.30, 1.11) | | |

| Caffeine (mg per day) | Person-years | Cases | Multivariable-adjusted RR* | P-trend | Person-years | Cases | Multivariable-adjusted RR* |
|-----------------------|--------------|-------|---------------------------|---------|--------------|-------|---------------------------|
| <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.
*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 ≥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.

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