**FOLIA HISTOCHEMICA
ET CYTOBIOLOGICA**
Vol. 47, No. 5, 2009
pp. S101-S105

Review article

PCOS and cancer risk

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Abstract: Polycystic ovary syndrome (PCOS) affects approximately 5 to 10% of women of reproductive age. It is the most common reason of anovulation in infertile women. PCOS is accompanied by such conditions as oligo- or anovulation, hipertestosteronism, lower cell sensitivity to insulin, type II diabetes, hyperlipidemia and obesity. Each of the above-mentioned conditions is an approved risk factor proved to predispose towards cancer. However, PCOS is also a disease entity which differs in its clinical manifestation. For example not all patients suffer from obesity or hipertestosteronism related symptoms. From the analysis of literature it is possible to draw conclusions, that there is a possible correlation between PCOS and endometrial cancer, which emerges from clinical trials or research focused on molecular changes in endometrium patients with PCOS. On the other hand, correlation between PCOS and breast or ovary cancer is not so strong, in spite of single papers which are showing the link. The main problem in researching the correlation between PCOS and any cancer risk, is there is a very small group of women or the trial is imperfect (*e.g.* no control group). There is no meta-analysis focused on this correlation in literature. The change of criteria of PCOS in the past is also a big problem, because there was a number of definitions of PCOS, which results in inconsistent PCOS diagnoses over time. In this paper we would like to provide a description of studies that aimed at showing correlation between PCOS and cancer risk and underlying theoretical assumptions.

Key words: Polycystics ovary syndrome, endometrial cancer, hiperinsulinemia, anovulation

Introduction

Polycystic ovary syndrome PCOS affects approximately 5 to 10% of women of reproductive age. It is the most common reason of anovulation in infertile women. PCOS is accompanied by such conditions as oligo- or anovulation, hipertestosteronism, lower cell sensitivity to insulin, type II diabetes, hyperlipidemia and obesity. Each of the above-mentioned conditions is an approved risk factor proved to predispose towards cancer. Women diagnosed with PCOS develop higher level of testosterone, insulin, growth factors such as IGF-1 (Insulin Growth Factor-1), which were experimentally proved to have potential for direct stimulatation of cancer cells proliferation. Direct stimulation of cancer cells may result both from binding testosterone to testosterone receptors on cell surface, as well as peripheral androgen aromatization to estradiol followed by binding estradiol to estrogen receptors, which may also result in cancer cells growth. IGF-1 and others growth factors also have a stimulating effect on cancer cells and cause intracellular conversion of estron to estradiol. Testosterone causes an increase in the level of EGF (Endothelial Growth Factor) and provides a mitogenic stimulus for cancer cells.

However, all the fore mentioned observations do not allow for an explicit conclusion that PCOS as a disease entity predisposes towards greater occurrence of cancer. This paper provides description of studies that aimed at showing correlation between PCOS and cancer risk and underlying theoretical assumptions.

Infertility, obesity and hiperinsulinemia in PCOS and their links with cancer

PCOS is a disease entity which differs in its clinical manifestation [1,2]. Not all the patients suffer from obesity (only 40-50%) [3], infertility (but problems with fertility affect 75% of women) [4] or hipertestosteronism related symptoms. On the other hand, all of these problems may coexist in one patient.

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Folia Histochem Cytobiol. 2009:47(5): S101 (S101-S105)
10.2478/v10042-009-0092-1

As mentioned above infertility problems affect ca. 75% of PCOS patients. Many papers provide conclusions on correlation between infertility and cancer. It seems that it is infertility that most eminently predisposes towards cancer in PCOS women. Correlation between infertility and cancer was proved in epidemiologic research and single case reports. In 1983 Coulam *et al.* [5] proved 3-times higher risk of endometrial cancer in patients suffering from chronic anovulation. Another research team [6] traced back cases of patients with 1964-1974 history of infertility treatment. In this research the most frequent cause of infertility was of hormonal nature, followed by other causes (male factor, mechanical infertility). Researchers showed 4.8-fold risk of endometrial cancer and 10.8-fold risk of cancer in infertile patients with chronic anovulation. In the following paper [7], risk of endometrial cancer was linked to childlessness as researchers found out that there were more nullipara in the group of patients with cancer, and women who were infertility-treated (diagnosed with infertility) displayed 7.6-fold risk of endometrial cancer. From the above mentioned research, as well as other papers [8] one can conclude that infertility increases risk of endometrium cancer, especially if accompanied by chronic anovulation. This coincidence takes place in PCOS.

These conclusions are not that explicit, when one tries to link infertility to other types of cancer diagnosed in women. Many papers aimed at linking breast cancer to hormonal factors. In the case of infertile patients there exist both papers which show higher incidence, as well as reverse effect. Risk factors that lead to breast cancer development are conditions connected with higher production of endogen hormones, which is also the case in PCOS. Ron *et al.* [6] and Brinton *et al.* [7] did not show correlation between infertility and breast cancer. These conclusions were confirmed in other research. [9,5]. However, one research [10] showed 1.8-fold risk in infertile patients with chronic anovulation, and yet another one showed 5.4-fold incidence of breast cancer in pre-menopause women who were previously diagnosed with anovulation. Two other papers seem very interesting with respect to PCOS patients. One of them [11] showed that in breast cancer patients suffering from ovulation problems the risk of breast cancer was 3.5-times higher. If the same patients had signs of hyperandrogenism (persistent acne, excess of body hair), the risk was 6.8 higher. At the time of diagnosis most of patients in this research were in postmenopausal age (60%). The second paper [5] showed that in patients with obesity, hypertension and diabetes (conditions that frequently coincide with PCOS) the risk of breast cancer is 3-times higher.

Contrary to the fore-mentioned papers there are also papers on correlation between ovarian cancer and infertility. Most research show correlation. One of basic factors of ovarian cancer is childlessness and anovulation [12]. In a research by McGovan *et al.* [13] risk of ovarian cancer in nullipara was 2.45-times higher compared to multipara and 1.27-times higher compared to unipara. The analysis of 12 case control studies [14] showed 2.1-fold risk in nullipara with infertility history.

Obesity, which coincides with PCOS, is a risk factor in all the above mentioned types of cancer. Meta-analysis of studies into coincidence of ovarian cancer and obesity showed that in 10 per 28 population-based studies correlation was statistically significant, and pooled effect estimate for adult obesity was 1.3 (95% CI 1.1-1.5)[15], which had previously been showed in one smaller paper [16]. Recent epidemiologic studies have shown a positive relationship between BMI and breast cancer with a significant relative risk ranging from 1.26 to 2.52 [17].

Theoretical premises for correlation of PCOS and cancer are based on very specific observations. Unopposed stimulation of the endometrium in the setting of chronic anovulation in women with PCOS is an acknowledged factor leading to endometrial cancer development [18]. Estrogens are also an acknowledged factor of breast cancer, as they stimulate duct breast tissue. They also stimulate – under laboratory conditions – cancer cell growth [19]. In cell lines, estrogens have been shown to have a variety of actions, specifically to increase concentrations of Transforming Growth Factor (TGF) and Insulin Growth Factor 1 (IGF-1) [20]. In PCOS estrogen concentration may rise as a result of a number of mechanisms. First and foremost, chronic anovulation does not lead to higher concentration, but to chronic endometrial stimulation with estrogens. Stimulation, which is not antagonized by progesteron in the course of disturbed cycle, may lead to persistent endometrial proliferation. Estrogen concentration may rise in obese patients. In PCOS patients the main source of estrogens are androgens, whose concentration also rises in the course of PCOS. In the case of obese patients concentration of sex hormone-binding globulin (SHBG) decreases, which leads to higher concentration of free androgens, followed by their peripheral conversion to estrogens. PCOS accompanying hyperinsulinemia also leads to higher estrogen concentration by direct impact of insulin on androgen production in ovaries. Androgens may also individually stimulate endometrial growth. Insulin receptors are present both in endometrium of healthy patients, as well as in patients with endometrial cancer, which may suggest the role of hyperinsulinemia in genesis and progression of endometrial cancer [21]. Hyperinsulinemia also causes IGF-1 (Insulin Growth Factor-1) concentration to rise. Its concentration rises as well as a result of estrogen stimulation, by inhibited production of Insulin Growth Factor Binding Protein I (IGFBP I) [22]. IGF-1 is

10.2478/v10042-009-0092-1

growth factor which can stimulate tumor genesis and tumor progression. In mice growth factors have malignant transforming potential [23,24]. Growth factors can be chemotactic to blood vessels [25,26]. Insulin also causes higher concentration of another growth factor, i.e. VEGF (Vascular Endothelial Growth Factor) [27]. IGF receptors were detected in breast cancer cells, and its mitotic activity was greater than that of estradiol [28]. Within the uterus gen activity for IGF is stimulated by estrogens [29]. The actions of insulin on the endometrium in vivo are difficult to distinguish from the actions of androgens because hyperandrogenism and hyperinsulinemia are positively correlated in women with anovulation [30]. In obese women there is also higher concentration of adipokines, proteins synthesized in fat cells. Adipokines include i.a.: leptin, TNF-α (Tumor Necrosis Factor α), interleukin-6, hepatocyte growth factor, and heparin-binding epidermal growth factor-like growth factor (HB-EGF). Leptin, for example can be proliferative factor for breast cancer cells in vitro [17].

Endometrial cancer

From both clinical and experimental research one can conclude that correlation between PCOS and endometrial cancer is the strongest. Endometrium of PCOS patients is known to be more sensitive to steroid hormones. Women with PCOS exhibit elevated endometrial androgen receptor expression compared to normal, fertile controls [31], and endometrium of PCOS patients shows higher concentration of estrogen receptors [32]. It was also proved that PCOS patients exhibit higher Cyr61 protein expression [33], protein which is integrin-binding, angiogenic factor, that also promotes cell migration and adhesion. This protein is also an apoptosis regulator and is associated with tumorgenesis [34]. Higher Cyr61 expression was also present in uterine myoma [35] and in endometriosis [36]. In the case of breast cancer its elevated expression was found both in tumor biopsy and in metastasis [37]. In the course of PCOS endometrial homeostasis is disturbed. Apart from a change in Cyr61 production, a number of other modifications are identified; a change in Ki-67 expression, lower p53 production, higher cyclin D1 expression and higher bcl-2/bax ratio [38,39]. Disturbed homeostasis may result from intensified proliferation which may in turn lead to abnormal cell division possibly followed by tumorgenesis. However, clinical studies do not provide straightforward answer to the question about correlation between PCOS and endometrial cancer. This correlation was observed as early as 1949, 14 years after the first description of the syndrome [40]. However, both this and some other studies on this problem [41,42] did not include study controls, which disqualifies explicit conclusions. Remaining studies [43-45] did not show correlation between PCOS and endometrial cancer. In a number of studies PCOS patients were not identified in the overall study group [46-48]. One study showed that obesity caused risk to rise 3-fold in patients diagnosed with endometrial cancer compared to non-obese patients, which may imply that infertility does not have to be an independent risk factor of endometrial cancer in PCOS women [49]. There was also an attempt to conclude that PCOS may provide better prognosis once endometrial cancer has been diagnosed [50], as histopathological research of preparations from PCOS patients showed well differentiated tumors or moderately well differentiated. However, this study was carried out on only 6 patients and did not include study control, which precludes talk of correlation.

Ovarian cancer

The most quoted paper showing correlation between ovarian cancer and PCOS is by Schildkraut *et al.* [51]. It showed 2.5-fold risk of ovarian cancer in PCOS women and as high as 10.5-fold risk in patients who did not receive OC. Data were analyzed from a population-based, case-control study, the Cancer and Steroid Hormone Study, i.e. a study that did not aim to evaluate ovarian cancer in PCOS women. In the group of patients diagnosed with ovarian cancer there were only 7 PCOS women who accounted for 1.5% of the group, while in the study control there were 24 cases of PSOC, i.e. 0.06% of the control. Conclusions on correlation between ovarian cancer and PCOS seem inaccurate based on such a small group of PCOS patients in research groups. Most studies on correlation between PCOS and ovarian cancer failed to show a link [52,46]. An interesting exception is a paper by Rossing *et al.* [53], investigating connections among infertility, ovarian cancer and ovulation inducing drugs. Clomiphen treatment caused 2.3-fold risk of ovarian cancer in these women. These results were confirmed in other studies [54-56].

Breast cancer

In the case of correlation between breast cancer and PCOS proofs are also not convincing, and research results even show reverse correlation [57,58]. The basic problem underlying theses studies was the fact that in the second study PCOS women accounted just for 0.94% of the study control and for 0.49% of breast cancer group, while in the first study for 1.35% of the overall study group. Another drawback of these studies was that patients reported PCOS by themselves. It seems one cannot talk of correlation between breast cancer as PCOS, just as in the case of ovarian cancer.

Problems with proper evaluation of correlation between PCOS and respective factors are present in

10.2478/v10042-009-0092-1

a paper showing higher mortality of PCOS patients from breast cancer compared to healthy population [59]. This paper traces back medical records of patients diagnosed with PCOS in their lifetime in order to determine standardized mortality ratio (SMR). It was proved that SMR for breast cancer was 1.48 in this group, while mortality was not higher from circulation diseases at the same time. However, as soon as 2 years later the same study group released study results that did not show correlation between deaths from breast cancer and PCOS despite the same patient group. Different conclusions resulted from modified methodology of the study [60].

Based on available literature one may draw a conclusion that correlation between adenocarcinoma of endometrium and PCOS is likely to exist. This results both from clinical trials and papers on changes of endometrium in PCOS patients. However, despite single papers that report on the link, correlation between ovarian or breast cancer and PCOS is doubtful.

Conclusions

Fundamental problem in estimating correlation between PCOS and tumor formation exists primarily in a limited number of reports on this problem. If research does exist, there has been either too small patient group or it has not been properly conducted from the very beginning (*e.g.* no control group). This is why no meta-analysis was developed on this issue. Another problem in estimation of correlation between PCOS and tumor formation is changeability of criteria for PCOS diagnosis. Changes have been proposed three times since modern criteria for PCOS diagnosis (NIH) were first determined in 1990 (Homburg 2002, ESHREVASRM-Rotterdam 2003, AES 2006). This may affect the results of retrospective studies, which are most commonly the case in investigating correlation between PCOS and tumor formation. A case diagnosed as PCOS does not have to be qualified as such based on present-day criteria. What seems indispensable for proper evaluation of the issue is large randomized research that will enable to draw final conclusions based on proper theses and appropriate patient selection.

Acknowledgements: Tadeusz Issat is a recipient of a START stipend from the Foundation for Polish Science.

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