Epidemiology, Risk Factors, and Prevention for Endometrial Cancer

5

Johanna Mäenpää

5.1 Epidemiology

Globally, endometrial cancer is the sixth most common cancer in women [1]. The incidence of endometrial cancer is highest in North America and Western Europe. In 2015, the number of new cancers diagnosed in the U.S. was almost 55,000 [2], while in 2012, Europe showed close to 100,000 new cases [3]. Endometrial cancer has, in general, a favorable prognosis. For example, in the U.S, its incidence (25.1/100,000) far exceeds the mortality rate (4.4/100,000) [2]. Endometrial cancer mortality rates throughout 12 European countries are also generally low (shown in Table 5.1). Endometrial cancer is a disease linked to a high standard of living and, thus, the majority of cases are diagnosed in developed countries. Endometrial cancer is predominantly a disease of postmenopausal women, with a median age of 63 years at presentation and less than 10% occurring in women younger than 50 years of age [4].

Asides for geographical differences in the incidence of endometrial cancer, racial differences have also been found. As an example of a country with multiethnic population, the incidence rates of endometrial cancer in England have been documented according to the ethnic background (shown in Table 5.2) [5]. Women with black ethnicity appear to have the highest incidence, while South Asian women tend to have the lowest incidence. Interestingly in the U.S., the incidence of endometrial cancer is lower amongst African Americans compared to the white population [6].

J. Mäenpää (✉)
Faculty of Medicine, Tampere University, Tampere, Finland

Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland
e-mail: johanna.maenpaa@tuni.fi

M. R. Mirza (ed.), *Management of Endometrial Cancer*,
https://doi.org/10.1007/978-3-319-64513-1_5

Table 5.1 Endometrial cancer mortality rates in 12 European countries in 2000–2004 [1]

Country	Mortality/100,000
Ireland	1.7
United Kingdom	2.0
Italy	2.2
Netherlands	2.2
Spain	2.5
France	2.6
Denmark	2.6
Belgium	2.6
Germany	2.7
Finland	3.0
Austria	3.1
Sweden	3.6

Table 5.2 Age Standardized Incidence Rates of Endometrial Cancer in different ethnic groups in England, 2001–2007, using the incidence in whites as reference [5]

Ethnic group	Incidence/100,00 person-years	Incidence Rate Ratio 99% (FCI/CI)
White	5.3	1.00 (0.98–1.02)
South Asian	4.5	0.90 (0.80–1.01)
Black	6.3	1.16 (1.03–1.31)
Chinese	6.3	1.21 (0.94–1.54)

Eighty percent of women with endometrial cancer have a disease confined to uterine corpus at presentation. For localized disease, the 5-year survival rate exceeds 90%. However, the survival rate is much lower for women having either regional (68%) or especially distant spread (17%), respectively [2].

Most endometrial cancers are sporadic, with Lynch syndrome being the most important familial form. The underlying genetic defect in Lynch syndrome involves mutations in MMR genes. Female members of Lynch syndrome families are at as great risk for endometrial cancer as for colorectal cancer, or 30–70% vs. 25–70%, respectively [7]. Women from Lynch syndrome families get the disease younger (median age 46–62 years) than women in general [8].

Endometrial carcinoma is usually divided into two types: Type I (endometrioid) cancer which is the most prevalent (80–90%), estrogen-dependent, slowly growing, metastasizes late, and has in general, a good prognosis and Type II cancer, estrogen-independent, faster growing, metastasizes early, and has markedly poorer prognosis than Type I [9]. Women with Type II cancer are typically older than women with Type I cancer [4, 10]. Serous and clear-cell carcinomas belong to Type II cancers, as well as approximately 25% of the high grade endometrioid carcinomas [11, 12]. The proportion of Type II cancer is higher in women with Lynch syndrome than in women in general, but also among them, Type I is the prevalent type [13]. The properties of Type I and Type II cancers are summarized in Table 5.3.

Table 5.3 Properties of Type I and Type II endometrial cancer

	Type I	Type II
Median age at presentation	63	67 [10]
5-year survival rate	85%	58%
Histology	Endometrioid Grade 1, 2, 3 (75%)	Papillary serous Clear-cell Carcinosarcoma Undifferentiated carcinoma Endometrioid G3 (25%)
Estrogen-dependent	Yes	No
Genetic alterations	PTEN, KRAS, CTNNB1, PIK3CA, MSI and MLH1 [14]	TP53 (mainly serous)
Known risk factors	Metabolic syndrome, obesity, Type II DM, unopposed estrogen	No known risk factors
Sensitivity of vaginal ultrasound in detection	Good [15]	Fair [10]

5.2 Risk Factors

The risk factors of Type I endometrial cancer are listed in Table 5.4. As all risk factors are linked to Type I carcinoma, there are no known risk factors for Type II cancer. Most of the risk factors are either directly or indirectly linked to unopposed estrogen.

Metabolic syndrome is a disorder being increasingly diagnosed in U.S. and EU and characterized by (abdominal) obesity, hyperandrogenism, hyperinsulinemia, and hypertension. Of the components of metabolic syndrome, obesity is the most important as related to endometrial cancer, with a risk ratio (RR) of 2.21 [16]. Also hypertension and hypertriglyceridemia contribute to the risk, although, to a lesser extent. Insulin resistance is prone to the onset of Type II diabetes mellitus (T2DM), which in turn is one of the classical risk factors of endometrial cancer, with an OR of 2.1 [17]. However, a recent epidemiological study implies that the role of T2DM is more indirect, associated rather to the accompanying obesity than to DM per se [20].

Infertility has long been linked to endometrial cancer. Of the causes leading to infertility, polycystic ovary syndrome (PCOS) is the most important one in this respect, with an OR of 2.8 [18]. PCOS is a disorder characterized by unusually thick-walled small follicular cysts situated in a pearl-like pattern (Fig. 5.1) in the periphery of the ovaries. A high luteinizing hormone (LH) to follicle stimulating hormone (FSH) ratio is associated with PCOS, of which patients suffer from chronic anovulation leading to prolonged estrogenic stimulation of endometrium. This stimulation in turn causes hyperplastic changes and, ultimately, endometrial carcinoma. PCOS is

Table 5.4 Risk factors for Type I endometrial carcinoma

Factor	Risk
Metabolic syndrome [16]: – Obesity [16] – Hypertension [16] – Hypertriglyceridemia [16]	RR 1.89 (95% CI 1.34–2.67) – RR 2.21 (95% CI 1.50–3.24) – RR 1.81 (95% CI 1.08–3.03) – RR 1.17 (95% CI 1.10–1.24)
Type II diabetes mellitus: – Unadjusted [17]	– OR 2.1; 95% CI 1.40–3.41
PCOS: – Unadjusted [18] – Adjusted [19]	– OR 2.79–2.89 – OR 2.2 (95% CI 0.9–5.7)
Other: Estrogen-producing ovarian tumors: 20% have simultaneous endometrial cancer Early (<12-year) menarche: RR 2.4 Late (≥55-year) menopause: RR 1.8 Unopposed estrogen (≥5 years) 10–20-fold risk Postmenopausal use of tamoxifen: 4.0 (95% CI 1.70–10.90)	

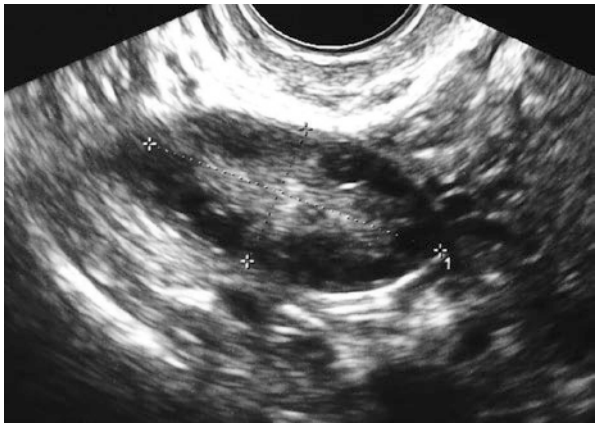

Fig. 5.1 A typical polycystic ovary (PCO). Courtesy of Dr. Helena Tinkanen

often associated with metabolic syndrome, which is likely to increase the carcinogenic potential; BMI-adjusted OR is lower than unadjusted OR, or 2.2 [19].

Estrogen-producing ovarian tumors, or granulosa and theca cell tumors, are important, yet rare, risk factors of endometrial cancer. In fact, 20% of women carrying these tumors have a simultaneous endometrial cancer [21], undermining the importance of preoperative endometrial sampling. Of constitutional risk factors besides genetic susceptibility (Lynch syndrome), both early menarche and late menopause are associated with approximately double the risk of endometrial cancer [22, 23].

There are also iatrogenic risk factors of endometrial cancer. Unopposed estrogen therapy is associated with up to a 30-fold increased risk, if the duration of the therapy is at least 5 years [24]. Postmenopausal use of tamoxifen in the prevention or treatment of breast cancer is paradoxically associated with a fourfold increased risk of endometrial cancer [25].

5.3 Prevention

Taking into account the risk factors, in general, women should be encouraged to pay attention to weight control if obese, and DM should be kept under careful control. It should, however, be taken into account that these measures merely decrease, and not abolish, the risk of endometrial cancer.

There are also pharmacological measures in the risk reduction. Successful treatment of infertility decreases substantially the risk of endometrial cancer within the anovulating population of women. If conception is not desired, cyclic progestin [26] and preferably, provided no contraindications exist, combined oral contraceptives can be used to counteract the stimulatory effect of estrogen on endometrium [27]. An efficacious alternative is levonorgestrel-releasing intrauterine device (LNG-IUD) [28]. Recent evidence suggests that also nulliparous women can safely use LNG-IUD [29]. Each of these hormonal treatments are also active in preventing endometrial stimulation caused by unopposed estrogen therapy. Moreover, LNG-IUD has been used to oppose the effect of tamoxifen on the endometrium, although its efficacy in this setting is still somewhat controversial [30].

5.4 Cancer Registry

In many countries, Cancer Registries have been founded to facilitate the follow-up of the epidemiology, standardization of the treatment, and collection of survival data of different forms of cancer at national level. In Europe, 60–85% of the funding of the registries comes from governmental sources (http://www.eurocourse.org). Cancer Registries are also a powerful tool for epidemiological research especially in the Nordic Countries, either at national or Nordic level (NORDCAN, or the Association of the Nordic Cancer Registries). From the NORDCAN database, it is easy to find statistical data of cancers at Nordic, national, or even regional level.

References

1. Weiderpass E, Antoine J, Bray FI, Oh J-K, Arbyn M. Trends in corpus uteri cancer mortality in member states of the European Union. Eur J Cancer. 2014;50:1675–84.
2. SEER Database 2005–2011.
3. WHO. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed 3 Apr 2015.
4. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109:655–62.
5. Shirley MH, Barnes I, Sayeed S, Finlayson A, Ali R. Incidence of breast and gynaecological cancers by ethnic group in England, 2001–2007: a descriptive study. BMC Cancer. 2014;14:979.. http://www.biomedcentral.com/1471-2407/14/979
6. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58(2):71–96.

7. Vasen HFA, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical managemen t of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812–23.
8. Tzortzatos G, Andersson E, Soller M, et al. The gynecological surveillance of women with Lynch syndrome in Sweden. Gynecol Oncol. 2015;138:717–22.
9. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15:10–7.
10. Billingsley CC, Kenne KA, Cansino CD, et al. The use of transvaginal ultrasound in Type II endometrial cancer. Int J Gynecol Cancer. 2015;25(5):858–62.
11. ACOG. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol. 2005;106:413–25.
12. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67–73.
13. Broaddus RR, Lynch HT, Chen LM, et al. Pathologic features of endometrial carcinoma associated with HNPCC: a comparison with sporadic endometrial carcinoma. Cancer. 2006;106:87–94.
14. O'Hara AJ, Bell DW. The genomics and genetics of endometrial cancer. Adv Genomics Genet. 2012;2012(2):33–47.
15. ACOG. ACOG Committee Opinion No. 426: the role of transvaginal ultrasound in the evaluation of postmenopausal bleeding. Obstet Gynecol. 2009;113:462–4.
16. Esposito K, Chiodini P, Capuano A, et al. Metabolic syndrome and endometrial cancer: a meta-analysis. Endocrine. 2014;45:28–36.
17. Rosato V, Zucchetto A, Bosetti C, et al. Metabolic syndrome and endometrial cancer risk. Ann Oncol. 2011;22:884–9.
18. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014;20:748–58.
19. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009;114:121–7.
20. Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer. 2014;111:1432–9.
21. Peiretti M, Colombo N. Sex cord-stromal tumors of the ovary. In: Textbook of gynaecological oncology. Ankara, Istanbul: Günes; 2012. p. 453–6.
22. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol. 1992;167:1317–25.
23. Zucchetto A, Serraino D, Polesel J, et al. Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. Eur J Cancer Prev. 2009;18:316–21.
24. Ali AT. Reproductive factors and the risk of endometrial cancer. Int J Gynecol Cancer. 2014;24:384–93.
25. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371–88.
26. Reed SD, Newton KM, Garcia RL, et al. Complex hyperplasia with and without atypia: Clinical outcomes and implications of progestin therapy. Obstet Gynecol. 2010;116(2 Pt 1):365–73.
27. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015;16(9):1061–70. https://doi.org/10.1016/S1470-2045(15)00212-0.

28. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E. Cancer risk in women using levonorgestrel-releasing intrauterine system: a nation-wide cohort study. Obstet Gynecol. 2014;124(2 Pt 1):292–9.
29. Kaislasuo J, Heikinheimo O, Lähteenmäki P, Suhonen S. Predicting painful or difficult intrauterine device insertion in nulligravid women. Obstet Gynecol. 2014;124:345–53.
30. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. Int J Clin Exp Pathol. 2014;7:6419–29.