How to Cite:
Putri, K. W. A., Seno, H. N. H., Warlisti, I. V., Partiningrum, D. L., & Cahyanti, R. D. (2022). Clinical profile of woman's cancer-associated diabetes mellitus patients in Dr. Kariadi hospital Semarang. *International Journal of Health Sciences*, *6*(S3), 960–976. https://doi.org/10.53730/ijhs.v6nS3.5341

Clinical Profile of Woman's Cancer-Associated Diabetes Mellitus Patients in Dr. Kariadi Hospital Semarang

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***Abstract*---**Background: Diabetes and womans cancers are chronic diseases, which are multifactorial, and its prevalence increases every years. Several epidemiological studies have shown that diabetes is the risk factor for severals cancers, including gynecologic and breast cancer. Aim: To determine the prevalence and clinical profile of DM-cancer patients who were hospitalized in Dr. Kariadi Hospital Semarang from January 2016 – May 2017. Methods: A descriptive study using medical reports obtained from Dr. Kariadi Semarang Hospital from January 2016 – May 2017. Result: The prevalence of DM-womans cancer in Dr Kariadi Semarang Hospital in January 2016-May 2017 was 87 cases (7.1%). The highest prevalence was vulvar cancer (14.3%). The majority of patients were in stage II and III (77.3%). The diagnosis of DM in most patients was made before the diagnosis of cancer (62.1%). The age when the DM was first diagnosed was mostly over 40 years (97%). The majority of cancer-DM patients did not have therapy routinely (39.4%) and have poor glycemic control

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
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Manuscript submitted: 18 Nov 2021, Manuscript revised: 09 Feb 2022, Accepted for publication: 27 March 2022

(47%). The most used DM therapy was combination therapy (28.8%). Risk factors for cancer in DM-cancer patients were age ≥50 years (80.3%), excess BMI (51.5%) and use of hormonal contraceptives (45.4%). Conclusion: DM-cancer patients mostly had their DM diagnosed prior to the diagnosis of cancer and had poor management of DM). The risk factors for woman's cancer, such as old age, excess BMI and hormonal contraception, are owned by the majority of woman cancer patients with DM.

***Keywords*---**clinical profile, diabetes, prevalence, woman's cancer.

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disorder caused by the pancreas not producing enough insulin or the body cannot use the insulin it produces effectively, resulting in an increase in the concentration of glucose in the blood (hyperglycemia) [1]. The International Diabetes Federation (IDF) states that more than 371 million people in the world aged 20-79 years have DM [2]. Basic Health Research Data (RISKESDAS) in 2013 showed that the prevalence of diagnosed DM patients in Indonesia was 6.9% or an estimated 12 million people [1].

Diabetes that is not well controlled will cause acute and chronic complications [3]. In addition to these complications, DM is known to increase the risk of some cancers and can also worsen the prognosis of the cancer itself [4]. A case control study of DM and cancer risk in Italy and Switzerland by Cristina Bosetti et al stated that people with DM have a high risk of developing pharyngeal, esophageal, colorectal, liver, pancreatic, breast and endometrial cancers [5]. According to the 2014 WHO Cancer Country Profiles, five types of cancer with the highest prevalence affecting women in Indonesia are breast, cervical, colorectal, ovarian and lung cancer [6]. Gynecological cancers with the highest prevalence in Indonesia are cervical, ovarian, uterine, vulvar and vaginal cancers, respectively [7].

The pathophysiology underlying the increased risk of cancer in DM patients is not known with certainty. Chronic hyperglycemia is thought to stimulate cancer directly by activating signaling pathways that affect cell proliferation, apoptosis and metastasis. Hyperinsulinemia is thought to increase cancer risk directly through stimulation of insulin receptors and insulin-like growth factor-I (IGF-1) receptors [8]. High blood insulin levels can also reduce the synthesis of liver products, including sex hormone binding globulin (SHBG) which will have an impact on increasing estrogen bioavailability [9]. In DM patients, it was found that increased levels of inflammatory mediators and production of Reactive Oxygen Species (ROS) would increase the risk of DNA damage resulting in oncogenesis and damage to tumor suppressor genes [10]. Additional factors such as obesity, physical activity, DM therapy with insulin analogues, exogenous insulin and sulfonylureas, glycemic control, family history of cancer, lifestyle, reproductive history and contraceptive use are also thought to have a role in increasing cancer risk in DM [4,9].

Along with the increasing prevalence of DM and cancer in Indonesia, there is no research that specifically explains the clinical profile of female cancer patients with Diabetes Mellitus in Indonesia. An understanding of this is needed to increase knowledge about female cancer in DM patients. Dr Kariadi Hospital was chosen by the researchers as the research site because Dr Kariadi Hospital is the largest hospital and also functions as a referral hospital for the Central Java region [11]. This study is expected to explain the clinical profile of female cancer patients with DM which includes prevalence, aspects of general characteristics, aspects of cancer characteristics, aspects of DM characteristics and cancer risk factors.

Method

This study is a retrospective descriptive study using the medical records of patients at the Dr. Kariadi Semarang. This research was conducted at Dr Kariadi Hospital, Semarang, Indonesia. The inclusion criteria for this study were female cancer patients which included breast, endometrial, ovarian, cervical, vulvar and vaginal cancers with DM (before or when cancer was diagnosed) recorded in the Medical Record of Dr Kariadi Hospital in the period January 2016 - May 2017. Exclusion criteria for this study this is an incomplete medical record and the patient refused to be contacted further. Samples were taken by means of total sampling. Sampling in this research is done by looking at the medical records of patients with female cancer coding and then contacting the patient if the required variable data has not been obtained from the medical record data.

The variables assessed in this study include the general characteristics of the patient, the characteristics of the cancer aspect, the characteristics of the DM aspect and the characteristics of the cancer risk factor aspects. General characteristics of patients include occupation and city of origin. The characteristic aspect of cancer is the stage of cancer. The characteristics of the DM aspect include establishing a DM diagnosis, age at diagnosis of DM, adherence to DM therapy, HbA1c levels and the type of therapy used. In variable data processing, the completeness of the data is checked, then the data is tabulated, coded, and entered into a computer program. Furthermore, the data were analyzed using descriptive analysis, where the collected data were grouped and presented in the form of a frequency distribution table for each variable being assessed.

Result

Sample analysis

Initial examination at the Medical Record Installation of Dr Kariadi Hospital found 1503 cases of female cancer. A total of 277 cases were excluded because medical record data could not be found and some of them were incorrectly coded for a cancer diagnosis. The total number of female cancer cases obtained was 1226 while female cancer cases with DM in January 2016-May 2017 were 95 cases or 7.7% of all female cancer cases. A total of 8 cases or 0.7% were excluded because the diagnosis of DM was made several years after the patient was diagnosed with cancer. Total cases of female cancer with a history of DM and newly diagnosed DM were 87 cases or 7.1% of all cancer cases. A total of 21 cases were excluded

because medical record data regarding cancer risk factors were incomplete and patients refused to be contacted. The research sample obtained was 66 female cancer patients with DM. More details can be seen in Figure 1.

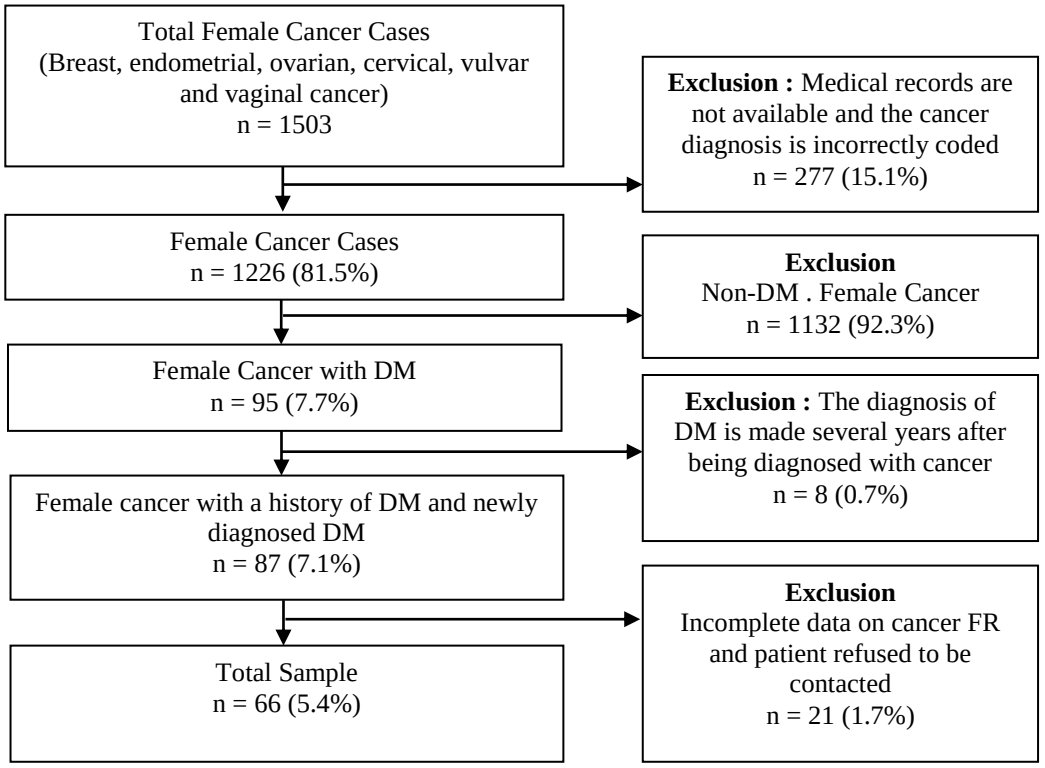

Figure 1. Consolidative of Report of female cancer patients at Dr Kariadi General Hospital

Prevalence of Cancer Patients with DM according to the type of cancer
The highest prevalence of female cancer with DM was found in vulvar cancer, followed by vaginal, endometrial, breast, cervical and ovarian cancers. More details can be seen in table 1.

Table 1
Prevalence of cancer patients with DM according to cancer type

Cancer Type	Cancer Cases	Cancer with DM	Prevalence Cancer with DM
Breast	446	24	5,4%
Endometrium	94	10	10,3%
Ovarium	322	14	4,3%
Cervix	348	16	4,6%
Vulva	7	1	14,3%
Vagina	9	1	11,1%
Total	1226	66	5,4%

General Characteristics of Cancer Patients with DM

Most female cancer patients with DM come from outside Semarang. The majority of female cancer patients with DM work as housewives. More details can be seen in table 2.

Table 2
General Characteristics of Cancer Patients with DM

Variabel	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
1. Hometown							
Semarang	6 (25%)	0 (0%)	6 (42,9 %)	2 (12,5 %)	1 (100%)	0 (0%)	15 (22,7%)
Outside Semarang	18 (75%)	10 (100%)	8 (57,1 %)	14 (87,5 %)	0 (0%)	1 (100%)	51 77,3%)
2. Occupation							
Housewife	15 (62.5%)	8 (80%)	2 (14.3 %)	12 (75%)	0 (0%)	1 (100%)	38 (57.6%)
Government employees	6 (25%)	0 (0%)	4 (28.6 %)	2 (12.5 %)	1 (100%)	0 (0%)	13 (19.7%)
Private employees	1 (4.2%)	1 (10%)	2 (14.3 %)	1 (6.3%)	0 (0%)	0 (0%)	5 (7.6%)
Farmer	1 (4.2%)	0 (0%)	2 (14.3%)	0 (0%)	0 (0%)	0 (0%)	3 (4.5%)
Entrepreneur	1 (4.2%)	1 (10%)	4 (28.6%)	1 (6.3%)	0 (0%)	0 (0%)	7 (10.6%)

Characteristics of cancer aspects of female cancer patients with DM

Most female cancer patients with DM are in stage II and III

Table 3
Characteristics of cancer aspects of female cancer patients with DM

Variable	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1. Stage							
I	2 (8.3%)	2 (20%)	6 (42.9%)	1 (6.3%)	0 (0%)	0 (0%)	11 (16.7 %)
II	12 (50%)	5 (50%)	5 (35.7%)	2 (12.5 %)	0 (0%)	0 (0%)	24 (36.4 %)
III	9 (37.5%)	3 (30%)	3 (21.4%)	11 (68.8 %)	0 (0%)	1 (100%)	27 (40.9 %)
IV	1 (4.2%)	0 (0%)	0 (0%)	2 (12.5 %)	1 (100%)	0 (0%)	4 (6.1%)

Characteristics of Aspects of Diabetes Mellitus in Cancer patients with DM

Most patients have been diagnosed with DM before being diagnosed with cancer. The age when cancer was first diagnosed, the majority were over 40 years old. Most patients take DM therapy but do not consume it regularly. The type of DM therapy used by most cancer patients with DM is combination therapy (a combination of insulin secretagogue and insulin sensitizer, or insulin secretagogue and exogenous insulin). Glycemic control of cancer patients with DM in terms of HbA1c levels when diagnosed with cancer, most of them have poor glycemic control. The details can be seen in table 4.

Table 4
Characteristics of Aspects of Diabetes Mellitus in Cancer Patients with DM

Variable	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
1. DM Diagnosis							
When diagnosed with cancer	8 (33.3%)	4 (40%)	8 (57.1%)	4 (25%)	0 (0%)	1 (100%)	25 (37.9%)
Before being diagnosed	16 (66.7%)	6 (60%)	6 (42.9%)	12 (75%)	1 (100%)	0 (0%)	41 (62.1%)

Variable	Breast Ca n (%)	Endometrium Ca n (%)	Ovarium Ca n (%)	Cervix Ca n (%)	Vulva Ca n (%)	Vagina Ca n (%)	TOTAL
with cancer							
< 5 year	10 (62.5%)	3 (50%)	4 (66.7%)	7 (58.3 %)	1 (100%)	0 (0%)	25 (61%)
≥ 5 year	6 (37.5%)	3 (50%)	2 (33.3%)	5 (41.7 %)	0 (0%)	0 (0%)	16 (39%)
2. DM Diagnosed Age							
< 40 y.o	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
≥ 40 y.o	22 (91.7%)	10 (100%)	14 (100%)	16 (100%)	1 (100%)	1 (100%)	64 (97%)
3. DM Therapy							
Routine	6 (25%)	1 (10%)	0 (0%)	4 (25%)	0 (0%)	0 (0%)	11 (16.7%)
Not a routine	9 (37.5%)	5 (50%)	5 (35.7%)	6 (37.5 %)	1 (100%)	0 (0%)	26 (39.4%)
No Consumption	9 (37.5%)	4 (40%)	9 (64.3%)	6 (37.5 %)	0 (0%)	1 (100%)	29 (43.9%)
3. HbA1c Level							
< 7% (Low)	3 (12.5%)	1 (10%)	1 (7.1%)	3 (18.8 %)	0 (0%)	0 (0%)	8 (12.1%)
≥ 7% (High)	15 (62.5%)	6 (60%)	4 (28.6%)	6 (37.5 %)	0 (0%)	0 (0%)	31 (47%)
Incomplete data	6 (25%)	3 (30%)	9 (64.3%)	7 (43.8 %)	1 (100%)	1 (100%)	27 (66%)
4. Type of Therapy							
Insulin Sensitizer	2 (8.3%)	3 (30%)	1 (7.1%)	1 (6.3%)	0 (0%)	0 (0%)	7 (10.6%)
Insulin secretagogue	3 (12.5%)	1 (10%)	2 (14.3%)	0 (0%)	0 (0%)	0 (0%)	6 (9.1%)
Exogenous insulin	1 (4.2%)	1 (10%)	1 (7.1%)	1 (6.3%)	1 (100%)	0 (0%)	5 (7.6%)
Combination	9 (37.5%)	1 (10%)	1 (7.1%)	8 (50%)	0 (0%)	0 (0%)	19 (28.8%)

Variable	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Therapy No Consumption	9 (37.5%)	4 (40%)	9 (64.3%)	6 (37.5 %)	0 (0%)	1 (100%)	29 (43.9%)

Characteristics of Aspects of Other Risk Factors for Female Cancer in DM patients

Based on the age at which cancer was diagnosed, most of the patients diagnosed at the age of more than 50 years. The minimum age for cancer patients with DM is 38 years. The highest age is at the age of 76 years. More details can be seen in table 5.

Table 5
Age characteristics of cancer patients with DM according to risk factors

Age	n (%)	Mean±SD
< 50 y.o	13 (19,7%)	55,41±7,6
≥ 50 y.o	53 (80,3%)	

Body Mass Index of cancer patients with DM mostly have overweight BMI. Most female cancer patients with DM have no family history of cancer. The majority of female cancer patients with DM experienced menopause at the age of <55 years or could be categorized as early menopause, as many as 55 patients or 83.3%. Most of the history of parity of female cancer patients with DM were multiparous, as many as 56 patients or 84.8%. Judging from the use of contraception, as many as 30 patients or 45.4% used hormonal contraceptives. Most female cancer patients with DM use hormonal contraceptives, namely in the form of birth control pills and injections. More details can be seen in table 6.

Table 6
Characteristics of Aspects of Other Risk Factors for Female Cancer in DM Patients

Variable	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1. BMI							
Underweight	2 (8.3 %)	0 (0%)	2 (14.3 %)	4 (25%)	0 (0%)	0 (0%)	8 (12.1%)
Normoweight	8 (33.3 %)	2 (20%)	7 (50.0 %)	6 (37.5 %)	0 (0%)	1 (100%)	24 (36.4%)

Variable	Breast Ca	Endometrium Ca	Ovarium Ca	Cervix Ca	Vulva Ca	Vagina Ca	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overweight	14 (58.3%)	8 (80%)	5 (35.7 %)	6 (37.5 %)	1 (100%)	0 (0%)	34 (51.5%)
2. Family History							
Exist	9 (37.5%)	0 (0%)	2 (14.3 %)	0 (0%)	0 (0%)	0 (0%)	11 (16.7%)
Not any	15 (62.5%)	10 (100%)	12 (85.7 %)	16 (100%)	1 (100%)	1 (100%)	55 (83.3%)
3. Menopause							
< 55 y.o	19 (79.2%)	10 (100%)	8 (57.1 %)	16 (100%)	1 (100%)	1 (100%)	55 (83.3 %)
>= 55 y.o	0 (0%)	0 (0%)	4 (28.6 %)	0 (0%)	0 (0%)	0 (0%)	4 (6.1%)
Not menopausal	5 (20.8%)	0 (0%)	2 (14.3 %)	0 (0%)	0 (0%)	0 (0%)	7 (10.6 %)
4. Parity							
Primipara	0 (0%)	3 (30%)	2 (14.3%)	1 (6.3%)	0 (0%)	1 (100%)	7 (10.6%)
Multipara	24 (100%)	5 (50%)	12 (85.7%)	14 (87.5%)	1 (100%)	0 (0%)	56 (84.8%)
Nullipara	0 (0%)	2 (20%)	0 (0%)	1 (6.3%)	0 (0%)	0 (0%)	3 (4.5%)
5. Contraceptive History							
Family planning pills	4 (16.7%)	2 (20%)	2 (14.3 %)	0 (0%)	0 (0%)	0 (0%)	8 (12.1%)
Inject	10 (41.7%)	0 (0%)	1 (7.1%)	11 (68.8 %)	0 (0%)	0 (0%)	22 (33.3%)
Non Hormonal	5 (20.8%)	2 (20%)	3 (21.4%)	2 (12.5 %)	1 (100%)	0 (0%)	13 (19.7%)
Not using contraception	5 (20.8%)	6 (60%)	8 (57.1 %)	3 (18.8 %)	0 (0%)	1 (100%)	23 (34.8%)

Discussion

Cancer cases with DM in January 2016-May 2017 were 95 cases or 7.7% of all female cancer cases. 8 cases or 0.7% were cases with a diagnosis of DM after the patient was diagnosed with cancer. The prevalence of long-term and newly diagnosed DM cancer patients is 87 cases or 7.1% of all cancer cases. Previous studies reported that the prevalence of female cancer patients with DM in New York, Italy and Switzerland was 4.3%; 6.7%; and 5.3%, respectively [12,13,5]. The prevalence of cancer with DM in Dr Kariadi Hospital is higher than studies in New York, Italy and Switzerland. This is thought to be related to the fact that Asian countries have a higher prevalence of DM patients than European and American countries [14]. When viewed from the therapy and glycemic control of cancer-DM patients in this study, most of the patients had poor glycemic control and DM therapy was not routinely carried out. So that exposure to metabolic factors that influence the incidence of cancer will also be greater, such as hyperglycemia and chronic inflammatory conditions which are some of the pathogenesis that is thought to underlie the relationship between DM and cancer [8,10].

Judging from the prevalence of each type of cancer, the highest prevalence was in vulvar cancer, followed by vaginal, endometrial, breast, cervical and ovarian cancers. Research by O'Mara et al in 1985 which also showed the highest prevalence of DM-cancer was in vulvar and vaginal cancer, which was 11.9%, followed by breast cancer at 4.3%, ovarian cancer at 3.4% and cervical cancer at 2.6%. High levels of the hormone estrogen in DM patients are thought to be the most important pathogenesis in increasing the risk of vulvar and vaginal cancer because the vulva and vagina are sensitive organs with high estrogen exposure [12]. In addition, vulvar and vaginal cancer is a type of cancer that is closely related to HPV infection [15,16]. Genital warts often occur in DM patients and are difficult to cure. This is thought to be related to the immunocompromised condition which is closely related to DM patients [17]. Bosetti et al in 2012 proved that endometrial cancer has the highest prevalence compared to breast and ovarian cancer, which is 10.2%. Meanwhile, the prevalence of breast cancer is 8.5% and ovarian cancer is 4.4%. Bosetti also proved that patients with diabetes mellitus are at high risk of developing breast and endometrial cancer, but not ovarian cancer [5]. DM is thought to play a very important role in increasing the risk of endometrial and breast cancer due to hyperinsulinemia and its role in IGF, increasing free estrogen levels, chronic inflammation and increasing the risk of genetic mutations [5,13].

Judging from the cancer stage of female cancer patients with DM, most of them, as much as 40.9% were in stage III. This is in accordance with research conducted by Lipscombe et al in 2015 which showed that most breast cancer patients with DM were at an advanced stage, namely at stage II and stage III [18]. Shah et al in their 2015 research also showed that the majority of ovarian cancer patients, or 82.3%, were in stage III [19]. The large percentage of cancer patients with DM who are already at an advanced stage is thought to be related to exposure to metabolic factors such as hyperglycemia, insulin resistance and hyperinsulinemia which can affect the aggressiveness and progression of cancer cells [18]. The delay in diagnosis of cancer in cancer patients is also thought to be related to the high percentage of patients who are already at an advanced stage.

Patients with DM are thought to be more likely to focus on the management of their DM treatment and its complications, thereby overriding the status of other health conditions such as cancer. Lipscombe et al in 2015 in their research also showed that most of the patients who were already at an advanced stage were patients who had long suffered from DM. So that the duration of diabetes mellitus is thought to be related to the progression of cancer cells [18].

Judging from the characteristics of the Diabetes Mellitus aspect, as many as 41 patients or 62.1% were long-term DM patients. Meanwhile, 25 patients or 37.9% just found out that they had DM at the same time as being diagnosed with cancer. Hui Lin Xu et al in 2015 showed that the percentage of cancer patients with a history of being diagnosed with DM was greater than that of cancer patients who had just been diagnosed with DM [20]. Junmei et al in their research in 2012 proved that the risk of cancer is not only present in patients who have been diagnosed with DM, but the risk of cancer is also high in pre-diabetes conditions or conditions where blood glucose levels are high but still below the criteria for the diagnosis of DM [21]. Stocks et al in 2009 proved that abnormal glucose metabolism is associated with an increased risk of cancer [22]. Although long-term DM patients and newly diagnosed DM are both at high risk of developing cancer, the risk of cancer in patients with a history of DM is higher than in patients newly diagnosed with DM [20]. The process of carcinogenesis is a process that consists of several phases and takes years until a cancer diagnosis is established [23].

Insulin resistance occurs decades before the onset of type 2 diabetes. Diabetes often goes undetected and the onset of diabetes is 7 years before the diagnosis is made [24]. Physiologically, the body can overcome insulin resistance that occurs by increasing the amount of insulin secretion so that plasma glucose remains normal. This shows that at the beginning of the onset of DM, hyperinsulinemia will be found. Insulin resistance that occurs gradually and slowly will cause hyperglycemia. When diabetes is diagnosed, it is estimated that the patient has 50% destruction of pancreatic -cell mass and there is an imbalance between insulin secretion and insulin resistance. At this stage, the insulin level in the blood is low [25]. This supports several theories that several pathophysiologies are thought to underlie the increased risk of cancer in DM patients, including chronic hyperglycemia and hyperinsulinemia [10]. The higher risk of cancer in patients with a history of DM compared to patients with newly diagnosed DM indicates that hyperglycemia also plays a role in increasing the risk of cancer in DM patients. The high percentage of cancer patients with DM who only knew about their DM status when diagnosed with cancer was in accordance with Riskesdas data in 2007 which stated that more than 70% of DM patients did not know their DM status or could be said to be underdiagnosed [26].

Judging from the time span between being diagnosed with DM for the first time to being diagnosed with cancer in patients who have been diagnosed with DM before, most of them have a DM–cancer time span of <5 years. The study of Cristina Bosetti et al and Vecchia et al also stated that the time span of DM-cancer in endometrial cancer was mostly <5 years [13,5]. While the time span of DM-cancer in breast cancer differs between the results of the study and the research conducted by Cristina Bosetti et al where most of them were for > 10

years [5]. This difference is thought to be related to the glycemic control condition of most patients who have poor glycemic control so that exposure to cancer-causing factors such as hyperglycemic conditions will also be higher when compared to good glycemic control. It is also thought to be associated with several cancer risk factors, such as a high BMI in most breast cancer patients. There are no studies showing data regarding the time span of DM-cancer in patients with ovarian, cervical, vulvar and vaginal cancer.

The age at which DM was first diagnosed was mostly over 40 years old, as many as 64 patients or 97%. This is in accordance with a study conducted by Vecchia et al which showed that most cancer patients with DM were diagnosed with DM for the first time at the age of 40 years or older. This shows that the majority of cancer patients with diabetes mellitus are patients with type 2 diabetes [5]. Type 2 diabetes mellitus is characterized by long-term hyperinsulinemia at early onset, insulin resistance, and progressive hyperglycemia. Type 2 DM is also closely related to obesity which is also a risk factor for cancer [27].

Most cancer patients with DM undergo DM therapy. However, 26 patients or 39.4% of them did not routinely consume the therapy used. This condition is in accordance with laboratory data on HbA1c levels which show that most of the patients or as many as 31 patients (47%) had HbA1c levels of more than 7%, or could be said to be uncontrolled. HbA1c levels are used to assess the quality of long-term glycemic control and assess the effectiveness of therapy in patients with DM [5]. The high percentage of HbA1c levels supports the theory that one of the pathophysiologies underlying the increased risk of cancer in DM patients is chronic hyperglycemia. Hyperglycemia is thought to stimulate cancer directly by activating signaling pathways that affect cell proliferation, apoptosis and metastasis [8]. Stocks et al in 2009 proved that abnormal glucose metabolism is associated with an increased risk of cancer [22]. Hope et al in 2015 in their study showed that increased levels of HbA1c were associated with an increased risk of gynecological cancer [28]. Travier et al and Miao Jonasson et al in their research showed that there was an increased risk of breast cancer in DM patients with high HbA1c levels [5].

DM therapy used by cancer patients with DM is mostly combination therapy, namely metformin, glimepiride and exogenous insulin. Hyperinsulinemia is one of the pathogenesis that is thought to underlie the incidence of cancer in DM patients through stimulation of insulin receptors and insulin like growth factor-I (IGF-1) receptors [8]. DM therapy that can increase insulin levels in the blood is thought to also play a role in the incidence of cancer. Onitilo et al in 2014 stated that therapies that increase insulin levels, such as exogenous insulin, insulin analogues, and insulin secretagogues tend to increase the risk of cancer. Meanwhile, therapies that lower blood insulin levels, such as metformin, tend to reduce the risk of cancer [27]. The theory is different from the research results obtained. Only a small proportion of cancer patients with DM were using exogenous insulin therapy and insulin secretagogue monotherapy. Most patients actually use combination therapy, where metformin or an insulin sensitizer is thought to reduce the incidence of cancer. Judging from the adherence to taking medication, most of the patients in this study were not routinely taking medication. So the results of this study are not strong enough to support the

theory that some DM therapy is one of the factors that increase the risk of cancer in DM patients. This study is supported by research conducted by Lorraine et al in 2006 which stated that insulin therapy, insulin secretagogue or insulin sensitizer did not increase the risk of cancer [29]. Overall, the association between DM therapy and cancer risk is considered not to have strong evidence and is still controversial [9].

The results showed that the age at which cancer was diagnosed, the most of the six types of cancer, namely at the age of more than 50 years. This is in accordance with the existing theory, that one of the risk factors for cancer is old age (> 50 years) [30,31,32,15]. Bosetti et al in their 2012 research also stated that as many as 77% of cancer patients with DM were aged 60 years and over [5]. Old age is closely related to the reduced ability of immune cells to fight pathogens and prevent tumor formation. This condition causes older people to be more at risk of developing cancer [33]. Obesity, family history, history of parity, menopause and history of contraceptive use are some of the risk factors for female cancer [30,32,31,34,15,16]. Based on the results of the study, most cancer patients with DM had an overweight body mass index according to the WHO classification for Asia. A total of 34 patients or 51.5% had BMI Overweight. Obesity is one of the risk factors for cancer, because in this condition there will be an increase in long-term estrogen exposure from the conversion of androstenedione to estrone derived from fat tissue [35]. This shows that most cancer patients with DM have risk factors for excess BMI. Research conducted by Kentaro Shikata et al in 2013, more than 80% of DM patients had an overweight BMI. Obesity is one of the confounding factors between DM and cancer. Diabetes mellitus and obesity are both characterized by high blood insulin levels and a high incidence of cancer. Thus, it will be difficult to find a relationship between DM and cancer because DM and obesity go hand in hand [4].

Judging from the family history, as many as 55 patients or 83.3% of female cancer patients with DM did not have a family history of cancer. The results of previous studies also showed that most of the patients with breast, endometrial and cervical cancer had no history of cancer in their family [36,37,38]. The low percentage of cancer patients with DM without a family history of cancer theoretically has several possibilities. This can happen if women who have a family history of cancer are more likely to maintain a healthy lifestyle. In contrast, women who do not have a family history of having an unhealthy lifestyle such as eating fatty foods and high in exposure to carcinogenic substances. As has been stated that genetics is not the only risk factor for cancer, but many things can trigger cancer [36]. So it can be concluded that most cancer patients with DM do not have a family history of cancer, as a risk factor for cancer.

Menopausal history of cancer patients with DM is mostly early menopause, namely menopause that occurs before the age of 55 years. The risk of female cancer will increase if there is a delay in menopause (menopause at the age of> 55 years) because in this condition women will be exposed to endogenous estrogen exposure for a longer time than women with early menopause [35,32,31]. This shows that the delay in menopause, which is one of the risk factors for cancer, is mostly not found in cancer patients with DM. Most of the parity history of female cancer patients with DM was multiparous, as many as 56 patients or 84.8%. The

risk of female cancer will be reduced in women who give birth and breastfeed. This happens because exposure to endogenous estrogen will decrease in women who have given birth and breast-feed [30,39]. Previous research has shown that most female cancer survivors have multiparity parity [36]. This shows that most cancer patients with DM do not have a history of poor parity, as a risk factor for cancer.

A total of 38 patients or 57.6% of female cancer patients with DM used hormonal contraceptives (injection and birth control pills). Previous research showed that the use of hormonal contraceptives had a significant relationship with the incidence of breast cancer in women at Dr Soetomo Hospital in 2013. The use of hormonal contraception can cause increased exposure to the hormone estrogen in the body [40]. Other studies have also reported an association between the use of hormonal contraception and the incidence of cervical cancer [41]. In breast cancer, most of the patients used injectable contraception, which was 41.7%. This is in accordance with the previous theory which showed that DMPA injection contraceptives could increase the risk of breast cancer [42]. This shows that most cancer patients with DM have one of the risk factors for cancer, namely the use of hormonal contraception.

Conclusion and Suggestion

Conclusion

The prevalence of female cancer with DM at Dr Kariadi Hospital Semarang in January 2016-May 2017 was 87 cases or 7.1%. The highest prevalence is in vulvar cancer. The cancer stages of female cancer patients with DM are mostly at an advanced stage, namely stages II and III. The characteristics of the DM aspect include that most patients have been diagnosed with DM before being diagnosed with cancer, the age when DM was first diagnosed, most of them were > 40 years old. Most cancer patients with DM are not routinely taking therapy and have poor glycemic control. The type of DM therapy that is mostly used by cancer patients with DM is combination therapy. Risk factors for cancer, which are mostly owned by cancer patients with DM, include obesity and the use of hormonal contraception.

Suggestion

It can be further investigated the relationship between DM and the incidence of cancer using more accurate research methods, such as the cohort method in order to find out the major risk factors. Writing more detailed and complete medical records at Dr. Kariadi Hospital, Semarang.

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