Serum levels of insulin-like growth factor-I, IGF-binding protein 1 and 3, and insulin and endometrial cancer risk

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Insulin-like growth factor-I (IGF-I) and IGF-binding protein-1 and 3 (IGFBP-1, IGFBP-3) are expressed in normal and neoplastic endometrium. Their role and the role of insulin in the aetiology of endometrial cancer, is unclear. We performed a population-based case-control study in Sweden, including 288 endometrial cancer patients and 392 control women and analysed total serum IGF-I, IGFBP-1, IGFBP-3, insulin and BMI levels stratified by disease and hormone replacement therapy status (HRT). Non-parametric statistical tests and logistic regression analyses were performed to assess associations with endometrial cancer. There were no substantial differences between the mean serum levels of IGF-I between cases (115.5, s.d. 61.3) and controls (110.6; s.d. 50.4; Wilcoxon P = 0.84), or between subgroups of women classified according to other risk factors for endometrial cancer. There were no trends of increasing risk according to quartiles of IGF-I, IGFBP-1, IGFBP-3 and insulin serum levels. There was an increasing risk of endometrial cancer according to the serum levels of IGFBP-1, which was observed only among women who had ever used HRT. Serum IGF-I, IGFBP-1, IGFBP-3 and insulin levels seem unrelated to endometrial cancer risk. Among users of HRT, increasing IGFBP-1 levels seem to increase endometrial cancer risk.

British Journal of Cancer (2003) 89, 1697 – 1704. doi:10.1038/sj.bjc.6601312  www.bjcancer.com

Keywords: endometrial neoplasms; insulin-like growth factor-I (IGF-I); insulin-like growth factor binding protein-1 (IGFBP-1); insulin-like growth factor binding protein-3 (IGFBP-3); insulin; hormone replacement therapy (HRT)

Endometrial cancer has high incidence rates in Western, industrially developed societies. In these countries, obesity has been associated with a 2-to-5-fold increase in endometrial cancer risk in both pre- and postmenopausal women (IARC, 2002) and has been estimated to account for about 40% of endometrial cancer incidence (Bergstrom et al, 2001). Apart from excess weight, epidemiological evidence suggests that lack of regular physical activity may also be a risk factor (IARC, 2002).

A major metabolic link between obesity, lack of physical activity, and development of ovarian androgen excess is chronic hyperinsulinaemia. Obesity and physical inactivity lead to insulin resistance, and increased fasting and nonfasting insulin levels. Furthermore, type II diabetes mellitus (Type II DM) – a condition associated with chronic endogenous insulin excess for many years both before and after diagnosis – is a well-established risk factor for endometrial cancer (Persson and Adami, 2002). One previous case–control study showed that risk of endometrial cancer was increased among women (also nondiabetic) who had elevated fasting serum levels of C-peptide, a marker of pancreatic (pro)insulin secretion (Troisi et al, 1997).

In addition to insulin, there is evidence that endometrial cancer development is related to alterations in insulin-like growth factor-I (IGF-I) metabolism. Oestrogens increase endometrial cell proliferation by inducing the production of IGF-I in stromal tissue, and it is IGF-I that, in turn, provides the major mitogenic stimulus. Progesterone opposes these effects by inducing the local synthesis of IGFBP-1 (Giudice, 1994; Lee et al, 1997) – the most abundant IGF-binding protein in endometrial tissue. Insulin inhibits IGFBP-1 synthesis in liver and other tissue, and this may be one key mechanism through which insulin increases endometrial cancer risk (Brismar et al, 1994; Lee et al, 1997).

We present here results of a population-based case–control study in Sweden, in which we assessed the relationships of endometrial cancer risk with serum levels of fasting insulin, IGF-I, and IGFBP-1, as well as IGFBP-3, IGF’s major binding protein in the circulation. We also explored whether these associations differ in subgroups of women who used exogenous hormones (oral contraceptives (OCs) and hormone replacement therapy (HRT)).

SUBJECTS AND METHODS

Study population

Our study included women aged 50–74 years, resident between February 1996 and November 1997 in 12 Swedish counties on the coasts of the Gulf of Bothnia, the Baltic Sea, and the largest Swedish lakes. Women were eligible if they were born in Sweden, had no prior hysterectomy, and had no previous history of cancer. In a component of this study, we have previously analysed serum
organochlorine levels and endometrial cancer risk (Weiderpass et al, 2000). We assumed that the intake of organochlorine compounds through ingestion of possibly contaminated fish would be higher in these fish-producing counties than in other parts of Sweden.

Women with incident histopathologically confirmed endometrial cancer diagnosed between February 1996 and November 1997 were identified through a network of personnel at the 26 departments of gynaecology/gynaecology—oncology in the study area (one of the departments did not collaborate). The health-care system in Sweden is organised in such a way that people must seek services in the health-care unit/hospital closest to their home. Therefore, it is highly unlikely that cancer cases residing in the study area would be operated outside the study area. A total of 396 cases were reported, approximately 95% of the number expected on the basis of national incidence rates (National Board of Health and Welfare, 1998). Of these, 288 (73%) were contacted before surgery, volunteered to donate blood samples, and subsequently completed the study questionnaire a few months after surgery; 41 patients refused to participate and 67 cases were not approached (due to failure of the medical staff to collect a blood sample before surgery).

Population controls, who were resident in the study area, were randomly selected from a continuously updated population register and frequency matched to cases by 5-year age groups. Controls were not matched to cases by geographic area of residence (county) or any other characteristic. The period of control recruitment coincided with that of the cases, since we sampled and enrolled controls in four phases: the spring of 1996, the fall of 1996, the spring 1997, and the fall 1997. In contrast to the cases, the controls were approached first for questionnaire information, and subsequently asked to donate a fasting blood sample. Of 688 control women selected, 505 (73.4%) responded to the questionnaire, and 438 (63.7%) also agreed to donate blood samples. After exclusion of 46 women because of prior hysterectomy, 392 control women were included in the study.

The self-administered study questionnaire requested information on weight 1 year preceding the interview, height, reproductive history, smoking, physical activity 1 year preceding the interview, medical history (as having had a diagnosis of diabetes mellitus), and use of exogenous hormone (of HRT and OCs), among others. Information about use of HRT and OCs included brand, dosage, date of first and last use of each treatment period, and – for HRT – treatment indication. Recall was aided by picture charts of all variables. The period of residence (county) or any other characteristic. The period of control recruitment coincided with that of the cases, since we sampled and enrolled controls in four phases: the spring of 1996, the fall of 1996, the spring 1997, and the fall 1997. In contrast to the cases, the controls were approached first for questionnaire information, and subsequently asked to donate a fasting blood sample. Of 688 control women selected, 505 (73.4%) responded to the questionnaire, and 438 (63.7%) also agreed to donate blood samples. After exclusion of 46 women because of prior hysterectomy, 392 control women were included in the study.

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Blood sampling

Blood samples from fasting case women were drawn at the hospital departments before surgery or any cancer treatment and from controls at a primary health-care unit or at home. Case patients and control women were requested to fast overnight, for at least 8 h.

Laboratory analysis

Laboratory analysts in charge of measuring IGF-I and IGFBP-1, IGFBP-3, and insulin were blinded to the case–control status of the samples, as well as other subject characteristics.

Total IGF-1 Serum concentrations of IGF-I were determined by RIA after separation of IGFs from IGFBPs by acid ethanol extraction and cryoprecipitation (Bang et al, 1991). To minimise the interference of remaining IGFBPs in the acid ethanol extracts, Des(1–3)IGF-I was used as a radioligand. The recovery of unlabelled IGF-I was 95% and the intra- and interassay coefficients of variation were 5 and 11%, respectively. The lowest detectable quantity of IGF-I was 0.01 ng tube$^{-1}$. Crossreactivity with insulin was less than 0.1% and with IGF-II less than 2%.

Serum levels of IGF-I are age dependent, decreasing with age. Thus, IGF-I values were also expressed as standard deviation (s.d.) scores, calculated from the regression of the values of 247 healthy adult subjects (Hilding et al, 1995).

IGFBP-1 Serum IGFBP-1 concentrations were determined by RIA as described by Povoa et al (1986). The intra- and interassay coefficients of variation were 3 and 11%, respectively, and the detection limit was 3.0 μg l$^{-1}$. Crossreactivity with IGFBP-2 and IGFBP-3 was less than 0.5 and 0.05%, respectively. The geometrical mean and range of IGFBP-1 were 34 and 12–91 μg l$^{-1}$ in healthy subjects, aged 20–66 years (Hall et al, 1988).

IGFBP-3 IGFBP-3 was analysed using a commercial RIA (DSL 6700, Diagnostic System Laboratories, Webster, TX, USA). The mean and normal range was 3.8 and 2.3–5.3 mg l$^{-1}$ in women.

Insulin Serum insulin was measured using an RIA technique (RIA 100, Pharmacia, Uppsala, Sweden). The detection limit was <2 μU ml$^{-1}$. The within-assay CV was 5.8 for a mean value of 11.6 μU ml$^{-1}$ and 5.7 for a mean value of 65.2 μU ml$^{-1}$.

Statistical analysis

As the distributions of IGF-I, IGFBP-1, IGFBP-3, and insulin measurements were heavily skewed, we used the nonparametric two-sample Wilcoxon’s test for unpaired data to conduct unadjusted comparisons of IGF-I, IGFBP-1, IGFBP-3, insulin levels in case and control women and in ever, never, and former users of HRT. Quartiles of the distribution of the IGF-I, IGFBP-1, IGFBP-3, and insulin levels were calculated based on the values assumed from the controls (reference group), and included in the logistic regression analysis as dummy variables.

We first estimated age-adjusted odds ratios (ORs) of IGF-I, IGFBP-1, IGFBP-3, and insulin levels, and subsequently included in the logistic regression models variables known or hypothetically associated with endometrial cancer risk, and that may be in the 'IGF-I, IGFBP-1, IGFBP-3, insulin, and endometrial cancer pathway. These variables were age (as a continuous variable), age at menarche (as a continuous variable), menopausal status (pre- or postmenopausal), body mass index (BMI, that is, weight in kg height$^{-2}$ in m$^2$, as a continuous variable), physical activity levels, use of oral contraceptives (ever or never), clinical history of diabetes mellitus and hypertension (self-reported), and use of different HRT (classified according to ever or never exposure to the following compounds: oestrogens without progestins, oestrogens with cyclic addition of progestins, progestins without oestrogens, oral oestriol, and vaginal use of oestril, dienestrol, or oestradiol. Ever users were further classified as 'current users', meaning control women who were using HRT at the time of blood sample collection and case women who were using HRT at the time of surgery.
of blood sample collection during the process of endometrial cancer diagnosis).

We analysed the effect of all the variables mentioned above on IGF-I, IGFBPs, and insulin among control women only, to understand which were strong determinants of these endogenous hormone levels among women without cancer. In these analyses, the use of HRT and OCs was the only women's characteristic strongly influencing all endogenous hormones levels of interest (IGF-1, IGFBPs, and insulin). Therefore, here we will also present stratified analysis according to the use of HRT and OCs.

Maximum-likelihood estimates of ORs and 95% confidence intervals were produced using the unconditional logistic regression model procedure in Stata 7 (Breslow and Day, 1980; Stata, 2000).

RESULTS

Compared to controls, cases were slightly older, had a higher age at menopause, a lower parity, and a greater BMI. Proportionally, more cases than controls reported being nulliparous, having never smoked or used oral contraceptives, having used HRT, having a history of diabetes mellitus or hypertension, and being extremely sedentary (Table 1).

Table 1 Selected characteristics of endometrial cancer patients and control women

|            | Cases (n = 288) | Controls (n = 392) |
|------------|----------------|-------------------|
| **Cases/controls** |                |                   |
| Age (years) | 288/392        | 64.7 (7.2)        | 63.0 (7.0)        |
| Age at menopause | 258/363        | 51.2 (3.3)        | 50.3 (3.7)        |
| Parity (all women) | 288/381        | 1.9 (1.2)         | 2.2 (1.2)         |
| Age at last birth | 288/381        | 30.0 (5.5)        | 30.0 (5.5)        |
| Body mass index | 288/291        | 27.6 (5.0)        | 25.9 (4.4)        |

**Proportions**

|                  | Cases (%) | Controls (%) |
|------------------|-----------|--------------|
| Premenopausal    | 288/392   | 7.7%         | 6.4%          |
| Nulliparous      | 288/381   | 14.6%        | 9.4%          |
| Ever smoked      | 288/392   | 29.2%        | 39.5%         |
| Ever used OCs    | 288/392   | 71 (24.7%)   | 154 (39.3%)   |
| Ever used HRT    | 288/392   | 150 (52.1%)  | 166 (42.3%)   |
| Diabetes mellitus| 288/392   | 10.4%        | 3.1%          |
| Hypertension     | 281/391   | 35%          | 24%           |
| Extreme sedentarism | 208/366   | 20 (9.6%)    | 4 (1.1%)      |

*Number of study subjects for whom data are available for each variable. Excluding 22 cases and 25 controls who were premenopausal. * Among parous. Weight in kg/height in m². HRT = hormone replacement therapy. Women may have used more than one kind of oestrogen replacement. Self-reported. At 1 year before study enrolment in a scale of physical activity ranging from 0 to 4.

The correlation coefficients between the different endogenous hormones studied did not differ substantially from those calculated separately for cancer patients and controls (Table 2).

Table 3 Distribution of IGF-I, IGFBP-1, IGFBP-3, and insulin among endometrial cancer cases and control women

|                      | Cases (n = 288) | Controls (n = 392) |
|----------------------|----------------|-------------------|
| **igf-1** (ng ml⁻¹)  | 274            | 1155 (61.3)       | 103.0       |
| **IGFBP-1** (ng ml⁻¹) | 274            | 32.2 (20.4)       | 28.2        |
| **IGFBP-3** (ng ml⁻¹) | 257            | 6.1 (2.3)         | 5.7         |
| **Insulin** (ng ml⁻¹) | 260            | 14.0 (13.9)       | 10.0        |

*P-value for the difference between cases and controls (within lines).
### Table 4

**Distribution of IGF-I, IGFBP-1, IGFBP-3, in subgroups of endometrial cancer cases and control women, classified according to use of HRT and OCs**

|                      | Cases (n = 288) | Controls (n = 392) |
|----------------------|-----------------|--------------------|
|                      | n               | Mean (s.d.) | Median | P-value* | Range          | n               | Mean (s.d.) | Median | P-value* | Range          |
| **IGF-I (ng ml⁻¹)**  |                 |             |        |          |               |                 |             |        |          |               |
| HRT never used       | 129             | 107.9 (55.7) | 98.0   | 0.0584   | 27–333        | 203             | 100.8 (45.5) | 94.0   | 0.0000   | 18–290        |
| HRT ever used        | 145             | 122.2 (65.3) | 108.0  | 0.22–403 | 22–381        | 110             | 128.8 (54.2) | 118.5  | 0.0168   | 57–373         |
| HRT former user      | 116             | 122.8 (62.5) | 111.0  | 0.0382   | 22–381        | 25              | 129.2 (56.2) | 109.0  | 0.0018   | 57–278         |
| OC never used        | 204             | 112.8 (61.3) | 99.0   | 0.1150   | 27–403        | 203             | 105.8 (53.6) | 94.0   | 0.0007   | 18–373         |
| OC ever used         | 70              | 123.4 (61.0) | 110.0  | 0.22–333 | 22–333        | 110             | 119.4 (42.7) | 113.5  | 0.41–290 | 41–290         |

**IGFBP-1 (ng ml⁻¹)**

|                      | Cases          | Controls       |
|----------------------|----------------|----------------|
| HRT never used       | 129            | 33.1 (21.6)    | 26.9 | 0.6611 | 1.9–98.6   |
| HRT ever used        | 145            | 31.3 (19.4)    | 27.2 | 0.32–101.0 |
| HRT former user      | 116            | 31.4 (20.2)    | 27.5 | 0.6062 | 3.9–101    |
| OC never used        | 204            | 32.2 (20.2)    | 28.2 | 0.9484 | 3.9–101    |
| OC ever used         | 70             | 32.2 (21.2)    | 29.0 | 1.9–95.4 | 20.6        |

**IGFBP-3 (ng ml⁻¹)**

|                      | Cases          | Controls       |
|----------------------|----------------|----------------|
| HRT never used       | 120            | 6.1 (2.3)      | 5.7  | 0.8092 | 0.1–11.9  |
| HRT ever used        | 137            | 6.1 (2.3)      | 5.7  | 2.2–12.4 | 109        |
| HRT former user      | 112            | 6.1 (2.3)      | 5.7  | 0.9415 | 2.2–12.4  |
| OC never used        | 192            | 6.0 (2.4)      | 5.6  | 0.1–11.4 | 99         |
| OC ever used         | 65             | 6.0 (2.4)      | 5.6  | 1.9–95.4 | 20.6        |

**Insulin (ng ml⁻¹)**

|                      | Cases          | Controls       |
|----------------------|----------------|----------------|
| HRT never used       | 120            | 14.8 (13.4)    | 10.0 | 0.0727 | 7.0–81.0 |
| HRT ever used        | 140            | 13.2 (14.2)    | 9.0  | 2.0–119.0 | 109        |
| HRT former user      | 115            | 12.3 (11.7)    | 9.9  | 0.0773 | 2.0–71.0  |
| OC never used        | 194            | 14.2 (14.1)    | 10.0 | 0.5930 | 2.0–119.0 |
| OC ever used         | 66             | 13.3 (12.9)    | 10.0 | 2.0–81.0 | 102        |

HRT = hormone replacement therapy; OC = oral contraceptives. *P-value for the difference within categories in each column (i.e. comparing cases who used HRT with cases who never used HRT or who were former users of HRT, or ever vs never users of OCs within cases and within controls). **P-value for the difference between cases and controls (within lines).

### Table 5

**Serum levels of IGF-I, IGFBP-1, IGFBP-3, insulin, and risk of endometrial cancer**

|                      | Quartiles of the distribution among control women* |
|----------------------|-----------------------------------------------|
|                      | 2                     | 3                     | 4                     | P trend |
| Age-adjusted and multivariate models** | OR (95 CI)* | OR (95 CI)* | OR (95 CI)* |          |
| IGF-I                |                     |                      |                      |          |
| Model A              | 1.0                  | 0.63 (0.39–1.01)     | 0.84 (0.53–1.33)     | 0.98 (0.62–1.53) | 0.85 |
| Model B              | 1.0                  | 0.51 (0.29–0.89)     | 0.66 (0.38–1.24)     | 0.89 (0.52–1.58) | 0.86 |
| Model C              | 1.0                  | 0.59 (0.32–1.10)     | 0.82 (0.44–1.54)     | 0.86 (0.46–1.58) | 0.78 |
| IGFBP-1              |                     |                      |                      |          |
| Model A              | 1.0                  | 0.96 (0.59–1.56)     | 1.29 (0.81–2.07)     | 1.43 (0.90–2.27) | 0.07 |
| Model B              | 1.0                  | 1.16 (0.64–2.11)     | 1.50 (0.85–2.63)     | 1.63 (0.90–2.94) | 0.07 |
| Model C              | 1.0                  | 0.91 (0.45–1.81)     | 1.21 (0.63–2.35)     | 1.09 (0.54–2.20) | 0.85 |
| IGFBP-3              |                     |                      |                      |          |
| Model A              | 1.0                  | 0.93 (0.58–1.50)     | 0.76 (0.47–1.24)     | 0.90 (0.55–1.46) | 0.51 |
| Model B              | 1.0                  | 0.99 (0.56–1.74)     | 0.81 (0.45–1.48)     | 1.08 (0.60–1.92) | 0.95 |
| Model C              | 1.0                  | 0.77 (0.41–1.46)     | 0.80 (0.41–1.56)     | 1.22 (0.63–2.36) | 0.51 |
| Insulin              |                     |                      |                      |          |
| Model A              | 1.0                  | 1.18 (0.72–1.95)     | 1.09 (0.65–1.83)     | 1.04 (0.62–1.75) | 0.94 |
| Model B              | 1.0                  | 1.13 (0.62–2.08)     | 0.77 (0.40–1.51)     | 0.64 (0.32–1.24) | 0.07 |
| Model C              | 1.0                  | 1.24 (0.62–2.50)     | 0.87 (0.40–1.90)     | 0.72 (0.33–1.58) | 0.19 |

OR = odds ratio. *The first quartile is always considered as a reference category (1.0). The quartiles are: IGF-I (ng ml⁻¹): <77.5, 77.5–100, 101–134, and >134. IGFBP-1 (ng ml⁻¹): <142, 142–245, 246–386, and >386. IGFBP-3 (ng ml⁻¹): <4.5, 4.5–5.9, 6–7.6, and >7.6. Insulin (mg ml⁻¹): <6, 6–9.9, 10–16.9, and >16.9. ** The multivariate models include indicators for: Model (A) age, Model (B) age, BMI, diabetes mellitus, and physical activity, Model (C) as in Model (B), adding menopausal status, different types of hormone replacement therapy and oral contraceptives.**
levels) did not differ meaningfully from the analysis without such mutual adjustment (data not shown).

Although globally there were no clear associations of endometrial cancer risk with levels of the various peptides, certain differences are shown in Table 6 by HRT status. Among HRT users, higher IGF-I and IGFBP-3 levels were associated with a (nonsignificant) decreased risk of endometrial cancer, while among never users there was no such association. Furthermore, among HRT users increasing levels of IGFBP-1 and lower levels of insulin were associated with increased endometrial cancer risk, while among nonusers the risk was not associated with IGFBP-1 and directly associated with insulin. The differences between HRT users and nonusers in the relationships of risk with IGFBP-1 and insulin were statistically significant ($P_{\text{interaction}} = 0.02$ for IGFBP-1 and $P < 0.000$ for insulin).

We found no clear evidence of an interaction between the use of oral contraceptives levels of IGF-I, IGFBPs, and insulin (Table 7). Women in the two highest quartiles of the IGFBP-1 distribution levels of IGF-I, IGFBP-1, IGFBP-3, insulin, and endometrial cancer, according to use of HRT (ever or never used during lifetime)
who used OCs were at increased endometrial cancer risk, while no clear association was observed among those who never used OCs (P for interaction = 0.08). There was no indication of any differential effect of insulin according to the use of oral contraceptives (P for interaction = 0.82).

**DISCUSSION**

This first large case-control study on endometrial cancer risk in relation to serum levels of IGF-I and IGF-binding proteins-1 and -3, globally showed no association of risk with any of these peptides. Furthermore, risk globally appeared not to be associated with serum insulin levels. Other case-control differences in our study in relation to age, age at menopause, parity, BMI, smoking history use of OCs and HRT, history of diabetes, hypertension, and sedentarism are fully in line with known epidemiological associations (Persson and Adami, 2002).

Considerable evidence suggests that these relationships of risk with lifestyle may be mediated by alterations in the metabolism of endogenous sex steroids. Endometrial cancer risk is increased among both pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women with increased levels of circulating oestrone and estradiol (Persson and Adami, 2002).

Given the increased risk of endometrial cancer among type II diabetics and obese women, and given the results from the previous case-control study by Troisi et al (1997), we anticipated that elevated insulin would have been related to higher endometrial cancer risk. We have postulated a number of mechanisms through which this increase might occur (Kaaks et al, 2002).

The anticipated direct association of risk with serum insulin levels was clearly present only when we restricted our statistical analyses to women who never used any oestrogen or oestrogen plus progestogen HRT. In this subgroup, we also observed an inverse association with levels of IGFBP-1, but only after multiple
tumour types (e.g. colorectum, prostate) is IGFBP-2, and this may lead to some increase in circulating levels (which are much lower than those of IGF-I and IGFBP-3). However, this binding protein was not measured in the present study.

With respect to the laboratory assays, analysts were blinded to the case or control status of the samples, and hence could not have led to any systematic observation bias. However, one possible source of bias that could explain case-control differences in the levels of insulin as well as IGFBP-1 would be the differences in fasting vs nonfasting conditions of cases and controls at the time of blood sampling as (IGFBP-1 levels drop acutely as insulin rises, after food consumption). Another possibility would have been an increase in IGFBP-1 levels due to elevated cortisol, which stimulates hepatic IGFBP-1 synthesis, and which might reflect greater psychological stress among the cancer patients, for example. While such factors might have explained a global case-control difference in the levels of these hormones, it is less evident how they would have led to case-control differences in the relationship of risk with hormone levels within subgroups of HRT users and nonusers separately. However, we cannot exclude the play of chance in our findings, particularly in small subgroups such as HRT users.

Globally, risk was not associated with levels of circulating levels of IGF-I. Over 80% of IGF-I in the circulation originates from the liver. The main physiological stimulus for hepatic IGF-I synthesis is growth hormone. In endometrial tissue, however, oestrogens provide the main stimulus for IGF-I synthesis. Given these differences in physiology, it is quite possible that, contrary to several other forms of cancer (Kaaks and Lukanova, 2001), endometrial cancer risk is relatively independent of circulating IGF-I levels. In some other, small case-control studies, cases were found to have lower levels of IGF-I. Among HRT users, we observed an increased risk of endometrial cancer among women in the lowest quartile level of IGF-I (P for trend = 0.23), which remained after adjustment for BMI.

In conclusion, our study does not show any evidence of an overall association between endometrial cancer risk and serum levels of IGF-1, IGFBP-1, IGFBP-3, and insulin. Our suggestive finding of an association between IGFBP-1 levels and endometrial cancer risk among women who used HRT needs confirmation by a study with greater statistical power to detect weak associations.

ACKNOWLEDGEMENTS

This work was supported by grants from the Swedish Cancer Society, the Chlorine Chemistry Council, USA, and the Swedish Medical Research Council (Grant MFR 04224). We thank Professors Ingemar Persson, Hans-Olov Adami, and John A. Baron for participation in the early phases of this study. We also thank an anonymous reviewer who contributed with important and constructive comments, which improved the manuscript substantially.

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