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Review

C-reactive protein as a diagnostic and prognostic factor of endometrial cancer.

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Abstract: Endometrial Cancer (EC) is the sixth most commonly occurring cancer in women with 380 000 cases in 2018. Sadly, EC morbidity and mortality are continuously increasing, therefore the medical society have a substantial need for an accurate and inexpensive diagnostic test for EC early detection and a prognostic tool for treatment planning and evaluation.

Considering experience with different types of cancers C-reactive protein (CRP) appears to be a promising diagnostic and prognostic factor. Aiming to investigate its potential and in view of EC authors, this paper reviewed the following databases for metanalysis, randomized controlled trials and review articles published up to June 2020: Pubmed, Scopus, Google scholar and ClinicalKey. Studies indicate CRP >3.33 mg/l correlate with EC incidence with HR = 2.29 ($p<0.05$). Moreover, High-sensitivity CRP assay allows to detect CRP in very low concentrations and distinguish patients with endometriosis, soft tissue sarcomas and possibly EC. Preoperational and postoperational CRP, as well as its dynamic change are independent prognostic factors for EC and are more reliable if analyzed together. However, CRP-to-albumin ratio as well as Glasgow Prognostic Scale have greater prognostic value that CRP alone. Additionally, CRP is possibly a mediator of carcinogenesis and cancer progression through activation of inter alia FcgRs/MAPK/ERK, FcgRs/IL-6/AKT/STAT3 and FcgRs/NF-κB/NLRP3 pathways.

Keywords: C-reactive protein, hs-CRP, albumins, Glasgow Prognostic Score (GPS), Endometrial Cancer (EC), CRP to albumin ratio (CAR).

1. Introduction

Endometrial Cancer (EC) is one of the most common cancers among women and important problems in gynecology [1–3]. According to the World Cancer Research Fund endometrial cancer is the sixth most commonly occurring cancer in women and the 15th most commonly occurring cancer overall.

In 2018 there was 380 000 new cases worldwide [1]. The American Cancer Society estimated that in 2020 there will be 65620 new cases of uterine body malignant neoplasm and 12590 deaths related to endometrial cancer and that it would be the cause of 90 % or more cases [2] . Moreover, Sorosky reported that for last few decades EC morbidity was increasing year to year and EC related mortality doubled [3]. Although approximately 75 % of endometrial cancers are diagnosed at stage 1, its treatment is very challenging, especially in groups of elderly women. Approximately 73 % of EC

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cases concerns women are older than 54 years of age [4,5]. Furthermore, Moore et al. reported that women over 70 years old account for 25 % of new cases and 50 % of EC associated deaths [5]. Moreover, in this group of patients hysterectomy (the most efficient treatment) was performed much less often then in group of younger patients [5,6]. Premenopausal women only account for around 25 % of EC cases, they are more likely to be diagnosed with stage II-IV cancer. In histological examination it is more often serous or clear cell EC of which are associated with much worse prognosis [4,5]. One of the main reasons is that first symptom reported by patients is an unexpected uterine bleeding, which is clearly detected by postmenopausal women but not premenopausal women [6,7]. Based on this fact there is a great need for an accurate and inexpensive diagnostic test for EC early detection and creditable prognostic tool for treatment, planning and evaluation. This applies particularly among younger patients but is also especially relevant among elder patients who often have some contraindications for a radical surgery and need very careful consideration of substitute or additional therapies, i.e. adjuvant chemotherapy. These challenges are problems of not only endometrial cancer but other types of cancers as well, therefore, many scientists seek for a resolution [8–10]. Regarding papillary thyroid carcinoma Stanciu et al. reported significant correlation of high-sensitivity C-reactive protein (hs-CRP) with persistent/recurrent cancer [8]. Therefore, researchers indicated that hs-CRP could be used as a prognostic tool for patient stratification [8]. Furthermore, Ose et al. assessed 754 cases of epithelial ovarian cancer showing significantly increased risk of cacner occurrence among patients with CRP >10 mg/L in compare to patients with CRP ≤1 mg/L, with odds ratio of 1.67 (95 % CI 1.03 - 2.70) [9]. Moreover, in similar study Kodama et al. show that a CRP level is an independent prognostic factor for ovarian cancer [10]. These studies raised questions of whether CRP is similarly associated with endometrial cancer, could it be used as a diagnostic marker for early detection of EC, could it be used as a screening test and prognostic tool or is CRP merely a marker or is it a mediator of carcinogenesis? The aim of this study it to review current literature and answer these questions in order to facilitate future research and advance in clinical approach regarding endometrial cancer.

2. CRP association with endometrial cancer

Obesity is a well-known risk factor of endometrial cancer (EC) development [11]. Considering experience with other neoplasms many researchers hypothesized that inflammation may be the mediator between obesity and endometrial cancer [11–14]. In order to confirm that assumption Wang et al. conducted a case-cohort study, investigating blood samples of 151 postmenopausal women with endometrial cancer and 301 matching controls [12]. Researchers assessed concentrations of CRP, IL-6 and TNF-α for at least 12 months before cancer detection and all molecules correlated positively with EC incidence [12]. However, after Body Mass Index (BMI) adjustment only CRP correlated with EC incidence with hazard ratio (HR) of 2.29 (95% CI= 1.13–4.65) comparing CRP concentrations of <0.64 mg/l to >3.33 mg/l [12]. A similar was conducted by Friedenreich et al. who also proved that CRP, but not IL-6 or TNF-α correlates with EC incidence [13]. Interestingly, multivariable adjustment of results revealed that CRP correlated with type 1 endometrial cancer but there was no significant correlation regarding type 2 EC. Moreover, the higher the BMI was, the greater the correlation was. This indicates that CRP is substantially connected with obesity and could be not an independent risk factor of EC [13]. In order to investigate if the CRP is an independent risk factor of endometrial cancer and, if there is any genetic ground of EC development regarding C-reactive protein, Wen et al. assessed CRP gene polymorphism in association with the EC [14]. Whilst analyzing Chinese population researchers discovered six CRP single-nucleotide polymorphisms (SNP). Assessment of these SNPs associated with waist-to-hip ratio measurements of 1046 patients with EC and 1035 matching controls led to conclusions that CRP polymorphism alone is not associated with endometrial cancer occurrence. However, among women with higher waist circumference certain alleles of CRP gene were associated with increased EC incidence [14]. Possibly obesity is a triggering factor of systemic low-grade inflammation which contributes to EC development and intensity of the inflammatory response is dependent on the CRP polymorphism. Although these studies do not delineate if

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C-reactive protein is merely a marker of EC or takes part in its development, they clearly prove that elevated concentrations of CRP are associated with EC, therefore it could be useful in diagnosis and prognosis of endometrial cancer.

3. Hs-CRP as a diagnostic factor of early stage endometrial cancer

According to the American Cancer Society the incidence of endometrial cancer is increasing every year [15]. Approximately 33 % of cases are stage III or IV and the 5-year survival rate for stage IV is only 17 % [15]. Therefore, a specific diagnostic test for early detection of endometrial cancer is of great need in order to improve treatment outcome. Such a diagnostic tool is desired not only in view of EC, but other types of neoplasm as well. Therefore many scientists were trying to find it, and C-reactive protein appears to be a perfect candidate. Li et al. in their metanalysis assessed findings of 14 publications, with 89995 participants, regarding high-sensitivity C-reactive protein (hs-CRP), inflammation and cancer mortality [16]. Researchers report that hs-CRP can accurately detect low-grade inflammation. Moreover, comparison of 1st and 4th quartile or 1st and 3rd tertial of hs-CRP concentrations in examined populations show significant association of high hs-CRP concentrations with the cancer related mortality, with RR = 1.25 (95 % CI 1.13-1.38) [16]. In order to investigate if hs-CRP is associated particularly with endometrial diseases, and if it is more accurate that classical CRP assay, Vodolazkaia et al. assessed plasma samples of 204 women with endometriosis and 91 matching, healthy controls [17]. Researchers report that hs-CRP assay detected C-reactive protein in 100 % of samples, while the classical assay detected CRP only in 42.7 % of samples. Moreover, with cut-off CRP value of >0.71 mg/L, hs-CRP show 80.7% sensitivity and 63.9% specificity in diagnosis of moderate-severe stages of endometriosis [17]. These studies indicate correlation of hs-CRP with both malignant and nonmalignant diseases of endometrium, of which leads to the question of whether hs-CRP analysis allows to differentiate between patients with malignant tumors and those with benign tumors and other diseases? The answer was provided by Nakamura et al. who assessed hs-CRP levels of 60 patients with soft tissue sarcomas, 35 patents with benign soft tissue tumors and 14 healthy individuals [18]. Researchers reported that with the cut-off CRP value of 0.95 mg/l the serum hs-CRP level exhibited 50 % sensitivity and 94.4 % specificity for identification of soft tissue sarcomas, with area under the curve of 0.747 [18]. There was no difference between healthy patients and those with benign tumors. However, aforementioned studies indicate significant correlation of hs-CRP with cancer and its effectiveness in endometrial cancer detection, CRP is associated with various diseases and pathological stances, such as diabetes mellitus and obesity, which can interfere with the interpretation of the results. Moreover, Engelsen reported that hs-CRP is significantly higher among patients with obesity and metabolic syndrome in compare to patients with obesity only, and hs-CRP concentrations were the higher the more components of metabolic syndrome patients had [19]. Furthermore, Dossus et al. reported that detected correlation of CRP with endometrial cancer was abolished after BMI adjustment [20]. On the other hand, Heidari show that there is now difference between CRP levels among patient with type 2 diabetes mellitus and EC in compare to patients with EC alone, and in both groups CRP concentrations were higher than those measured among patients with diabetes only [21]. However, CRP measurement appears to be a reasonable diagnostic strategy for endometrial cancer, the problem of interference of other diseases must be addressed by clinicians who would like to introduce hs-CRP assays as an endometrial cancer screening test. It is relevant mentioning that the fact of early diagnosis stages in EC is more likely among postmenopausal women due to an unexpected bleeding as a symptom, but not among menstruating women who also less likely would suffer for obesity, diabetes mellitus, etc. Therefore, endometrial cancer detection by the hs-CRP measurement could be more accurate and beneficial within this group from such a screening [15]. Assessment of cut-off CRP levels in particular regions and risk groups, i.e. obese, obese with diabetes mellitus, etc. appear to be a rational approach in order to make hs-CRP measurement reliable by increasing its sensitivity and specificity. However, although this hypothesis has some clinical ground it needs a further investigation and confirmation.

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4. CRP as a prognostic factor of endometrial cancer

As it was described in previous sections C-reactive protein (CRP) is strongly associated with endometrial cancer and its measurement can be used for EC detection. In reference to this data, researchers raised a question whether CRP is associated with endometrial cancer staging, grading, progression free survival (PFS) and mortality. Therefore, could CRP analysis be also used in the prognosis of EC?

Aiming to answer this question Gathirua-Mwangi et al. analyzed a medical history of 10014 adult women [22]. Within two decades of follow-up, performed by the U.S. National Center for Health Statistics, 400 of these women died from cancer, including 140 deaths from obesity-linked cancers like EC. Interestingly women with a metabolic syndrome without CRP elevation and women with high CRP concentrations without metabolic syndrome show non-significant increase of obesity-linked cancer mortality and total cancer mortality. However, women with both a metabolic syndrome and CRP concentrations higher than 10 mg/l show significantly increased obesity-linked cancer mortality and total cancer mortality in comparison to healthy controls with hazard ratios of 1.91 (CI 95 % 0.97-3.75) and 1.78 (CI 95 % 1.18-2.61) respectively [22]. This association was confirmed also by Endo et al., who performed retrospective analysis of 2867 patients of whom underwent percutaneous coronary intervention [23]. Researchers divided patients into two groups based on their CRP concentrations, that is less than 1 mg/l and equally or greater than 1 mg/l. Patients with higher concentrations had significantly increased total cancer mortality risk in compare to the other group, with hazard ratio (HR) of 1.74 (CI 95 % 1.18–2.61) [23]. These studies prove that increased concentrations of C-reactive protein indicates high cancer mortality risk.

In order to investigate this association particularly in endometrial cancer and delineate connection of CRP concentrations with staging, grading and metastases Schmidt et al. examined 403 women with EC [24]. Researchers measured plasma CRP concentrations in blood samples collected within 48 hours before surgery and followed-up patients up to 42 months. Serum CRP levels were significantly higher among patients with stage II-IV EC in compare to patients with stage 1. Moreover, women with 5 mg/l or less had higher rates of disease-free survival and overall survival in compare to these with CRP concentrations of >5 mg/l, with HR 1.2 (1.1–1.3) and 1.1 (1.05–1.3) respectively [24]. There was no correlation between serum CRP concentrations and grading or lymph node metastases. However, in similar study Wang et al reported significant association of high CRP levels with not only with overall survival rate and disease-free survival but also with tumor stage and lymph node metastases [25]. Therefore, pretreatment analyses of serum CRP concentrations would allow to distinguish patients with increased risk of cancer progression and cancer-related death and possibly assess the risk of lymph nodes involvement. Aforementioned correlations and hazard ratios are however still quite low and there is a substantial need to make the inflammation analysis more significant and informative for clinicians.

An interesting approach is an assessment of albumin concentrations together with CRP levels. Glasgow prognostic score (GPS) is an inflammatory-based cancer prognostic tool created with assumption that decrease of albumin concentration and increase of CRP level proportionally reflects systemic inflammation, this is an unfavorable prognostic sign for cancer bearing patients [26]. The GPS scale is from 0 to 2, where the GPS 0 indicates no inflammation and the GPS 2 considerable inflammatory response. Cut-off values are <35 g/l for albumin and >10 mg/l for CRP. Patient's gain one point for each value in described ranges as it is showed in table 1. GPS has been reported as a useful prognostic tool in relation to, inter alia, ovarian, breast, colorectal and pancreatic cancers, Saijo et al. conducted a study in order to assess its effectiveness in determination of endometrial cancer prognosis [26]. Researchers measured pretreatment plasma concentrations of CRP and albumin of 431 women with endometrial cancer [26]. Patients were followed-up to maximum 140 months after blood sample analysis. After multivariate adjustment hazard ratios for GPS1 were 1.847 (CI 95 %0.919–3.714, p = 0.085) and 1.847 (CI 95 % 0.723–4.573, p = 0.204), PFS and overall survival respectively [26]. Therefore, after multivariate adjustment and in contrast to univariate analysis, correlation of GPS1 with progression-free survival was not statistically significant for GPS1.

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However, for GPS2 both HR were statistically significant with values 5.17 (CI 95 % 2.311–11.565, P<0.001) and 5.984 (CI 95 % 2.820–18.287, P<0.001), for PFS and overall survival respectively [26]. Moreover, Glasgow Prognostic Score was significantly associated with tumor stage (P = 0.001), myometrial invasion (P = 0.016), cervical invasion (P = 0.003), lymphovascular space involvement (P = 0.004), lymph node metastasis (P = 0.015), and CA125 level (P < 0.001) [26]. These findings indicate that the GPS is more informative and efficient in prognosis assessment of patients with EC that solitary CRP analysis.

Interestingly, measurement of CRP concentration is not only a prognostic indicator associated with C-reactive protein. Kito et al. investigated the relationship between CRP 1846C>T genetic polymorphism and lymph node metastasis and lymphovascular space involve in 130 EC patients [27]. Among women with C/T or T/T polymorphism 7 % had lymph node metastasis and 6 % had moderate to prominent vascular invasion whilst none of the women with C/C genotype had such symptoms [27]. Interestingly, plasma CRP concentration difference between these two groups was not statistically significant indicating that CRP gene polymorphism could be another independent prognosis predictor for patients with endometrial cancer. Aforementioned studies indicate that CRP and GPS can be used as a reliable prognostic tool in assessment of patients with endometrial cancer. The Glasgow Prognostic Score appear to be more accurate than solitary CRP analysis and correlate better cancer progression indicators i.e. lymph node metastasis. These tools could be very useful in planning of a proper treatment, i.e. surgery extension, post-operative chemotherapy, etc. and in choosing a proper control examination schedule for patients with increased risk of cancer recurrence. However, more in depth broad studies are needed, multicenter in order to fully assess the potential these prognostic tools and create new, universal guidelines for management of patients with endometrial cancer.

Table 1. Glasgow Prognostic Score.

Glasgow Prognostic Score	Albumin ≥ 35 g/L	Albumin < 35 g/L
CRP ≤ 10 mg/L	GPS0	GPS1
CRP > 10 mg/L	GPS1	GPS2

5. CRP in follow-up after endometrial cancer surgery

Since it has been proven that the CRP concentration can be a reliable prognostic indicator for patients with endometrial cancer, researchers decided to evaluate its effectiveness in post-operative evaluation of patients [28]. Also, very helpful in developing that concept was a study performed by Shinohara et al. retrospectively reviewed 336 patients with non-small cells lung cancer were treated with lung resection [29]. Patient CRP levels were measured 4-8 weeks post operation, with the average being 6 weeks. Based on the results patients were divided into two groups, CRP less than 5 mg/l or CRP equal or higher than 5 mg/l. Five-year overall survival and recurrence-free survival were worse in the high-CRP group than in the low-CRP group 62.9% vs. 82.9% (p<0.001) and 48.4% vs. 76.1% (p<0.001) respectively. Furthermore, researchers indicated that after multivariate adjustment post-operative high CRP concentration was an independent predictor for worse overall survival with HR = 2.23 (95% CI 1.44-3.47, p<0.001) [29]. A similar study was conducted by Katsurahara et al. who examined 187 patients who underwent esophagectomy for esophageal squamous cell carcinoma [30]. Interestingly, CRP levels within the first month after surgery did not correlate with overall survival rate and recurrence-free survival rate. CRP concentrations however, measured 2 months after the surgery show significant correlation with overall survival and recurrence-free survival, HR = 2.27 (95 % C 1.03-3.34, p=0.005) and HR = 1.65 (95 % CI 1.08-2.52, p=0.020) respectively [30]. The cut-off value for CRP concentrations was 1.5 mg/l, and the group with

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high CRP levels had significantly worse overall survival rate, 41.4 vs. 71.4 %, (p=0.0002) and recurrence-free survival rate RFS, 28.9 vs. 51.3 % (p=0.007) [30]. The nonrelevance of the first month measures could be a result of increased CRP production as a response to surgery associated tissue damage of which interfered with the baseline CRP measurement. Therefore, a question emerged; what is the time of decline of damage associated CRP levels and what time after the surgery CRP measurement will be reliable as a prognostic factor? With partial answer for that question came Pilka et al. who had measured preoperative and postoperative CRP concentrations of women with endometrial cancer [31]. Researchers compared CRP levels of patients after open, laparoscopic and robotic surgeries in patient blood samples obtained one day before the surgery and every day for the next five following days.

Although CRP concentrations differ between groups and were highest after open and lowest after robotic surgery, in every group the peak of CRP concentrations was on the second/third day and notably decreased on the fourth and fifth day [31]. Unfortunately the follow-up period was too short and researchers were unable to observe when C-reactive protein levels dropped back to the preoperation values. However, considered CRP half-time, which is approximately 19 hours, and previously described researches it could be assumed that this would take place between the first and the second month after the operation. Therefore assessment of CRP level two months after the surgery would be a most likely reliable prognostic indicator [28–32].

In order to reduce the impact of various processes on prognostic value of CRP the Glasgow Prognostic Score could be used, like in preoperative prognosis. Tomita et al. assessed 312 patients who underwent resection of non-small cell lung carcinoma [32]. Patients had CRP and albumin levels measured before the surgery and one to two months after and were assigned into groups GPS0-2 as it is delineated in table 1 [32]. The 5-year survival rate for patients with GPS0 before and after the surgery was 74.3 %. Interestingly, the rate was similar for patients who had GPS1 or GPS2 before the surgery but GPS0 after [32]. The 5-year survival rate for patients who had GPS0 before but GPS1 or GPS2 after the surgery was circa 50 %. The worst 5-year survival rate, below 20 %, had patients with GPS1 or GPS2 before and after the surgery [32]. This data indicates that assessment of Glasgow Prognostic Score before and after the operation can have a great prognostic value. The usefulness of GPS was also assessed by Zhuo et al. who examined 516 patients with primary resection of colorectal cancer [33]. Researchers measured not only GPS but also CRP to albumin ratio (CAR) before and one month after the surgery. After multivariable adjustment of the preoperative GPS show no significant association with overall survival or PFS, however, postoperative GPS was significantly correlated with overall survival and PFS with HR 1.66 (95 % 0.98–2.80) and 1.21 (95 % 0.83–1.77) respectively. Moreover, hazard ratios of overall survival and PFS for dynamic change of pre and postoperative GPS were 2.70 (95 % 1.19–6.11) and 1.63 (95 % 0.96–2.75) for overall survival and PFS respectively [33]. Considering CAR, patients were divided into two groups by the cut-off value of 0.09, and those with CRP to albumin ratio of 0.09 or higher had overall survival rate of approximately 52 % in compare to approximately 78 % of <0.09 group. The HR values for postoperative CAR were 1.38 (95 % 0.85–2.24) and 2.74 (95 % 1.31–5.74), PFS and overall survival respectively. Considering dynamic change hazard ratios were 1.65 (95 % 1.03–2.67) and 2.55 (95 % 1.21–5.38), PFS and overall survival respectively [33]. Aforementioned studies indicate that analysis of both CRP and albumin allows for more accurate prognostic assessment than CRP alone. Moreover, postoperative assessments undertaken a minimum of one month after the surgery appear to be more informative that preoperative assessment and aforementioned findings of Zhuo et al. the dynamic change CRP and albumin values can further improve prognosis accuracy [33]. Therefore, simple and inexpensive tests such as CRP and albumin measurements could greatly improve the management of patients with endometrial cancer and allow to distinguish the group of patients with increased risk of cancer recurrence and cancer related death. The group, which needs more extensive diagnostic and therapeutic strategies. However, the value of preoperative and postoperative CRP and albumin assessment still needs confirmation in clinical studies, particularly in a group of patients with endometrial cancer.

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6. Increased CRP as a bad prognostic sign – potential mechanism

Considering aforementioned studies, the connection of CRP with cancer appears to be undeniable and can be used in diagnosis and prognosis of malignant neoplasms. However, this association raises a question of whether C-reactive protein is just a marker of cancer related inflammatory response or an important mediator of cancer development and progression? Reported successes of immunomodulatory therapies in cancer treatment, along with a genetical and histochemical analysis of cancer samples indicate an important role of immunological system in its development and progression [34–38]. Focusing directly on the C-reactive protein Schimmack et al. investigated impact of CRP and IL-6 on pancreatic neuroendocrine neoplasms cell lines BON1 and QGP1 in vitro [36]. Incubation with CRP in concentration of 20 mg/l for 48 h resulted in significant increase of IL-6 secretion by BON1 cells in compare to control specimen. Moreover, after the incubation BON1 cells showed notably increased invasion through a basal membrane and significantly elevated viability/proliferation assessed with MTS assay in compare to control specimen [36]. However, assessment by bromodeoxyuridine-ELISA revealed no increase in proliferation that may indicate CRP stimulates invasion and cancer cell activity, but not proliferation. There was no impact of CRP on QGP1 cell line, therefore CRP effect appear to be dependent on cancer genotype. Interestingly, 48 h of incubation with 25 ng/ml of IL-6 resulted in two-fold increase of CRP concentration in BON1 cell culture and nine-fold increase in QGP1 cell culture [36]. Furthermore, the incubation resulted in significant enhancement of invasion in both cell cultures. This would indicate that CRP induces IL-6 production and secretion and IL-6 induces CRP production and secretion if cells have proper receptors. For CRP these receptors are FcgRI, FcgRII and FcgRIII [36]. Interestingly, western blot analyses revealed that CRP significantly elevated extracellular signal-regulated kinases (ERKs) levels and IL-6 notably elevated signal transducer and activator of transcription 3 (STAT3) levels [36]. Therefore, researchers stated that CRP activates MAPK/ERK pathway and IL-6 activates Akt/STAT3 pathway were both strongly associated with carcinogenesis [37–40]. ERKs have a pleiotropic effect on neoplasms where they activate pro-survival pathways leading to cell proliferation and migration, modulate apoptosis, cell differentiation and senescence and according to research by Salaroglio et al. ERKs this plays a major role in tumor resistance for immune system responses and chemotherapy [37]. Moreover, Ma et al. reported that inhibition of MAPK/ERK pathway by insulin-like growth factor binding protein-related protein 1 or PD98059 resulted in inhibition of endometrial cancer cell growth, its G1 faze arrest and senescence [38]. Furthermore, blockade of MAPK/ERK inhibitors had quite the opposite effect and resulted in a significant increase of EC cell proliferation in vitro [38]. Moreover, Maik-Rachline et al. reported that ERK is crucial for carcinogenesis and it regulates expression of dozens of genes including proto-oncogenes such us FOS, JUN, JUNB, MYC, etc. and suppressor genes like Rb1, TP53, NR0B2 etc. [39]. Researchers indicated that ERK is stored in cytoplasm and its activation and translocation into the nucleus is substantial for gene expression modification, therefore, this translocation is a potential target for anticancer therapies [39]. Regarding IL-6 and AKT/STAT3 pathway Wu et al. conducted an in vitro study on gastric cancer cell lines indicating that inhibition of AKT/STAT3 pathway resulted in decreased cell proliferation and invasion, therefore this pathway appears to be crucial for gastric cancer development [40]. Another interesting mechanism through which CRP most likely induces carcinogenesis and neoplasm progression was described by Ghazo-Khanloosani et al. who investigated impact of C-reactive protein on colorectal cancer cells [41]. CRP in dosage 10 mg/l significantly increased expression of low-density lipoprotein receptor-1 (LOX-1). This was reported to promote cancer cell proliferation, angiogenesis, migration and invasion [41]. Another interesting finding was made by Ma et al. who had revealed strong correlation between CRP concentrations and expression of autophagy-related protein 9B (ATG9B) in clear cell renal cell carcinoma samples [42]. ATG9B regulates cell autophagy process and if increased it can promote cell survival and proliferation of different types of neoplasms, such as renal cancer, breast cancer, cervical cancer, etc. [42–44]. Therefore, autophagy alteration could be an additional mechanism through which C-reactive protein can possibly promote endometrial cancer development and progression. An interesting study was performed by Bian et al. who investigated

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impact of C-reactive protein on human umbilical cord cells [45]. Western blot analyses revealed CRP induced expression and activation of NLRP3 (NOD-like receptor family, pyrin domain-containing protein 3) and its product, IL-1β, through FcgR/NF-κB (nuclear factor κB) pathway [45]. Liu et al. examined tumour samples of 31 women with endometrial cancer, showing that NLRP3 overexpression is significantly associated with increased proliferation, migration and invasion of EC cells [46]. The possible mechanism through which C-reactive protein facilitates development and progression of endometrial cancer is summarized in figure 1. It appears that CRP affects cancer cell proliferation, migration, invasion, chemoresistance and immune system resistance through alteration of proto-oncogenes and inhibitory gene expression. It also indicates that immunomodulation by different pathways, such as FcgRs/MAPK/ERK, FcgRs/IL-6/AKT/STAT3, FcgRs/NF-κB/NLRP3, LOX-1 and auto-phagocytosis alteration. However, this hypothetical pathomechanism in relation to endometrial cancer needs a meticulous investigation and confirmation, although considering experiences with other types of cancer it is very plausible.

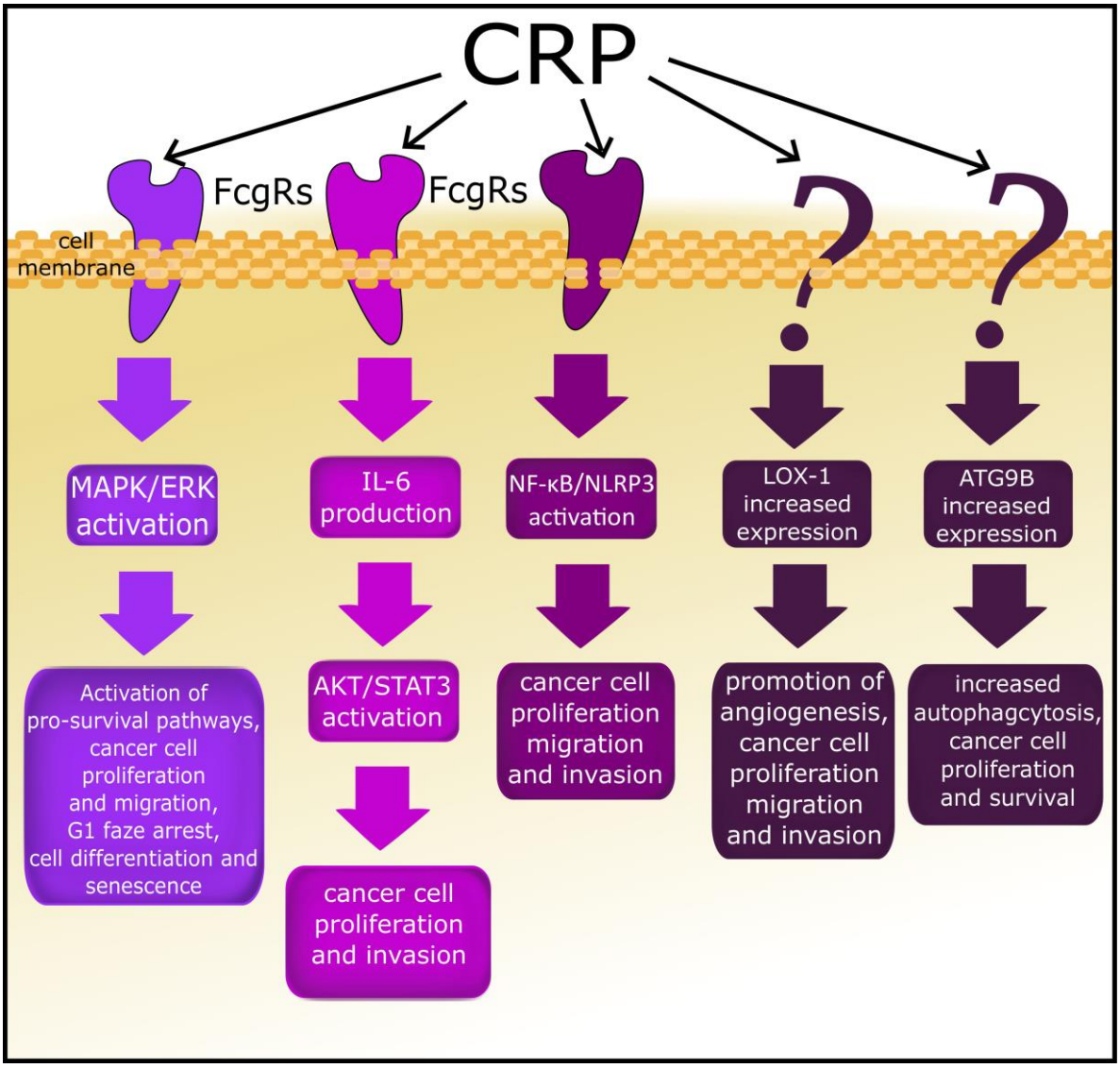

Figure 1. Potential role of CRP in carcinogenesis and cancer progression. FcgRs – Fc (fragment crystallizable) immunoglobulin G receptors, MAPK/ERK - mitogen-activated protein kinase/extracellular signal-regulated kinase, AKT/STAT3 – protein kinase B/signal transducer and activator of transcription 3, NF-κB – nuclear factor κB, NLRP3 - NOD-like receptor family, pyrin domain-containing protein 3 (forming NLRP3 inflammasome), LOX-1 - low-density lipoprotein receptor-1, ATG9B - autophagy-related protein 9B.

7. Discussion

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Although many studies show significant correlation of C-reactive protein with malignant neoplasm development, progression and mortality, some researches do not confirm this association in view of endometrial cancer. For example, metanalysis by LI et al. indicate that correlation of CRP with total cancer mortality was statistically significant for men but not form women [16]. In this paper scientists do not however perform statistical analysis specifically for endometrial cancer and only refers to mortality not morbidity [16]. Furthermore, Albisinni et al. evaluated patients with bladder cancer and show that postoperative CRP levels do not correlate with progression-free survival and overall survival [47]. Although these studies do not refer directly to endometrial cancer, they indicate that precise analysis of CRP diagnostic and prognostic value is of great demand to confirm and establish its clinical usefulness. An analysis of additional factors, like albumin level and GPS assessment, may be helpful in increasing creditability of CRP measurement. An interesting approach is a postoperative measurement of white blood cells (WBC). Toyokawa et al. examined 75 patients with esophageal squamous cell carcinoma and revealed that postoperative white blood cell level was an independent prognostic factor [48]. Moreover, postoperative WBC was better correlated with overall survival rate than CRP, however, only if increase of leukocyte level wasn't associated with infection. Thereby it could be another inexpensive prognostic factor, which could supplement information gained from CRP measure. It is also worth mentioning the fact that increased CRP levels and increased endometrial cancer risk are strongly associated with obesity and fat tissue is hormonally active [49]. Moreover, adipose tissue through estrogen and leptin promotes AKT/STAT3 and MAPK/ERK pathways and therefore these hormones could be as important or even more important in carcinogenesis and cancer progression than CRP and their role in endometrial cancer development and progression need an investigation [49–51]. Furthermore, natural or surgical fat loss decreases levels of CRP, leptin and estrogen, therefore, could be consider as prophylaxis and adjuvant treatment of endometrial cancer [52]. Considering value of CRP measurement and a great demand for large clinical studies, alternative, noninvasive method of CRP measurement would be very useful. Ouellet-Morin et al. assessed serum and saliva of 61 healthy individuals and revealed a moderate-to-strong association between CRP measured in saliva and in serum ($r = .72$, $p < .001$) [53]. Therefore, saliva CRP measurement could be an interesting option for broad studies or endometrial cancer screening programs. Considering aforementioned studies C-reactive protein analysis has a great potential to become informative and clinically useful diagnostic and prognostic tool and further studies regarding its usage and role in carcinogenesis should follow.

8. Materials and Methods

8.1. Literature search strategy and study selection

The following electronic databases were reviewed up to June 2020: Pubmed, Scopus, Google Scholar, and ClinicalKey. The search included: clinical trials with human subjects, original studies with rat or mouse models, original studies on cell lines, metanalyses, systematic reviews and reviews, all in English.

Combinations of following search terms were used:

Population: CRP, hs-CRP, endometrial cancer, prognosis, diagnosis, cancer, carcinogenesis, MAPK/ERK, AKT/STAT3, NLRP3, Glasgow Prognostic Score, GPS.

Intervention: CRP measurement, diagnosis, prognosis and follow-up of cancer with CRP, assessment of CRP effect on cell lines

Three reviewers (Maciej Socha, Micha Wiciński and Oskar Puk) independently performed the primary search and screened the titles and abstracts of 523 articles of which 132 were pre-selected for further analysis. Afterwards, the same reviewers assessed full manuscripts and choose those meeting the following inclusion criteria. Finally, 53 scientific papers were included in this review.

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8.2. Inclusion and exclusion criteria

The inclusion criteria for the study were defined with use of population–intervention–comparison–outcome (PICO) formula. Abstracts were considered if the following inclusion criteria were fulfilled.

Population: patients with endometrial cancer, patients from endometrial cancer risk group, patients with other types of cancer reliable rat or mouse models, cell line studies.

Intervention: diagnosis, prognosis and follow-up of cancer (desirable endometrial cancer) with CRP, assessment of CRP effect on cell lines

Comparison: comparison of CRP to other markers, comparison of CRP levels between patients with or without cancer or patients with stage II-IV cancer to patients with stage I, comparison of CRP levels between different groups, i.e. obese patients to patients with normal weight.

Outcome: diagnostic and prognostic value of CRP, delineation of CRP role in carcinogenesis and cancer progression

Study design: Clinical, animal or in vitro studies investigating efficiency of CRP as a prognostic and diagnostic tool. Metanalyses and reviews summarizing such trials.

Studies were excluded for the following reasons: too short follow-up time, examination of only a specific group, i.e. obese patients

8.3. Outcome measures

The primary outcome measure to assess the efficacy of investigating efficiency of CRP as a prognostic and diagnostic tool. Other measures were investigated to determine if CRP takes part in carcinogenesis and what is its exact role.

8.4. Data extraction

The following data for each study was extracted: number of subjects, population specification, animal species, cell line specification, type of treatment, period and frequency of CRP measures.

8.5. Data analysis and synthesis

To compare and summarize the studies, data was extracted and value of CRP assessment in view of endometrial cancer was investigated. The methodology was critically assessed and results of animal or in vitro studies have been referred to clinical conditions. The statistical significance was defined as a $p\text{-value}<0.05$.

8.6. Assessment of risk of bias

The studies were evaluated for quality and risk of bias by assessment of creditability of used scales and measurement tools and analysis of author's statements.

9. Conclusions

C-reactive protein is strongly associated with endometrial cancer and it could be used in diagnosis and prognosis of EC. High sensitivity CRP assay can be used as a tool for diagnostic of early stage endometrial cancer however, cut-off values for designation of the risk group needs to be evaluated for regional population. It can be useful especially regarding young patients, without

CRP-increasing metabolic syndrome, who are more often diagnosed with stage III/IV cancer. Furthermore, preoperative and postoperative analysis of CRP appears to be an excellent prognostic tool for EC patients.

Pretreatment CRP levels are significantly correlated with progression-free survival and overall survival of cancer patients. Furthermore, CRP measurement minimum one month after the surgery and analysis of its dynamic change significantly increases CRP prognostic value. Moreover, association of CRP with albumin concentrations in Glasgow Prognostic Scale and CRP-to-albumin ratio appear to further increase the prognostic sensitivity and specificity of CRP. Importantly, CRP gives the impression of being not only marker but also mediator of carcinogenesis and cancer progression through activation of inter alia FcgRs/MAPK/ERK, FcgRs/IL-6/AKT/STAT3 and FcgRs/NF-κB/NLRP3 pathways. Further clinical and laboratory studies are needed to fully comprehend the role of CRP in carcinogenesis, its diagnostic and prognostic value and designation of population and risk groups specific cut-off values.

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