

Effect of demographic factors on brachytherapy treatment results in patients with endometrial cancer 1995–2010

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Abstract

Introduction: Approximately 1 in 20 female cancers in Europe is of the endometrium. Endometrial carcinoma is the most common gynaecologic cancer. Considering the fact that an upward tendency has recently been observed in morbidity due to this type of cancer, this is a serious medical problem.

Objective: The presented report describes the results of the analysis of selected demographic factors and their effect on the incidence of endometrial cancer. Analysis of the results of treatment of endometrial cancer during 1995–2010 was also an objective of the study.

Materials and methods: Based on medical records obtained from the HDR Laboratory of Brachytherapy at the Gynaecological & Obstetrics Clinical Hospital, University of Medical Sciences in Poznań, the results of treatment of patients with endometrial cancer by brachytherapy were analyzed. The analysis covered a group of 400 patients.

Results: More than a half of the patients completed their education on the level of elementary or secondary school. Taking into consideration the weight of the patients, it appeared that most women had excessive body weight. Most frequently, concomitant hypertension was observed. Moreover, the age at menarche was 12 and 13.

Conclusions: Demographic factors exert a significant effect on the incidence of endometrial cancer. 1. Overweight and obesity are important risk factors of endometrial cancer. 2. A strong relationship is observed between the occurrence of hypertension or diabetes, and the development of endometrial cancer. 3. Women who come from the rural environment and continue to live in this environment are more likely to contract endometrial cancer.

Key words

endometrial carcinoma, morbidity, demographic factors, treatment, population

INTRODUCTION

Endometrial carcinoma (EC) is considered to be a post-menopausal disease. Apart from cervical cancer and ovarian cancer, it is among the most frequently diagnosed malignant tumours in women, and the incidence of this cancer is constantly increasing. Endometrial cancer is 10 times more frequently noted in the western countries with an elevated standard of living (Europe, United States), compared to the regions of Africa and Asia, where the level of globalization is considerably lower. Worldwide, approximately 150,000 new cases are noted annually. In Poland within the last 50 years, a dramatic increase in morbidity has been observed, and recently an increase has also been noted in death rates due to this type of cancer – from 1.4–2.2/100,000 [1]. The higher the stage of clinical advancement of the disease the higher the risk of failure. At stages I, II and III, according to FIGO, the risk of recurrence within the period of 2 years after the completion of cancer treatment is 4%, 9.2% and 24.3%, respectively. In addition, the risk of recurrence is over 4 times higher in patients with the serous or clear-cell forms of cancer, compared to other histologic types [2]. It seems that evaluation of cancer lesions for expression of VEGF and

VEGFR-1 by immunochemistry may be useful in establishing a 5-year survival for endometrial cancer [3].

Many factors exert an effect on the occurrence of relative risk of contracting endometrial cancer which, to a considerable degree, may also be due to the ageing of society, uncontrolled administration of estrogens, or increase in industrialization, and consequently, contamination of the natural environment. The development of EC is significantly related to genetic, hormonal and reproductive factors. Nevertheless, many studies confirm that the development of endometrial cancer is also associated with environmental factors, style of life or constitutional factors [1]. Many authors in the medical literature focus their attention on metabolic syndrome X (obesity, hypertension, diabetes mellitus), which is more frequently recognized in women living in rural areas [1, 2, 3]. The latest studies confirmed the role of CYP1A1 in the development of ovarian and endometrial cancers. The presence of mutated CYP1A1 polymorphic variants influencing the CYP1A1 activity may be related with variability in the sensitivity of female reproductive organs to carcinomas [4].

There are no characteristic and clear signs of endometrial cancer. Abnormal bleeding is considered as a basic symptom. The treatment of endometrial cancer is based on surgical treatment, which consists in the removal of the reproductive organ, and subsequently, the use of such treatments as radiotherapy, chemotherapy, hormonal therapy, and

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hyperthermia. In the case of endometrial cancer, the prognosis is assessed as favourable, because this disease is characterized by a limited tendency to metastasis, and the duration of survival depends on the stage of the disease.

The presented report describes studies carried out based on the records of patients who received treatment for endometrial cancer stage IB, grade G3 at the HDR Laboratory of Brachytherapy, at the Gynaecological & Obstetrics Clinical Hospital, University of Medical Sciences in Poznań. The selected factors and their effect on the incidence of cancer were subjected to detailed analysis.

MATERIALS AND METHOD

The results of treatment of patients diagnosed with endometrial cancer stage IB, grade G3 were analyzed based on medical records obtained from the HDR Laboratory for Gynaecological & Obstetrics, the Clinical Hospital, University of Medical Sciences in Poznań. In the presented study, special attention was paid to the selected demographic factors, presented below. The analysis covered 400 patients who had undergone treatment at the above-mentioned HDR Laboratory in Poznań in the years 1995–2010. Evaluated in the work, demographic factors and their influence on the incidence of endometrial cancer, have been statistically analysed. It was assumed that the group of 400 patients is a definitive population, with chosen quantitative characteristics (age of the population examined, body weight BMI, place of birth and place of residence, number of births).

RESULTS

The conducted research showed that 76 women had a university education level, 92 patients – secondary school education, 124 – vocational education, and 108 women suffering from endometrial cancer stage IB, grade G3 reported that they possessed elementary education. As many as 232 women were born in a rural area, and 168 patients were born in an urban area. Subsequent, more detailed analysis revealed that 204 of the women analyzed continued to live in rural areas, while 196 patients spent the rest of their lives as urban inhabitants. Considering the body weight of patients from the study group, it was found that almost every woman had an excessive body weight. None of the 400 patients in the study was underweight, 80 patients had a normal BMI value, 112 patients were overweight, and 208 obese.

Analysis of the incidence of concomitant diseases in women suffering from endometrial cancer showed the following: arterial hypertension was the most frequent concomitant disease and was observed in 140 women, while 156 patients were diagnosed with arterial hypertension accompanied by diabetes. There was no case in which diabetes occurred without arterial hypertension. The study provided information that 24 women suffered from hypothyroidism, and 80 patients had depression. Evaluation of chosen quantitative characteristics of the entire group leads to interesting results. Over 50% of women of the analyzed population are characterized by following factors: obesity (> 30), place of birth – rural area and place of residence – rural area. Moreover 37% of the population were women aged 56–65, with arterial hypertension and diabetes. Tables 1 and 2 present the remaining data.

Table 1. Characteristics of the study population.

Analysis	No. of patients (n=400)	Total (%)	
education level	University	76	19
	secondary school	92	23
	Vocational	124	31
	elementary	108	27
place of birth	rural area	232	58
	urban area	168	42
place of residence	rural area	204	51
	urban area	196	49
body weight (BMI in kg/m ²)	underweight (<18.4)	0	0
	normal weight (18.5- 25)	80	20
	overweight (25.1 a 29.9)	112	28
	obesity (> 30)	208	52
occurrence of other types of cancer	ovarian cancer	36	9
	breast cancer	16	4
	no cancerous diseases	348	87
occurrence of other concomitant diseases	arterial hypertension	140	35
	arterial hypertension and diabetes	156	39
	Hypothyroidism	24	6
	Depression	80	20

Table 2. Characteristics of the study population.

Analysis	No. of patients (n=400)	Total (%)	
use of contraceptive pills	YES	12	3
	NO	388	97
cigarette smoking	YES	12	3
	NO	388	97
age at menarche	8–11	40	10
	12	80	20
	13	100	25
	14	120	30
	15–18	60	15
number of births	0	152	38
	1	76	19
	2	68	17
	3	60	15
	4–5	44	11
	25–45	20	5
	46–55	92	23
age of population examined	56–65	148	37
	66–75	104	26
	76–95	36	9

DISCUSSION

The majority of cases of endometrial cancer concerned endometrial adenocarcinoma (EC). An increasing morbidity due to EC is explained by a longer life span, change in nutritional habits and improvement of the conditions of habitation. To-date, many factors have been identified which

favour the development of this cancer, such as obesity, diabetes, advanced age of patients, elements of obstetric interview and menstrual cycle, or hormone therapy [5]. The presented study covered patients treated at the HDR Laboratory of Gynaecological & Obstetrics Clinical Hospital, University of Medical Sciences in Poznań. The patients had undergone brachytherapy treatment due to the diagnosis of endometrial cancer stage IB, grade G3.

Analysis of education level and assessment of its effect on the incidence of endometrial cancer. The effect of selected demographic factors on the incidence of endometrial cancer was evaluated. Education level was the first of the factors analyzed. Among 400 respondents, 108 women admitted that they possessed elementary education. According to the literature review, a similar study was conducted by Levi et al. [6], who analyzed the level of education in 357 women suffering from endometrial cancer. The researchers confirmed that 76.2% of women had not completed 7 grades, and 23.8% had an education level higher than 7th grade, and drew the conclusion that this type of cancer is more common in women with a lower level of education [6]. However, Wynder et al. [7] obtained different results. In a group of 112 ill women with various levels of education, they did not find any differences between the risk of endometrial cancer and the level of education [7]. The education level exerts a significant effect on the incidence of endometrial cancer: women, who have university education level, and therefore a higher standard of living, more often visit a gynaecologist and undergo regular health check-ups. Awareness of the risk of developing various types of cancer, including endometrial cancer, is much higher in women with university education.

Analysis of the effect of place of birth and place of residence on the incidence of endometrial cancer. The women in the study were analysed with consideration of the place of birth, and place of residence, according to the division into rural and urban areas. Based on this division, the following results were obtained: 232 women were born in a rural area, and 168 patients were born in an urban area. More detailed analysis confirmed that 204 respondents still lived in a rural area, and 196 were urban inhabitants. Evaluation of chosen quantitative characteristics of the entire group leads to interesting results. Over 50% of women of the analyzed population are characterized by following factors: obesity (>30), place of birth – rural area and place of residence – rural area. These results allow the conclusion that the women who came from rural areas and continued to live there, were more likely to contract endometrial cancer.

Many epidemiological studies have shown a higher incidence of endometrial cancer among women who had better living conditions. As early as in the 1970s and 1980s, Rosenberg et al. [8] and Kelsey et al. [9] conducted studies which confirmed that women from higher social classes, especially those with early menopause, more often use hormone replacement therapy, which results in a higher incidence of endometrial cancer [8, 9]. On the other hand, Schottenfeld et al. [10], while analyzing women in the United Kingdom, did not find any relationship between the incidence of endometrial cancer, and the affiliation to the socio-economic class [Schottenfeld]. The results of the presented study show that women who came from rural areas and continued to live there, more often fell ill with endometrial

cancer. Undoubtedly, the effect of place of residence is also connected with the previously conducted analysis, which concerned the effect of the education level. Thus, it may be presumed that women living in rural areas possess less knowledge pertaining to the incidence of endometrial cancer, and therefore are less likely to visit a gynaecologist, and to a smaller extent, undergo health check-ups.

Analysis of body weight of women suffering from endometrial cancer. While assessing body mass index (BMI), in all patients participating in the study it was found that the largest group of women had a BMI between 30.1 – 60.5, which meant that these patients were obese. According to Brinton et al. [11], the relative risk of EC for women with $BMI \geq 32 \text{ kg/m}^2$ is $RR=4$, and for women with $BMI > 35$ this risk increases to $RR=6$, compared to those with $BMI < 23 \text{ kg/m}^2$ [11]. Weiderpass et al. [12] reported similar results: BMI between 28 – 29.99 kg/m^2 was associated with an increased risk of endometrial cancer – by 50%. Body mass index between 30 – 33.99 kg/m^2 was associated with a 3-fold increase in the risk of endometrial, compared to the normal values, whereas for the $BMI > 34 \text{ kg/m}^2$ the risk was up to 6 times higher [12]. Furberg et al. [13] confirmed the influence of obesity on an increased risk of endometrial cancer, while observing for 15.7 years a large group of 36,761 Norwegian women. Obese women ($BMI \geq 30 \text{ kg/m}^2$) were at 2.6 times higher risk of endometrial cancer, compared to those who had normal weight ($BMI < 25 \text{ kg/m}^2$) ($RR = 2.57$, $95\% \text{ CI} = 1.61-4.10$) [13]. Yang et al. [14] confirmed that among 249,791 postmenopausal women with 7.3 years of follow-up, the risk of endometrial cancer ($n=1,410$ cases) was strongly associated with current (BMI) at baseline ($RR=1.87$ per 5 kg m^{-2}) increase in BMI, $95\% \text{ CI}: 1.77-1.96$). Compared with girls slimmer than the average at the age of 10, an increased risk among girls plumper at the age of 10 ($RR=1.27$, $95\% \text{ CI}: 1.09-1.49$) disappeared after adjustment for the current BMI ($RR=0.90$, $95\% \text{ CI}: 0.77-1.06$). Similarly, compared with women who were clothes size 12 or less at the age of 20, an increased risk among women with clothes size 16 or larger ($RR=1.87$, $95\% \text{ CI}: 1.61-2.18$) was not significant after adjustment for the current BMI ($RR=1.03$, $95\% \text{ CI}: 0.88-1.22$) [14].

Analysis of the incidence of other cancers in women suffering from endometrial cancer. The subsequent factor evaluated was the co-occurrence of other types of cancer in patients treated for EC. In the group of 400 women in the study, 36 had ovarian cancer. Breast cancer occurred in 16 patients, and the remaining 348 women participating in the study did not suffer from any other cancer. Based on the relevant literature, some information may be obtained concerning genetic predispositions to cancer. The knowledge acquired is clinically useful in the identification of women who are burdened with increased genetic risk of genital cancer. Among genital cancers, the genetic dispositions play a special role in endometrial cancer, breast cancer and ovarian cancer. According to the literature reports, endometrial cancer is the second most common type of cancer among patients with Lynch II syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, an autosomal-dominant inherited cancer susceptibility syndrome caused by a germline mutation in one of the DNA mismatch repair genes, accounts for the majority of inherited cases [15, 16].

Nevertheless, according to other researchers, endometrial cancer, while occurring in the Lynch II syndrome, concerns a small group of patients, i.e. from 1 – 3.1%. Also, according to literature reports, in 20–43% of women from families in which the Lynch II syndrome was diagnosed, endometrial cancer will develop before the age of 70 [15]. Based on the studies by Vasena et al. [15] carried out among the group of 125 women, EC occurring in the Lynch II syndrome was diagnosed at an average age of 48, 75% of all cases were diagnosed at the age of under 50, and more than 98% at the age of under 65 [15]. The lifetime cumulative risk of endometrial cancer for women with Lynch syndrome is 40% – 60%, which equals or exceeds their risk of colorectal cancer. Diagnosing EC patients with Lynch syndrome has important clinical implications for individual patients and their family members. Screening and prevention practices can decrease the likelihood of additionally developing other types of cancer [16].

Incidence of concomitant diseases in women suffering from endometrial cancer. Analysis of the effect of the occurrence of concomitant diseases in women with endometrial cancer showed that arterial hypertension was the concomitant disease most frequently observed in the study group, and concerned 40 women, while 156 women examined suffered from arterial hypertension accompanied by diabetes. Based on the results of the study, 24 women suffered from hypothyroidism, and 80 patients had depression. In the relevant literature, a close relationship has been described between the incidence of endometrial cancer and the occurrence of hypertension or diabetes. In the studies conducted by Garcia-Domenech et al. [17], 35.8% of women with endometrial cancer were also treated for hypertension [17]. Friedenreich et al. [18] analyzed data concerning 541 cases of endometrial cancer and 961 frequency age-matched controls in a population-based case-control study in Alberta, Canada from 2002 – 2006. Blood was analyzed for concentrations of leptin, adiponectin and insulin by immunoassay and fasting plasma glucose levels were determined by fluorimetric quantitative determination. Compared to the lowest quartile, the highest quartile of insulin and HOMA-IR was associated with a higher risk of endometrial cancer: by 64% (95%CI: 1.12–2.40) and 72% (95%CI: 1.17–2.53), respectively, while the highest quartile of adiponectin was associated with a decreased risk – by 45% (95%CI: 0.37–0.80) after multivariable adjustments. No relationships were observed between fasting glucose, leptin and A:L and endometrial cancer risk. Interventions aimed at decreasing both obesity and insulin resistance may decrease endometrial cancer risk [18].

Analysis of the age at menarche in women suffering from endometrial cancer. The subsequent factor analyzed was the age at menarche among women suffering from endometrial cancer. In the group of 100 patients in the study, the first period had occurred at the age of under 12 in 40 women. According to many researchers, the risk of endometrial cancer increases in women who experience early menarche. Elwood et al.[19] believe that the occurrence of the first bleeding in women before the age of 12, increases further risk of cancer incidence (RR=1,6 at 95%) [19]. La Vecchia et al. [20] determined RR equal to 3.9 for Italian women who had experienced menarche at the age of under 11 [20]. In the case of occurrence of the first bleeding at the age of over

15, the researchers did not note any influence on the risk of endometrial cancer [19, 20].

Analysis of the number of births given by patients suffering from endometrial cancer. While analyzing the group of 400 women diagnosed with endometrial cancer according to the number of given birth, it was found that 152 of them did not give birth at all, 76 patients gave birth once, and 68 patients gave birth two or more times. Analysis of the relationship between the number of given births and the incidence of endometrial cancer, before and after menopause, was conducted by La Vecchia et al. [20]. According to these researchers, the highest incidence rate of cancer was noted among women who had never given birth, in which case cancer developed before menopause (the percentage of women who had never given birth among those with endometrial cancer was 20–38%, RR=7,1) [20]. According to Parslov et al.[21], two full-term pregnancies decreased the risk of endometrial cancer by 88%, and preterm pregnancy by 16% [21].

Analysis of the age of patients suffering from endometrial cancer. The highest morbidity was observed among women aged from 55–70; however, endometrial cancer may also develop in young women at reproductive age, nearly 3% of cases concerned pre-menopausal women [22]. Despite the fact that endometrial cancer is relatively rare at the age of under 45, no age group can be disregarded, both at reproductive and post-reproductive periods, which would exclude the risk of development of endometrial cancer. Olejek et al. [22] presented the case of a 25-year-old patient who had undergone endometrial curettage because of irregular menstrual bleeding for the last 5 months. Histopathology revealed endometrial cancer. The researchers suggested that in selected cases of atypical hyperplasia and early endometrial cancer in young women, attempted hormonal treatment is acceptable [22].

For several years, studies have been conducted worldwide in order to search for new and proven prognostic and prognoses factors in endometrial cancer, among others [23]. The risk factors are already known, and a detailed recognition of the mechanisms in the biology of EC cancer and factors which would enable to foresee the response to treatment may considerably improve the effectiveness of therapy, and result in an improvement of the quality of life of the patients treated.

CONCLUSIONS

1. Overweight and obesity are important risk factors of endometrial cancer.
2. A close relationship is observed between the occurrence of hypertension or diabetes, and the development of endometrial cancer.
3. Women who come from the rural environment and continue to live in the rural environment are more likely to suffer from endometrial cancer and likely to suffer from metabolic syndrome X, which more frequently appears in patients with endometrial cancer.
4. The obtained results, based on the evaluation of the group of females, also confirms that women living in rural areas more frequently suffer from endometrial cancer.

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