EUROPEAN JOURNAL OF CANCER 44 (2008) 1632–1644

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Endometrial hyperplasia, endometrial cancer and prevention: Gaps in existing research of modifiable risk factors

Faina Linkov[a], *Robert Edwards*[b], *Judith Balk*[b], *Zoya Yurkovetsky*[a], *Barbara Stadterman*[a], *Anna Lokshin*[a], *Emanuela Taioli*[a,c,*]

[a]*University of Pittsburgh Cancer Institute, Department of Medicine, 5117 Centre Avenue, Pittsburgh, PA 15213, United States*
[b]*Magee-Womens Hospital of UPMC Health System, 300 Halket Street, Pittsburgh, PA 15213, United States*
[c]*Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, United States*

ARTICLE INFO

Article history:
Received 15 February 2008
Received in revised form
25 April 2008
Accepted 1 May 2008
Available online 29 May 2008

Keywords:
Uterus
Tumour markers
Risk factors
Diet
Obesity
Lifestyle
Endometrial carcinoma

ABSTRACT

Purpose: Endometrial carcinoma is the most common cancer of the lower female genital tract in Europe and the United States. Faced with the growing incidence of endometrial cancer in Europe and around the world, scientists, doctors and public health professionals are becoming more concerned with identifying effective preventive measures for this condition. This review paper presents the existing knowledge about modifiable risk factors leading to endometrial hyperplasia and endometrial cancer and highlights the need for more studies in this area.

Design/Methods: Extensive literature review of modifiable risk factors for endometrial cancer and endometrial hyperplasia has been performed. Additionally, biomarker approaches to cancer monitoring, existing therapies for endometrial hyperplasia and factors affecting patient survival are reviewed.

Results: Obesity and inactivity are two of the major risk factors associated with the development of endometrial cancer and endometrial hyperplasia. Other modifiable risk factors include dietary habits, exercise and the use of hormonal therapy. Similar factors, along with cancer biomarkers, may play an important role in the early detection of endometrial cancer and survival after the diagnosis. The majority of these factors fit well with the unopposed oestrogen theory. Diet and exercise programmes are currently not integrated into a standard treatment programmes for patients with endometrial hyperplasia or endometrial cancer.

Conclusions: More studies are needed to investigate modifiable risk factors for endometrial cancer and endometrial hyperplasia. Existing therapies for endometrial hyperplasia target hormone imbalance, which is just one aspect of endometrial cancer development. Next generation therapies for endometrial cancer and endometrial hyperplasia patients should include diet, exercise and weight loss plans, which would target other modifiable aspects of endometrial cancer risk.

* *Corresponding author*: Address: Department of Medicine, Division of Hematology and Oncology, University of Pittsburgh Cancer Institute, Division of Cancer Prevention and Population Science, Cancer Pavilion, 4th Floor, Room 464, 5150 Centre Avenue, Pittsburgh, PA 15232, United States. Tel.: +1 412 623 2217; fax: +1 412 623 3878.
E-mail address: taiolien@upmc.edu (E. Taioli).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.05.001

1. Introduction

The incidence of endometrial cancer has been increasing in Europe, United States (US) and other regions of the world in the past several decades. Nearly 40% of the 190,000 corpus uteri cancers diagnosed worldwide each year occur in Europe, representing one in every 18 new female cancers and ranking as the fourth most common neoplasm in women.[1] Endometrial carcinoma is the most common cancer of the lower female genital tract in the United States.[2] Rapid changes have occurred in the incidence of endometrial cancer in the United States since the 1960s are possibly related to the introduction of unopposed oestrogen therapy for postmenopausal women.[3]

Some of the highest incidence rates of endometrial cancer worldwide are found within European populations.[4] Despite the advances that have been made in the early detection and treatment of this disease, both the annual incidence of and the death rate associated with endometrial cancer appear to be rising[5,6] again. The main factors contributing to the increasing incidence of endometrial cancer in the past 20 years both in the US and in Europe are increasing life-expectancy, obesity, which increases circulating oestrogens and tamoxifen, a widely prescribed adjuvant treatment for breast cancer which increases incidence by as much as 6–8-fold.[7] Risk factors for endometrial cancer include age at menarche, age at menopause, history of infertility, obesity, diabetes, oestrogen therapy, polycystic ovarian syndrome, prior pelvic radiation therapy, hereditary non-polyposis colon cancer and westernisation of lifestyle.[8]

In Europe, incidence rates amongst postmenopausal women are highest in the Czech Republic, Slovakia, Sweden and Slovenia and lowest in France and the United Kingdom. Postmenopausal mortality rates are systematically higher in eastern Europe, with death rates in the Ukraine, Latvia, Czech Republic, Russia and Belarus being 2–3 times those seen in western Europe.[1] Declining mortality trends are seen in most populations, though in certain Eastern European countries the declines began rather recently, during the 1980s. In Belarus and Russia, recent postmenopausal death rates are stable or increasing.[1] In the United States, approximately 39,080 new cases of endometrial cancer are expected to be diagnosed in 2007 with the average occurrence at 63 years of age, and about 7400 women will die from the disease.[9] The most recent incidence rate of corpus uteri cancer varied between 9.2 (France) and 18 (Czech Republic) per 100,000 women. In most countries incidence rates remained stable, except in Norway, Ireland, the United Kingdom (UK) and Slovenia where rates were increasing.[10]

Latest figures from the International Agency for Research on Cancer (IARC scientific publications no. 160.) nicely illustrate great geographic variation in the incidence of endometrial cancer. Whereas the incidence rates are similar in Europe and the US, they are much lower in several Asian countries including Japan and Korea.[11] Endometrial cancer age adjusted incidence and mortality in 12 European countries have been described in detail by Bray and colleagues;[1] in Fig. 1 we provide the crude mortality rates from endometrial cancer in over 30 European countries. Faced with the growing incidence of endometrial cancer in Europe and in the US and around the world, scientists, doctors and public health professionals are becoming more concerned with identifying effective preventive measures for this condition. Endometrial cancer originates in the endometrial lining of the uterus and accounts for about 90% of uterine cancers; 90% of cases of endometrial cancer[13] are adenocarcinoma originating from the surface cells of the endometrium.

While the majority of early stage endometrial carcinomas produce symptoms such as bleeding, early detection is challenging in women who do not present with symptoms. One study from the early 1980s suggested that the prevalence and incidence rates of endometrial carcinoma were 6.96 per 1000 and 1.71 per 1000 women years, respectively, in asymptomatic women.[14]

Endometrial hyperplasia, an overgrowth or thickening of the uterine lining, can be the first warning sign of the pathological process eventually leading to endometrial carcinoma. Endometrial hyperplasia without atypia is likely to respond to hormonal treatment. Hyperplasia with atypia is considered to be a precancerous condition and is typically treated with total hysterectomy in postmenopausal women,[15] or with hormone therapy, especially in younger women who desire future pregnancy. Numerous hormonal treatments have been identified in the past three decades to treat endometrial hyperplasia. To our knowledge, no research studies have evaluated the efficacy of lifestyle and dietary changes in reversing the hyperplasia.

Although several review papers have been written in the area of endometrial cancer,[3,8,16–22] very few of the existing studies critically analysed the utility of modifying multiple risk factors for the prevention of this challenging disease. Additionally, very few updated reviews exist in the area of endometrial hyperplasia.[23,24]. In this manuscript, we will review the existing knowledge about modifiable risk factors leading to endometrial hyperplasia and endometrial cancer by synthesising research from Europe and other regions around the world. This article summarises the knowledge in the area of all major modifiable risk factors in the area of endometrial cancer progression and gives a detailed description of endometrial cancer biomarker studies.

2. Methods

2.1. *Search and selection of the literature*

A systematic literature search of publications on modifiable risk factors for endometrial cancer and endometrial hyperplasia has been performed using Pubmed search engine. Additionally, systemic literature search has been performed for publications in the area of serum and plasma biologic markers implicated in endothelial cell (EC) detection, progression and monitoring.

The following terms have been used in the database searches for studies on endometrial cancer risk factors: endometrial cancer, longitudinal, cross-sectional, retrospective, endometrial carcinoma, endometrial hyperplasia, survival, exercise, diet and risk factors. The criteria for inclusion of studies in the review were as follows: case control or cohort studies investigating the association between modifiable risk factors (physical activity, body mass index

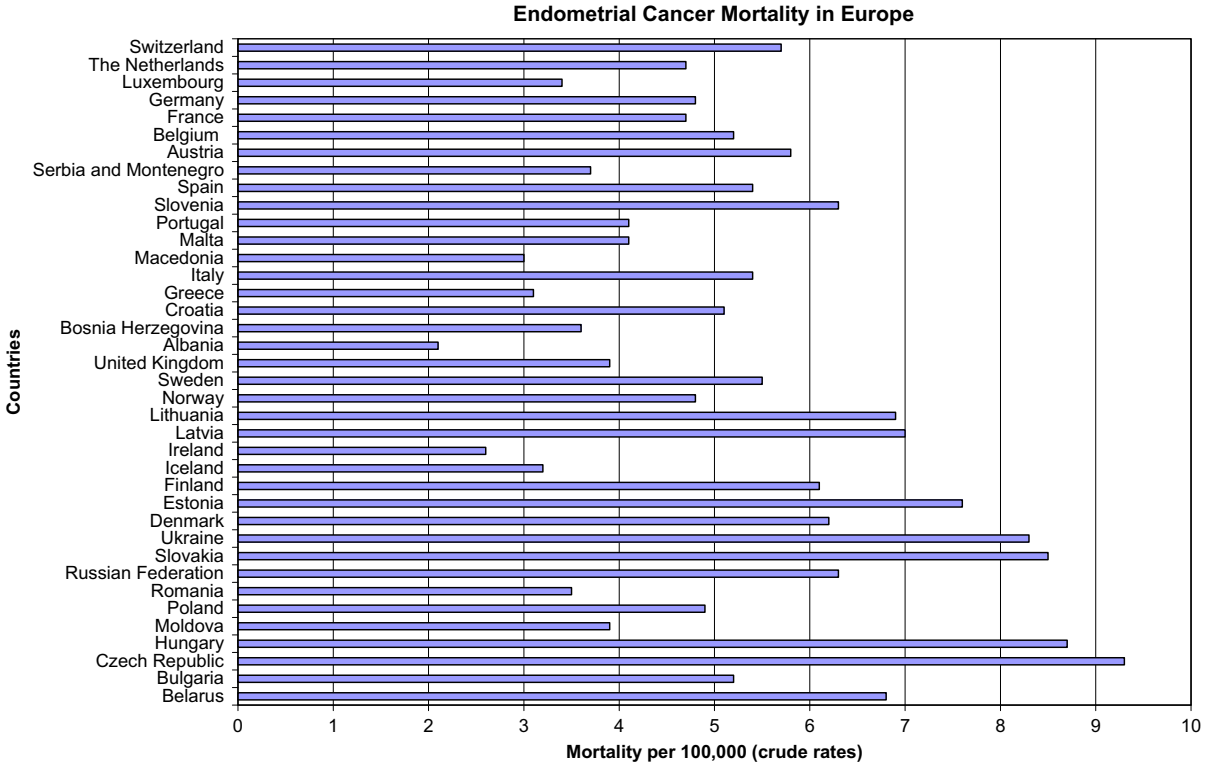

Fig. 1 – Endometrial cancer mortality in 25 European countries based on Globocan 2002 data.[12]

(BMI), use of exogenous hormones and nutrition) and endometrial cancer were published between 1978 and 2007, and were published in English or had an expanded abstract in English. Considering the fact that over 400 relevant articles have been identified in the area of modifiable risk factors, it has been decided to narrow this review to the evaluation of existing review studies in this field. Several excellent reviews exist in the area of modifiable risk factors associated with EC risk, providing in-depth overview of key modifiable risk factors for EC. Review studies were evaluated if they were published in the past 10 years and captured large percentage of existing studies for each modifiable risk factor this article is focusing on.

In the area of biologic markers, all papers dealing with serum and plasma markers involved in EC detection, development and progression published since 1989 have been evaluated. The following terms have been used in the database searches for studies on endometrial cancer biomarkers: endometrial cancer, biomarkers, serum, plasma, cancer antigen 125 (CA 125), carcinoembryonic antigen (CEA), CA 15-3, early detection, monitoring and disease progression. The bibliographic lists of relevant publications were hand searched to identify additional useful articles. Articles were excluded if they had <10 cancer cases included in the analysis and if they were not full length research publications.

2.2. *Data extraction and quality assessment*

The data were extracted and analysed by the authors of this review. Quality judgments have been supplied by two reviewers. In case of disagreement, third reviewer has been consulted before the final score is assigned. In cases where disagreement between judges exceeded three points, the score averages amongst all judges were reported. Study size, study type, study population methodology, and key findings were documented and reported in Tables 1, 3 and 4. A quality scoring system for this article was developed based on similar relevant scoring system utilised by Voskuil.[16] This quality assessment system captured both generic methodological issues, as well as issues specifically relating to the theme of endometrial cancer and biomarker research. The items in the scoring system were categorised according to the three important sources of error: selection bias, misclassification bias and confounding error. The quality scoring system contained 15 items: questions 1–5 evaluated issues relating to selection bias, questions 6–13 evaluated issues relating to misclassification bias and questions 14–15 evaluated issues relating to confounding bias. The maximum attainable score is 30 for studies had had control groups and 24 for studies did not have control groups. Final quality score is presented as a total number of points attained out of 30 or 24 possible points for each study (scoring sheet is attached in Appendix).

3. Results

Over 400 relevant articles in the area of EC modifiable risk factors have been identified through the Pubmed search. It has been decided to narrow down this result section to existing review articles. Thus, this systematic review includes six review papers on modifiable risk factors and 19 articles on EC biomarkers. The characteristics of these studies and factors evaluated are summarised in Tables 1, 3 and 4. There was a

Table 1 – Summary of review studies on EC modifiable risk factors

Risk factor	Author (reference)	Number of studies evaluated, countries	Number of cases	Study type	Contrast	Relative risk (RR) or Odds Ratio (OR) (95% confidence interval (CI))	Findings
Physical activity	Voskuil[16]	Ten cohort studies, 24 case control studies from 11 countries	15,236	Review of cohort and case case control studies	Most active versus least active	OR (OR) 0.73 (0.62–0.86)	Inverse association endometrial cancer/ high level of physical activity
Consumption of animal food	Bandera[22]	Three cohort studies and 16 case control studies from 11 countries	12,901	Meta analysis of cohort and case control studies	Intake frequency: high versus low intake	Meat OR 1.26 (1.03–1.54) Red meat OR 1.51 (1.19–1.93)	Increased risk of endometrial cancer with meat consumption
Consumption of fruits and vegetables	Bandera[21]	One cohort and 16 case control studies from 10 countries	10,158	Meta analysis of cohort and case control studies	Intake frequency: high versus low intake	Vegetables OR 0.71 (0.55–0.91) Cruciferous vegetables OR 0.85 (0.74–0.97) Fruits OR 0.97 (0.92–1.02)	Decreased risk of endometrial cancer with consumption of fruits and vegetables
Body mass index (BMI)	Renehan[58]	Nineteen cohort and case control studies from North America, Europe, Australia and Asia-Pacific	17,084	Meta analysis	Effects across BMI ranges	RR 1.59, $p < 0.0001$	Increased risk of endometrial cancer with every 5 kg/m^2 increase
Obesity endogenous hormones	Kaaks[8]	Over 200 articles reviewed	N/A	Review article	Several types of hormones; Excess weight versus normal weight	N/A	Supporting unopposed oestrogen hypothesis, increased risk with obesity
Exogenous and endogenous hormones	Akhmedhanov[59]	One hundred and fifty articles; three cohort studies on oestrone levels examined in detail	Three hundred and thirty-two cases (in 3 cohort studies)	Review article	High hormone level versus low hormone level	OR up to 3.8 (1.7–8.4) for high oestrone level	Increased risk of endometrial cancer with increased circulating levels of oestrogenic hormones

considerable variation amongst the studies in respect to study size, age of the participants, risk factor assessment tools and research methodology.

3.1. *Modifiable risk factors for EC: endometrial cancer and obesity*

Obesity and overweight have consistently been shown to be associated with an increased risk of endometrial cancer in the Europe, US and worldwide.[25–34] The risk of endometrial cancer increased with increasing BMI in the third decade of age (20–29 years), in the fifth decade (40–49 years) and in the seventh decade (60–69 years).[35] Both current adiposity and adult weight gain are associated with substantial increases in the risk of endometrial cancer.[36] Whilst some studies report that that risk increases with the incremental increases in weight or body mass, others find a strong elevation in risk only amongst obese women.[3]

3.2. *Modifiable risk factors for EC: endometrial cancer and diet*

Studies in the area of endometrial cancer and diet have not been entirely consistent. Foods that are high in fat and cholesterol, such as red meat, margarine and eggs, were positively associated with endometrial cancer in several case control studies,[34,37–39]; however, a large prospective cohort study suggested that energy dietary intake as well as most foods of animal origin are not or only weakly related to the risk of endometrial cancer amongst postmenopausal US women.[40]

Epidemiologic and experimental data suggest that the consumption of soybean-containing foods may protect against cardiovascular disease and decrease breast, prostate and endometrial cancer risk.[41] Soy and derivative diets deliver large doses of isoflavones to human and animals throughout their lifespan, including gestation. Isoflavonic phytooestrogens, or isoflavones, constitute a class of phytooestrogens that have properties similar to selective estrogen receptor modulators, and have attracted a substantial degree of attention in recent years, particularly as a possible alternative to the conventional hormone replacement therapy regimens used by postmenopausal women.[42] Phytooestrogens are strikingly similar in chemical structure to the mammalian oestrogen estradiol, and bind to the estrogen receptors (ER) with a preference for ER beta.[43] Obese postmenopausal women consuming relatively low amounts of phytooestrogens had higher risk of endometrial cancer in comparison to non-obese postmenopausal women consuming relatively high amounts of isoflavones.[44] Additional dietary factors that may decrease the risk of endometrial cancer include consumption of crude fibre, non-starch polysaccharide and dietary fibre, Vitamin A, possibly vitamin C. Preliminary data also suggest a link between endometrial cancer and vitamin D dietary consumption.[45]

Despite the fact that a reduction in endometrial cancer risk was also found with increased consumption of other sources of phytooestrogens such as whole grains, vegetables, fruits and seaweeds,[46] a recent review based solely on case control studies, with less than half being population-based, suggests only a modest inverse association with vegetable consumption, particularly for cruciferous vegetables.[21] Similarly, the analysis of a large prospective study did not support an association between vegetable or fruit consumption and endometrial cancer.[47]

Although limited evidence suggests that dietary phytochemicals are associated with decreased breast and endometrial cancer risk, the studies in this area are mainly observational, whilst much work needs to be done to explore basic mechanisms and the strategic exploitation of their interactions.[48]. In order to assess the effectiveness of isoflavones and other dietary factors on endometrial hyperplasia and endometrial cancer risk, large controlled trials will need to be implemented, as currently data in this area are very limited.

3.3. *Modifiable risk factors for EC: exercise and other lifestyle risk factors*

Many existing research studies, including several investigations from Europe, suggest a link between physical activity, inactivity and endometrial cancer risk.[30,34,49–53] It has been shown that women who spent 90 min/d or more performing non-occupational physical activities had a lower risk of endometrial cancer (relative risk (RR) = 0.54, 95% confidence interval (CI) = 0.34–0.85) compared with those who spent less than 30 min/d. High BMI and low physical activity are strong and independent risk factors for endometrial cancer.[49] A large cohort study in Norway suggested that inactivity and high energy intake are major risk factors for endometrial cancer independently from BMI, and that hypertension and relative hyperglycaemia are significant markers of risk, especially amongst the heaviest women.[54] A recent review indicated that 14 of the 18 studies on endometrial cancer and physical activity showed a definite or possible protective effect of physical activity on endometrial cancer, with an average relative risk reduction of around 30%.[20] However, recent results of the European prospective investigation into cancer and nutrition (EPIC) provided no evidence of a protective effect of physical activity on endometrial cancer in all women, and only limited support for a benefit amongst premenopausal women.[55] Further studies, preferably prospective cohort studies, are needed to determine the magnitude of risk reduction and to assess which aspects of physical activity contribute most strongly to the reduced risk, and in which period of life physical activity is most effective in changing endometrial cancer risk.[16]

3.4. *Link between unopposed oestrogens theory and modifiable risk factors*

The unopposed oestrogen hypothesis is the theoretical framework used to explain the relationship between endogenous steroid hormones and endometrial cancer risk.[56] This hypothesis proposes that that endometrial cancer may develop as a result of the mitogenic effects of oestrogens, when these are insufficiently counterbalanced by progesterone. In aetiological terms, any factor that increases exposure to unopposed oestrogens (such as oestrogen therapy, obesity and irregular menstrual cycles) tends to increase the risk of

the disease, whilst factors that decrease exposure to oestrogens or increase progesterone levels (such as oral contraceptives or smoking) tend to be protective.[57] Table 1 provides summary of the major existing review articles/meta analysis studies on modifiable risk factors for EC.

3.5. *Endometrial hyperplasia: risk factors and therapies*

Little information exists about the incidence and prevalence of endometrial hyperplasia with or without atypia. Studies suggested that unsuspected hyperplasia can be found in up to 10% of asymptomatic postmenopausal women,[60,61] whilst hyperplasia and other endometrial conditions seem to be very rare in premenopausal asymptomatic women.[62] In perimenopausal women with abnormal bleeding patterns other than amenorrhoea or oligomenorrhoea, there is a high incidence of endometrial hyperplasia and invasive endometrial cancer.[63] The majority of endometrial hyperplasia cases regress spontaneously.[64] Roughly 10% of the cystic or adenomatous hyperplasias, and more than 25% of atypical hyperplasias, progress to carcinoma after 1–20 years.[65] Additionally, 29.1% of patients with presumed atypical hyperplasia have a coexisting endometrial carcinoma discovered at the time of hysterectomy.[66]

Risk factors for endometrial hyperplasia are similar to those found to be associated with endometrial cancer. Obesity is a predominant risk factor for endometrial hyperplasia in younger women.[67] A recent study concluded that high education, obesity, diabetes and hormone replacement therapy use increase the risk of endometrial hyperplasia.[33]

3.5.1. *Hormonal therapies*

Current therapies for endometrial hyperplasia include various regimens of progesterone-based drugs (Table 2). Hysterectomy is a recommended treatment for endometrial hyperplasia with atypia and for endometrial cancer; however high dose hormonal therapy is sometimes recommended for women who want to retain fertility or who are poor surgical candidates. The standard therapy for endometrial hyperplasia with or without atypia currently does not include lifestyle interventions, other than recommending weight loss. Clearly, in order to better understand endometrial cancer prevention, it is important to understand the aetiology of endometrial hyperplasia and the common risk factors playing a role in endometrial hyperplasia and endometrial cancer development.

3.6. *Factors affecting endometrial cancer survival*

It has been observed that older endometrial cancer (age > 63 years) patients have a significantly decreased overall survival, cause-specific survival and greater risk of recurrence following postoperative radiation therapy independently from other prognostic factors and/or treatment techniques.[68] In a study by Kilgore et al. proper surgical staging with the removal of associated pelvic and para-aortic lymph nodes was associated with improved survival when compared to a retrospective cohort that did not have lymph node dissection.[69] Other conditions affecting endometrial cancer survival include stage at diagnosis and genetic factors. For the purpose of this paper, only modifiable risk factors affecting endometrial cancer will be discussed in detail.

Overweight and obesity are associated with elevated mortality from all causes in both men and women and the risk of death rises with increasing weight.[70] It has been suggested that obesity and diabetes may increase mortality after endometrial cancer diagnosis, and a modification of these characteristics may improve survival.[71] Another publication showed that BMI was not predictive of progression-free survival in the endometrial cancer population, although obese stage III and stage IV patients had decreased overall survival.[72] Because of the relationship between obesity and other confounding variables, it has been suggested that obesity alone is not an independent predictor of survival.[73]

Diabetes, although not always modifiable, is associated with poorer survival after incident endometrial cancer, independently of tumour stage and grade. It is possible that factors related to diabetes, such as hyperglycaemia or hyperinsulinaemia, contribute to the observed poorer endometrial cancer survival in diabetic women.[74]

Exercise has gained recognition as an effective supportive care intervention for endometrial cancer survivors, yet participation rates are low.[75] Despite the evidence of the benefits of exercise in cancer survivors, participation rates tend to decline after treatment for endometrial cancer patients.[76]

Table 2 – Overview of conventional therapies for endometrial hyperplasia and endometrial cancer

Condition	Commonly recommended therapies
Endometrial hyperplasia	Progesterone, medroxyprogesterone acetate, megestrol acetate, levonorgestrel, progestin-containing intrauterine device (IUD)
Endometrial hyperplasia with atypia	Hysterectomy High-dose continuous progestin therapy daily (medroxyprogesterone acetate, megestrol acetate) and repeat biopsies for women who want to retain fertility
Endometrial cancer	Total abdominal hysterectomy, bilateral salpingo-oophorectomy and evaluation for metastatic disease Radiation therapy (for patients whose cancers have progressed beyond stage IB (International Baccalaureate) grade 2)

Table 3 – Serum and plasma biomarkers investigated in endometrial cancer detection and development

Reference	Study type and size	Biomarker name	Biomarker function	Findings	Final Score Out of 30
Gunter[89]	250 endothelial cell (EC) 465 control	Insulin, total insulin-like growth factor-1 (IGF-1), free IGF-1, insulin-like growth factor (IGF) binding protein 3, glucose, oestradiol	*IGFs*-proteases *oestradiol*-sex hormone *Glucose*-source of energy for the living cells	Insulin levels positively associated with EC; Free IGF-1 inversely associated with EC	24
Troisi[90]	165 EC 180 community controls	C-Peptide Sex hormones	*C-peptide*-marker of insulin function	Data not consistent with the hypothesis that the effect of obesity on endometrial cancer risk is mediated through high insulin levels	21
Yurkovetsky[91]	115 EC and 135 healthy controls	Prolactin, Growth hormone (GH), eotaxin, E-selectin, Thyroid stimulating hormone (TSH)	*Prolactin*-stimulation of mammary gland *GH*-growth and cell reproduction Eotaxin-immune response *E-selectin*-cell adhesion molecule implicated in immune function *TSH*-regulation of endocrine function	Five biomarker panel was able to discriminate EC from controls with high sensitivity and specificity (standard error (SE) 98.3 serum prolactin (SP 98) for prolactin alone)	20
Cust[92]	284 cases/548 controls	Adiponectin	Protein hormone that plays a role in modulation of metabolic processes	Adiponectin levels were inversely associated with EC risk	23
Cust[93]	286 EC patients/555 healthy controls	Insulin-like growth factor binding protein 1 (*IGFBP-1*), Insulin-like growth factor binding protein 1 (IGFBP-2), C-peptide	*Insulin-like growth factor binding protein* 1 (IGFBP-1) modifiers of cell proliferation *C-peptide*-marker of insulin function	Modest support to the hypothesis that hyperinsulinaemia is a risk factor for EC	24.5
Soliman[94]	117 EC patients/238 healthy controls	Adiponectin	Protein hormone that plays a role in modulation of metabolic processes	Adiponectin level was independently and inversely associated with EC.	23
Dotters[95]	43 EC patients Prospective study	Cancer antigen 125 (CA 125)	Cancer antigen associated with endometrial and ovarian cancer development	CA 125 levels of >35 U/ml strongly predicted extrauterine disease, but lacked sensitivity in identifying patients needing staging	20.5
Beck[96]	192 EC patients, 34 controls (10 healthy, 5 with bleeding, 19 with endometriosis)	OVX1	Mucin marker	No correlation between OVX1 and stage	18.5
Kurihara[97]	110 EC patients/36 healthy postmenopausal women/111 HRT controls	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	A novel cutoff level of 20 U/ml of CA125 could detect myometrial invasion to more than one-half of the myometrium with sensitivity of	23

Table 3 (continued)

Reference	Study type and size	Biomarker name	Biomarker function	Findings	Final Score Out of 30
				69.0%, specificity of 74.1%, positive predictive value of 58.8%	
Lo[80]	100 healthy controls, 47 patients with benign gynaecological diseases and 97 EC patients. Survival analysis	CA 125 CA 15.3 CA 19.9	Cancer antigens implicated in EC development	Elevated CA 125, CA 15.3 and CA 19.9 were significantly associated with shorter survival	23
Xu[98]	45 EC cancer patients /184 healthy controls	OVX1	Mucin marker	Elevation of serum OVX1 was more frequent in patients with deep myometrial invasion and with poorly differentiated tumors	21

3.6.1. Biomarkers: implications for the early detection of early changes in the endometrium and prolonging survival in cancer patients

At this time, there are no early detection tests that can identify endometrial cancer early in women without common symptoms such as bleeding. The Pap test, which is very effective for the early detection of cervical cancers, can be useful in identifying some early endometrial cancers, but it is not the test of choice for this disease. Continuing challenges of endometrial cancer treatment include the need to improve screening and prevention efforts. The 5-year survival for early stage localised endometrial cancer is 75–95%; however prognosis is poor for endometrial cancers found at stages III–IV. The 5-year survival rate falls to 66% if cancer has spread regionally at the time of diagnosis. For women with disease that has spread beyond pelvis (stage IV) survival is less than 20%.[77]

Several biomarkers have shown association with endometrial cancer development and progression.

Biomarkers such as p53, hypoxia-inducible factor 1α (HIF-1α, HIF-2α), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2/neu) correlate with the development or progression of endometrial cancer.[78] VEGF has been implicated in the development of both endometrial cancer and endometrial hyperplasia.[79] Elevated levels of several cancer antigens including CA 125, CA 15-3 and CA 19-9 are significantly associated with shorter survival time in endometrial cancer patients.[80] CA 125 correlates with tumour size and stage of endometrial cancer[81–83], and is also a significant independent predictor of the extrauterine spread of disease.[84]

Various pathologies of female reproductive organs, including endometrial hyperplasia, have been linked to altered expression of VEGFs and/or fibroblast growth factors (FGFs).[85] Tumour necrosis factor alpha (TNF-alpha) is produced by the endometrium, and it has been shown to have cyclic variations through the menstrual cycle. Hyperplastic endometrial cells produce higher amounts of TNF-alpha in comparison to controls.[86]

At present, no serum biomarkers are available for screening for endometrial carcinoma or for monitoring recurrence in endometrial carcinoma survivors. Patients with recurrent disease are detected only as a consequence of symptoms or abnormalities in imaging assessments.[87]

Preliminary studies suggested that several biomarkers, including prolactin, eotaxin, growth hormone (GH), E-selectin and thyroid stimulating hormone (TSH), may play an important role in the early detection of endometrial cancer.[88] Similar markers can potentially be used for the monitoring of success of various types of therapies treating endometrial cancer and endometrial hyperplasia. Tables 3 and 4 provide a detailed summary of the existing studies in the area of serum and plasma biomarkers associated with EC detection, development and progression (Table 3 overviews studies that had a control group, whereas Table 4 overviews studies without control groups). Serum and plasma biomarker studies are especially promising, as they are exploring non-invasive ways to detect and diagnose EC early and monitor response to treatment.

3.6.2. Biomarkers of weight loss: potential implications for endometrial cancer research

Several biologic markers were investigated in relation to diet, exercise and weight loss. Markers of chronic subclinical inflammation such as high-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) are closely related to insulin resistance and obesity. Recent evidence suggests that adiponectin, a protein whose circulating levels are decreased in obesity, has anti-inflammatory properties, and also appears to enhance potently insulin action and therefore appears to function as a signal produced by adipose tissue that influences whole-body glucose metabolism.[105] It has been suggested that weight loss can improve systemic inflammation associated with obesity by decreasing the adipose production of pro-inflammatory cytokines; however the effect of weight loss on biomarkers has been a very controversial topic. A recent study suggested that decrease in cytokines associated

Table 4 – Serum and plasma biomarkers investigated in endometrial cancer development and progression

References	Study type and size	Biomarker name	Biomarker function	Findings	Final Score Out of 24
Schmid [99]	403 EC patients Survival analysis	C-reactive protein (CRP)	Acute phase protein associated with Inflammation	Elevated serum CRP levels are associated with a less favourable EC prognosis	17.5
Heyer [100]	336 EC patients, Retrospective review	Carcinoembryonic antigen (CEA)	Carcinoembryonic antigen – glycoprotein involved in cell adhesion.	Differential expression in women with and without metastases	14.5
Powell [83]	141 EC patients Retrospective review	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	High CA 125 levels and positive lymph vascular space invasion strongly correlated with advanced stage	16
Hsieh [82]	124 EC patients Review of hospital records	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	CA 125 level greater than 40 U/ml is suggested as a criterion for full pelvic lymphadenectomy in the surgical staging of endometrial cancer.	14
Sood [101]	210 EC patients Retrospective followup	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	Elevated CA 125 level was the most important predictor for poor survival and extrauterine disease	16
Scambia [102]	148 EC patients Longitudinal followup	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	CA 125 and CA 15-3 may be used as predictors of extrauterine spread and in monitoring of chemotherapy response in EC patients.	16.5
Takeshima [103]	225 EC/32 recurrent EC Evaluation of tumour markers before surgery	CA 125	Cancer antigen associated with endometrial and ovarian cancer development	The use of CA19-9 in combination with CA 125 is useful in the detection of recurrence	15.5
Panici [104]	47 EC patients and 20 hyperplasia patients. Longitudinal followup	CEA, CA 125, CA 15-3	CEA glycoprotein involved in cell adhesion CA 125 and CA 15-3 cancer antigens involved in EC development	CA 125 and CA 15-3 levels reflected the clinical course of the disease during chemotherapy; they could be useful for monitoring response to treatment	16

with weight loss could be due to energy restriction rather than to adipose mass loss, since inflammatory levels return to baseline soon after weight stabilization.[106]

In women who underwent weight loss by surgical intervention, marked reduction in C-reactive protein has been observed.[107] A multidisciplinary programme aimed to reduce body weight in obese women through lifestyle changes (Mediterranean diet and exercise) was associated with a reduction in markers of vascular inflammation and insulin resistance (IL-6, IL-18 and C-reactive protein (CRP)).[108]

Evaluation of the levels of adipose tissue related hormones, cytokines and antioxidative substances including insulin, leptin, resistin, IL-6, insulin-like growth factor 1 (IGF-1), TNF-alpha, adiponectin, CRP, glutathione peroxidase and isoprostane could be very useful in the monitoring of weight loss in endometrial hyperplasia and endometrial cancer patients.

4. Conclusions and future directions

The continuing increases in obesity and decreases in fertility forewarn that endometrial cancer, as a postmenopausal disease, will become a more important public health problem in future years.[109] Biomarkers are promising tools for the early detection and disease monitoring of endometrial cancer. Future studies in this area should concentrate on examining the longitudinal changes in serum concentrations of these biomarkers and investigating their associations with treatment response, relapse, complications and survival.[88] Increasing our understanding of the role of biomarkers in the aetiology and the course of endometrial cancer and combining the biomarker data with known risk factors have a great potential to facilitate the development of new early detection and treatment modalities for this challenging disease.

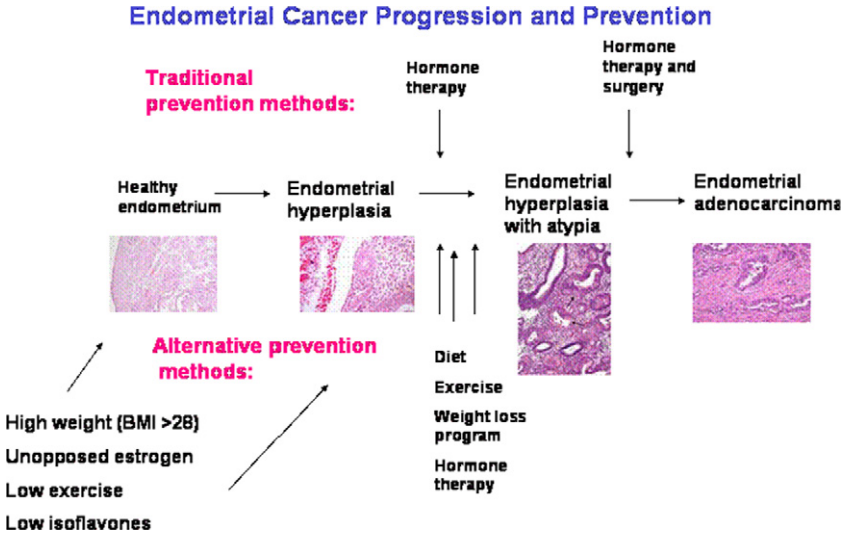

Fig. 2 – Endometrial cancer progression and prevention.

More studies are needed to investigate modifiable risk factors for endometrial cancer and endometrial hyperplasia. Existing therapies for endometrial hyperplasia target hormone imbalance, which is just one of the many risk factors for endometrial cancer development (Fig. 2). Next generation therapies should include other interventions, including diet, exercise and weight loss plans, which would target other modifiable aspects of endometrial cancer risk. Lifestyle interventions would be especially beneficial for younger women who desire to retain fertility.

Conflict of interest

None declared.

Acknowledgements

Research is supported by University of Pittsburgh Cancer Institute and ECNIS, European Network of Excellence in Nutrition and Cancer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2008.05.001.

REFERENCES

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. *Int J Cancer* 2005;**117**(1):123–31.
2. Mishell Jr MS, Stenchever M, Droegemueller W, Herbst AL. *Comprehensive gynecology*. 3rd ed. St. Louis: Mosby; 1997.
3. Cook L WN. *Endometrial cancer*. Academic Press; 2000.
4. Parkin DM, Whelan S, Ferlay J, Teppo L, Thomas DB. *Cancer incidence in five continents*. Lyon: IARC Press; 2002.
5. Sonoda Y, Barakat RR. Screening and the prevention of gynecologic cancer: endometrial cancer. *Best Pract Res Clin Obstet Gynaecol* 2006;**20**(2):363–77.
6. Somoye G, Olaitan A, Mocroft A, Jacobs I. Age related trends in the incidence of endometrial cancer in South East England 1962–1997. *J Obstet Gynaecol* 2005;**25**(1):35–8.
7. Kitchener H. Management of endometrial cancer. *Eur J Surg Oncol* 2006;**32**(8):838–43.
8. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 2002;**11**(12):1531–43.
9. NCI. *Endometrial cancer*; 2007.
10. Karim-Kos HE, de Vries E, Soerjomataram I, et al. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008.
11. Curado MP, Edwards B, Shin HR, et al., editors. *Cancer incidence in five continents*. Lyon, France; 2007.
12. IARC. GLOBOCAN. In: *Cancer mondiale*; 2007.
13. Oncology Channel. *Endometrial cancer. overview, types, incidence, and prevalence*.
14. Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser M. Detection of endometrial carcinoma and hyperplasia in asymptomatic women. *Obstet Gynecol* 1984;**64**(1):1–11.
15. Horn LC, Schnurrbusch U, Bilek K, Hentschel B, Einenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment. *Int J Gynecol Cancer* 2004;**14**(2):348–53.
16. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(4):639–48.
17. Pagel J, Bock JE. Endometrial cancer. A review. *Dan Med Bull* 1984;**31**(4):333–45.
18. Leo L, Tessarolo M, Febo G, et al. Tamoxifen and endometrial cancer: new data for an old problem. Review. *Eur J Gynaecol Oncol* 1997;**18**(5):429–33.
19. Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. *Int J Gynecol Cancer* 2007;**17**(5):964–78.
20. Cust AE, Armstrong BK, Friedenreich CM, Slimani N, Bauman A. Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods. *Cancer Causes Control* 2007;**18**(3):243–58.

21. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: a systematic literature review and meta-analysis. *Nutr Cancer* 2007;**58**(1):6–21.
22. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. *Cancer Causes Control* 2007;**18**(9):967–88.
23. Montgomery BE, Daum GS, Dunton CJ. Endometrial hyperplasia: a review. *Obstet Gynecol Surv* 2004;**59**(5):368–78.
24. Brun JL, Descat E, Boubli B, Dallay D. Endometrial hyperplasia: a review. *J Gynecol Obstet Biol Reprod (Paris)* 2006;**35**(6):542–50.
25. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. *Cancer Causes Control* 2007;**18**(4):399–413.
26. Austin H, Austin Jr JM, Partridge EE, Hatch KD, Shingleton HM. Endometrial cancer, obesity, and body fat distribution. *Cancer Res* 1991;**51**(2):568–72.
27. Olson SH, Trevisan M, Marshall JR, et al. Body mass index, weight gain, and risk of endometrial cancer. *Nutr Cancer* 1995;**23**(2):141–9.
28. Baanders-van Halewyn EA, Blankenstein MA, Thijssen JH, de Ridder CM, de Waard F. A comparative study of risk factors for hyperplasia and cancer of the endometrium. *Eur J Cancer Prev* 1996;**5**(2):105–12.
29. Hirose K, Tajima K, Hamajima N, et al. Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res* 1996;**87**(9):1001–9.
30. Kalandidi A, Tzonou A, Lipworth L, et al. A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. *Oncology* 1996;**53**(5):354–9.
31. Kelsey JL, LiVolsi VA, Holford TR, et al. A case-control study of cancer of the endometrium. *Am J Epidemiol* 1982;**116**(2):333–42.
32. La Vecchia C, Parazzini F, Negri E, et al. Anthropometric indicators of endometrial cancer risk. *Eur J Cancer* 1991;**27**(4):487–90.
33. Ricci E, Moroni S, Parazzini F, et al. Risk factors for endometrial hyperplasia: results from a case-control study. *Int J Gynecol Cancer* 2002;**12**(3):257–60.
34. Goodman MT, Hankin JH, Wilkens LR, et al. Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res* 1997;**57**(22):5077–85.
35. Levi F, La Vecchia C, Negri E, Parazzini F, Franceschi S. Body mass at different ages and subsequent endometrial cancer risk. *Int J Cancer* 1992;**50**(4):567–71.
36. Chang SC, Lacey Jr JV, Brinton LA, et al. Lifetime weight history and endometrial cancer risk by type of menopausal hormone use in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(4):723–30.
37. Shu XO, Zheng W, Potischman N, et al. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. *Am J Epidemiol* 1993;**137**(2):155–65.
38. Potischman N, Swanson CA, Brinton LA, et al. Dietary associations in a case-control study of endometrial cancer. *Cancer Causes Control* 1993;**4**(3):239–50.
39. Dalvi TB, Canchola AJ, Horn-Ross PL. Dietary patterns, Mediterranean diet, and endometrial cancer risk. *Cancer Causes Control* 2007;**18**(9):957–66.
40. Zheng W, Kushi LH, Potter JD, et al. Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa women's health study. *Am J Epidemiol* 1995;**142**(4):388–94.
41. Cardoso JR, Bao SN. Effects of chronic exposure to soy meal containing diet or soy derived isoflavones supplement on semen production and reproductive system of male rabbits. *Anim Reprod Sci* 2007;**97**(3-4):237–45.
42. Phipps WR, Duncan AM, Kurzer MS. Isoflavones and postmenopausal women: a critical review. *Treat Endocrinol* 2002;**1**(5):293–311.
43. Cassidy A. Potential risks and benefits of phytoestrogen-rich diets. *Int J Vitam Nutr Res* 2003;**73**(2):120–6.
44. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst* 2003;**95**(15):1158–64.
45. Salazar-Martinez E, Padilla L, Sanchez-Zamorano LM, et al. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. *Int J Gynaecol Cancer* 2005;**15**(5):938–45.
46. Goodman MT, Wilkens LR, Hankin JH, et al. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol* 1997;**146**(4):294–306.
47. McCullough ML, Bandera EV, Patel R, et al. A prospective study of fruits, vegetables, and risk of endometrial cancer. *Am J Epidemiol* 2007;**166**(8):902–11.
48. Cline JM, Hughes Jr CL. Phytochemicals for the prevention of breast and endometrial cancer. *Cancer Treat Res* 1998;**94**:107–34.
49. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. *J Natl Cancer Inst* 2004;**96**(21):1635–8.
50. Levi F, La Vecchia C, Negri E, Franceschi S. Selected physical activities and the risk of endometrial cancer. *Br J Cancer* 1993;**67**(4):846–51.
51. Sturgeon SR, Brinton LA, Berman ML, et al. Past and present physical activity and endometrial cancer risk. *Br J Cancer* 1993;**68**(3):584–9.
52. Moradi T, Weiderpass E, Signorello LB, et al. Physical activity and postmenopausal endometrial cancer risk (Sweden). *Cancer Causes Control* 2000;**11**(9):829–37.
53. Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA. Physical activity and risk of endometrial cancer. *Epidemiology* 1993;**4**(4):342–9.
54. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. *Int J Cancer* 2003;**104**(6):669–76.
55. Friedenreich C, Cust A, Lahmann PH, et al. Physical activity and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. *Int J Cancer* 2007;**121**(2):347–55.
56. Siiteri PK. Steroid hormones and endometrial cancer. *Cancer Res* 1978;**38**(11 Pt 2):4360–6.
57. Parazzini F, La Vecchia C, Bocciolone L, Franceschi S. The epidemiology of endometrial cancer. *Gynecol Oncol* 1991;**41**(1):1–16.
58. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371**(9612):569–78.
59. Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. *Ann NY Acad Sci* 2001;**943**:296–315.
60. Toppozada MK, Ismail AA, Hamed RS, Ahmed KS, el-Faras A. Progesterone challenge test and estrogen assays in menopausal women with endometrial adenomatous hyperplasia. *Int J Gynaecol Obstet* 1988;**26**(1):115–9.

61. Macia M, Novo A, Ces J, et al. Progesterone challenge test for the assessment of endometrial pathology in asymptomatic menopausal women. *Int J Gynaecol Obstet* 1993;**40**(2):145–9.
62. Kapali M, Agaram NP, Dabbs D, et al. Routine endometrial sampling of asymptomatic premenopausal women shedding normal endometrial cells in Papanicolaou tests is not cost effective. *Cancer* 2007;**111**(1):26–33.
63. Seltzer VL, Benjamin F, Deutsch S. Perimenopausal bleeding patterns and pathologic findings. *J Am Med Womens Assoc* 1990;**45**(4):132–4.
64. Hammond R, Johnson J. Endometrial hyperplasia. *Current Obstetrics &Gynaecology* **14**(2):99–103.
65. Zaino RJ. Endometrial hyperplasia: is it time for a quantum leap to a new classification? *Int J Gynecol Pathol* 2000;**19**(4):314–21.
66. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 2006;**106**(4):729–31.
67. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. *Fertil Steril* 2003;**80**(6): 1315–24.
68. Jolly S, Vargas CE, Kumar T, et al. The impact of age on long-term outcome in patients with endometrial cancer treated with postoperative radiation. *Gynecol Oncol* 2006;**103**(1): 87–93.
69. Kilgore LC, Partridge E, Alvarez RD, Austin JM, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol* 1995;**56**(1):29–33.
70. Hu FB. Overweight and obesity in women: health risks and consequences. *J Womens Health (Larchmt)* 2003;**12**(2):163–72.
71. Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. *Int J Gynecol Cancer* 2007;**17**(2):441–6.
72. Modesitt SC, Tian C, Kryscio R, et al. Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: a Gynecologic Oncology Group study. *Gynecol Oncol* 2007;**105**(1):59–65.
73. Temkin SM, Pezzullo JC, Hellmann M, Lee YC, Abulafia O. Is body mass index an independent risk factor of survival among patients with endometrial cancer? *Am J Clin Oncol* 2007;**30**(1):8–14.
74. Folsom AR, Anderson KE, Sweeney C, Jacobs Jr DR. Diabetes as a risk factor for death following endometrial cancer. *Gynecol Oncol* 2004;**94**(3):740–5.
75. Karvinen KH, Courneya KS, Campbell KL, et al. Exercise preferences of endometrial cancer survivors: a population-based study. *Cancer Nurs* 2006;**29**(4):259–65.
76. Karvinen KH, Courneya KS, Campbell KL, et al. Correlates of exercise motivation and behavior in a population-based sample of endometrial cancer survivors: an application of the Theory of Planned Behavior. *Int J Behav Nutr Phys Act* 2007;**4**:21.
77. ACS. *Endometrial cancer statistics*; 2007.
78. Schimp VL, Ali-Fehmi R, Solomon LA, et al. The racial disparity in outcomes in endometrial cancer: could this be explained on a molecular level? *Gynecol Oncol* 2006;**102**:440–6.
79. Erdem O, Erdem M, Erdem A, Memis L, Akyol G. Expression of vascular endothelial growth factor and assessment of microvascular density with CD 34 and endoglin in proliferative endometrium, endometrial hyperplasia, and endometrial carcinoma. *Int J Gynecol Cancer* 2007.
80. Lo SS, Cheng DK, Ng TY, Wong LC, Ngan HY. Prognostic significance of tumour markers in endometrial cancer. *Tumour Biol* 1997;**18**(4):241–9.
81. Gadducci A, Cosio S, Carpi A, Nicolini A, Genazzani AR. Serum tumor markers in the management of ovarian, endometrial and cervical cancer. *Biomed Pharmacother* 2004;**58**(1):24–38.
82. Hsieh CH, ChangChien CC, Lin H, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? *Gynecol Oncol* 2002;**86**(1):28–33.
83. Powell JL, Hill KA, Shiro BC, Diehl SJ, Gajewski WH. Preoperative serum CA-125 levels in treating endometrial cancer. *J Reprod Med* 2005;**50**(8):585–90.
84. Patsner B, Mann WJ, Cohen H, Loesch M. Predictive value of preoperative serum CA 125 levels in clinically localized and advanced endometrial carcinoma. *Am J Obstet Gynecol* 1988;**158**(2):399–402.
85. Reynolds LP, Grazul-Bilska AT, Redmer DA. Angiogenesis in the female reproductive organs: pathological implications. *Int J Exp Pathol* 2002;**83**(4):151–63.
86. Zupi E, Sbracia M, Marconi D, et al. TNFalpha expression in hyperplastic endometrium. *Am J Reprod Immunol* 2000;**44**(3):153–9.
87. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. *Gynecol Oncol* 1984;**17**(1):85–103.
88. Yurkovetsky Z, Ta'asan S, Skates S, et al. Development of multimarker panel for early detection of endometrial cancer. High diagnostic power of prolactin. *Gynecol Oncol* 2007.
89. Gunter MJ, Hoover DR, Yu H, et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2008;**17**(4):921–9.
90. Troisi R, Potischman N, Hoover RN, Siiteri P, Brinton LA. Insulin and endometrial cancer. *Am J Epidemiol* 1997;**146**(6):476–82.
91. Yurkovetsky Z, Ta'asan S, Skates S, et al. Development of multimarker panel for early detection of endometrial cancer. High diagnostic power of prolactin. *Gynecol Oncol* 2007;**107**(1):58–65.
92. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab* 2007;**92**(1):255–63.
93. Cust AE, Allen NE, Rinaldi S, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European prospective investigation into cancer and nutrition. *Int J Cancer* 2007;**120**(12):2656–64.
94. Soliman PT, Wu D, Tortolero-Luna G, et al. Association between adiponectin, insulin resistance, and endometrial cancer. *Cancer* 2006;**106**(11):2376–81.
95. Dotters DJ. Preoperative CA 125 in endometrial cancer: is it useful? *Am J Obstet Gynecol* 2000;**182**(6):1328–34.
96. Beck EP, Wagner M, Anselmino L, et al. Is OVX1 a suitable marker for endometrial cancer? *Gynecol Oncol* 1997;**65**(2):291–6.
97. Kurihara T, Mizunuma H, Obara M, et al. Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative evaluation and postoperative surveillance of endometrial carcinoma. *Gynecol Oncol* 1998;**69**(3):192–6.
98. Xu FJ, Yu YH, Daly L, et al. OVX1 as a marker for early stage endometrial carcinoma. *Cancer* 1994;**73**(7):1855–2858.
99. Schmid M, Schneitter A, Hinterberger S, et al. Association of elevated C-reactive protein levels with an impaired prognosis in patients with surgically treated endometrial cancer. *Obstet Gynecol* 2007;**110**(6):1231–6.
100. Heyer H, Grunwald S, Kohler G, Ohlinger R. Significance of laboratory studies for ruling out metastases in primary endometrial carcinoma. *Anticancer Res* 2007;**27**(3B):1673–7.

101. Sood AK, Buller RE, Burger RA, et al. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. *Obstet Gynecol* 1997;**90**(3):441–7.
102. Scambia G, Gadducci A, Panici PB, et al. Combined use of CA 125 and CA 15-3 in patients with endometrial carcinoma. *Gynecol Oncol* 1994;**54**(3):292–7.
103. Takeshima N, Shimizu Y, Umezawa S, et al. Combined assay of serum levels of CA125 and CA19-9 in endometrial carcinoma. *Gynecol Oncol* 1994;**54**(3):321–6.
104. Panici PB, Scambia G, Baiocchi G, et al. Multiple serum markers in patients with endometrial cancer. *Gynecol Obstet Invest* 1989;**27**(4):208–12.
105. Kopp HP, Krzyzanowska K, Mohlig M, et al. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. *Int J Obes (Lond)* 2005;**29**(7):766–71.
106. Salas-Salvado J, Bullo M, Garcia-Lorda P, et al. Subcutaneous adipose tissue cytokine production is not responsible for the restoration of systemic inflammation markers during weight loss. *Int J Obes (Lond)* 2006;**30**(12):1714–20.
107. Laimer M, Ebenbichler CF, Kaser S, et al. Markers of chronic inflammation and obesity: a prospective study on the reversibility of this association in middle-aged women undergoing weight loss by surgical intervention. *Int J Obes Relat Metab Disord* 2002;**26**(5):659–62.
108. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;**289**(14):1799–804.
109. Bray F, Dos Santos Silva I, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. *Cancer Epidemiol Biomarkers Prev* 2005;**14**(5):1132–42.