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Epidemiologic and Clinical Profiles of Uterine Cancer in the Gharbiah Province of Egypt

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Epidemiologic and Clinical Profiles of Uterine Cancer in the Gharbiah Province of Egypt

By

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A DISSERTATION

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achievement would not have been possible without them, and I dedicate this milestone to them.

Abstract:

Epidemiologic and Clinical Profiles of Uterine Cancer in the Gharbiah Province of Egypt

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Background: Uterine cancer is one of the top-ranking cancers of women with wide international variations in incidence rates. Egypt has a lower incidence of uterine cancer than other countries in the Middle East. In addition to the international incidence variation, there are also wide variations in incidence by rural and urban areas within countries. Therefore, this research project focused on the Gharbiah province, north of Cairo in the Nile Delta, with the aims of investigating demographic and clinical characteristics of uterine cancer, assessing rural/urban variation in incidence rates, and evaluating the possible role of hysterectomy in under-estimating the disease incidence in this population.

Methods: Uterine cancer data of 660 cases were obtained from the Gharbiah Population-based Cancer Registry in Gharbiah, Egypt during the period 1999-2010. The hysterectomy data of 1040 cases were abstracted from the main pathologic labs over the entire region. The Egypt 2006 data census was used to determine the total population of Gharbiah and the rural and urban subgroups. Crude, age-standardized (ASR), and age-specific rates were calculated and associated with demographic and clinical characteristics of patients. The uterine cancer incidence pre- and post- adjustment for hysterectomy prevalence were compared and 95% confidence intervals (CIs) were calculated.

Results: The results confirmed the low ASR of uterine cancer in Gharbiah, [4.1 per 100,000 (95% CI: 3.8-4.4)]. The incidence rate significantly increased over the 12-year period. The ASR was 2.5 times higher in urban areas compared to rural areas (6.9 and 2.8 per 100,000), in urban and rural areas, respectively. The prevalence of hysterectomy did not have a significant impact on the uterine cancer incidence rate.

Conclusions: The study confirmed the low incidence rate of uterine cancer in the Gharbiah province of Egypt and a statistical significant increase in incidence in recent years. Although, the rate of uterine cancer in this population increased over the past decade, it is still lower than the corresponding global rates. The lack of evidence about the possible role of hysterectomy in lowering of uterine cancer rates adds to the need for research to identify the apparent protective factors for uterine cancer in this population.

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List of Abbreviations

AJCC	American Joint Committee On Cancer
ASR	Age-Standardized Rate
BMI	Body Mass Index
CAPMAS	Central Agency For Public Mobilization And Statistics
CI	Confidence Interval
EDHS	Egyptian Demographic And Health Survey
EIC	Endometrial Intraepithelial Carcinoma
FIGO	Federation International De Gynecology And Obstetrics
FSH	Follicle–Stimulating Hormone
GCS	Gharbiah Cancer Society
GPCR	Gharbiah Population-Based Cancer Registry
HNPCC	Hereditary Non Polyposis Colorectal Cancer
HRT	Hormone Replacement Therapy
IARC	International Agency For Research On Cancer
ICD-O	International Classification Of Diseases For Oncology
IGF-1	Insulin-Like Growth Factor 1
IRR	Incidence Rate Ratio
LH	Luteinizing Hormone
MECC	Middle East Cancer Consortium
MMMT	Malignant Mixed Mullerian Tumor
NCCN	National Comprehensive Cancer Network
NOS	Not Otherwise Specified
RR	Relative Risk
SES	Socioeconomic Status
SHBG	Sex Hormone Binding Globulin
TVUS	Transvaginal Ultrasonography
WHO	World Health Organization

Chapter 1:

Background

Anatomy and Histology of Uterus:

The uterus is the female muscular organ that lies in the pelvic area between the urinary bladder and the rectum. It has a pear shape and it goes through different developmental phases during women's life based on hormonal changes during the menstrual cycles. The most important role of the uterus is childbearing and reproduction. The uterus consists of three anatomical parts, the fundus, which is the upper part that has a dome shape, the corpus, the middle part that involves the body of the uterus, and the cervix uteri that is the distal part of the uterus. From a histologic standpoint, the uterus has two layers, the inner glandular layer that is called the endometrium and the outer muscular layer that is referred to the myometrium.

Physiology and Hormonal Changes:

The uterus undergoes regular monthly changes during menstrual cycles occurring throughout the childbearing period based on the fluctuations in blood hormonal levels. The menstrual cycle is usually about 28 days and has two phases. The first phase is known as the follicular or proliferative phase in which ovarian follicles develop and the second phase is known as the luteal or secretory phase in which the remaining ovarian follicles turn into a corpus luteum. The production of estradiol by the ovarian follicles initiates the Luteinizing Hormone (LH) surge, which is followed by ovulation. The LH subsequently induces the formation of the progesterone by the stimulation of luteinization of the granulosa cells in the ovary. Progesterone later enhances the follicle–stimulating hormone (FSH) surge. The luteal phase lasts for 14 days and ends by the menses that

lasts for approximately 4-6 days. The occurrence of pregnancy will maintain the progesterone and estrogen in high levels. [1,2]

Types of Uterine Cancer:

There are two types of uterine cancer based on the origin of the tumor. The first type is endometrial cancer that arises from the inner layer of the uterus and represents about 90% of all uterine cancers. Because the majority of uterine cancers are endometrial in origin, uterine cancer is usually referred to as endometrial cancer in most of the literature. The second type of uterine cancer is sarcoma that arises from the muscular (myometrium) or the supportive tissue of the uterus and represents about 8% of uterine cancer. [3] Other rare types of uterine cancer include malignant mixed Mullerian tumor, (MMMT). [4,5]

Pathologic Subtypes and Genomic Classification of Uterine Cancer:

Based on the sensitivity of the uterine tissue to hormones, endometrial cancers are classified into Type 1 and Type 2 tumors. Type 1 tumors are hormone-sensitive lesions influenced by high levels of estrogen while Type 2 tumors are less-driven by estrogen. Type 1 tumors constitute about 80% of endometrial cancers and are usually diagnosed at lower stages than Type 2 tumors. Type 2 tumors, represent 10% of endometrial cancers and are diagnosed at late stage and have high rates of recurrence. [6] In addition, based on the cell of origin, endometrial cancer could be classified into 7 subgroups: 1) endometrioid (75%–80%) which includes ciliated adenocarcinoma, secretory adenocarcinoma, papillary and villoglandular and adenocarcinoma with squamous differentiation; [7] 2) uterine papillary serous (<10%); 3) mucinous (1%); 4) clear cell (4%); 5) squamous cell (<1%); 6) mixed (10%); and 7) undifferentiated. [8,9] Therefore, all

cancer cell types that are not driven by estrogen and have poor differentiated carcinoma are classified as Type 2 endometrial cancers that include papillary serous carcinoma, clear-cell carcinoma, undifferentiated carcinoma, and grade III endometrioid carcinoma.[10]

Based on genomic studies, endometrial cancer is classified into 4 subtypes, POLE ultramutated, microsatellite instability hyper-mutated, copy-number low, and copy-number high. [11] There is a potential that the recent genomic classification has important value in prognostic and therapeutic implications. [11-13] Table1 shows the different characteristics of different types of endometrial genomic subtypes.

Table 1: Characteristics of four genomic classes of endometrioid and serous carcinomas

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/MLH1 methylation	Mixed MSI high<comma> low<comma> stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232 × 10−6 mutations/Mb)	High (18 × 10−6 mutations/Mb)	Low (2·9 × 10−6 mutations/Mb)	Low (2·3 × 10−6 mutations/Mb)
Genes commonly mutated (prevalence)	POLE (100%) PTEN (94%) PIK3CA (71%) PIK3R1 (65%) FBXW7 (82%) ARID1A (76%) KRAS (53%) ARID5B (47%)	PTEN (88%) RPL22 (37%) KRAS (35%) PIK3CA (54%) PIK3R1 (40%) ARID1A (37%)	PTEN (77%) CTNNB1 (52%) PIK3CA (53%) PIK3R1 (33%) ARID1A (42%)	TP53 (92%) PPP2R1A (22%) PIK3CA (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumor grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grades 1 and 2	Grade 3

Progression-free survival	Good	Intermediate	Intermediate	Poor
Reprinted from The Lancet Oncology, Murali,R., Soslow,R.A., Weigelt,B, Classification of endometrial carcinoma: more than two types, Copyright (2014), with permission from Elsevier[14]				

Pathogenesis of Uterine Cancer:

Type 1 and type 2 tumors have different pathogenesis. Type 1 tumors are believed to result from high and long exposure to estrogen that increases the probability of occurrence of atypical hyperplasia that precedes the development of Type 1 endometrial cancer. [6] This type of cancer is usually found in premenopausal young patients compared to Type 2 of endometrial cancer that occurs mainly in postmenopausal women. The hormonal and genetic mutations and abnormalities could influence the pathogenesis of this type. This includes microsatellite instability, K-ras and PTEN mutations, and defects in DNA mismatch repair. [15-17]

Although, the molecular pathway of developing type 1 is not clear, tumor suppressor gene (PTEN) expressions are identified in the endometrium after prolonged exposure to high estrogen levels. [6]

Mutations in the p53 gene are believed to play important role in Type 2 endometrial cancer. The mutations in the p53 gene are found in 80-90% of endometrial intraepithelial carcinoma (EIC). [18] EIC is the precursor of serous carcinoma (Type 2). [18,19]

The distribution of genetic mutations observed in Type 1 and type 2 tumors in different studies is illustrated in table 2 that summarized the result from a review article.

Table 2: Percentages of Genetic Alteration among the two types of Endometrial Cancers

Genetic Alteration	Type 1 Tumor	Type 2 Tumor
PTEN inactivation	Up to 83%	11%
PIK3CA mutation	26–36%	5%
KRAS mutation	10–30%	0–10%

β-catenin /CTNNB1 mutation	14–44%	0–5%
Microsatellite instability	20–45%	0–11%
p53 mutation	10–20%	90%
HER2/neu amplification	10–30%	18–80%
p16 inactivation	10%	40–45%
E-cadherin loss	10–20%	60–90%
Adapted from "Molecular Profiling of Endometrial Malignancies" by Samarnthai N, Hall K, Yeh IT., 2010, Obstetrics and Gynecology International.[20]		

Tumor Staging and Grading System:

There are two main systems used for endometrial cancer staging: the Federation International de Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer (AJCC). Both systems represent surgical staging that is based on characteristics of the resected tissue from the surgical procedures. Both systems were established based on the Tumor size (T), Lymph Node involvement (N) and tumor Metastasis to other organs (M). The differences between the two systems are that FIGO does not include stage 0 anymore. The most recent updated versions of these two systems consider pathologic and surgical criteria for staging.[21-23] The FIGO staging was last revised in 2009 and the AJCC was last revised in 2016.[24] However, the FIGO staging is the most commonly used in clinical practice and research (Table 3 and 4).[25]

Table 3: Staging uterine carcinoma: TNM and International Federation of Gynecology and Obstetrics (FIGO) Classification Systems.

Primary tumor (T) (surgical-pathologic findings)		
TNM categories	**FIGO stages**	**Definition**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (pre-invasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)		
TNM categories	**FIGO stages**	**Definition**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Distant metastasis (M)		
TNM categories	**FIGO stages**	**Definition**
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes intraperitoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa.)
Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer New York, Inc.[24]		

Table 4: staging of uterine sarcoma FIGO and TNM Systems:

Leiomyosarcoma and Endometrial Stromal Sarcoma Primary tumor (T)		
TNM categories	**FIGO stages**	**Definition**
Leiomyosarcoma and endometrial stromal sarcoma		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III¶	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum
Adenosarcoma		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor limited to the endometrium/endocervix
T1b	IB	Tumor invades to less than half of the myometrium
T1c	IC	Tumor invades more than half of the myometrium
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III¶	Tumor involves abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum
Regional lymph nodes (N)		
TNM categories	**FIGO stages**	**Definition**
Leiomyosarcoma and endometrial stromal sarcoma		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis
Adenosarcoma		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis
Distant metastasis (M)		

TNM categories	FIGO stages	Definition
Leiomyosarcoma and endometrial stromal sarcoma		
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)
Adenosarcoma		
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)
Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer New York, Inc.[24]		

Symptoms and Diagnosis of Uterine Cancer:

Uterine cancer has early symptoms compared to other types of gynecological cancers. About 90% of women diagnosed with uterine cancer presented with abnormal vaginal bleeding. [26] It is the most common symptom that can lead to early diagnosis. [6]

The diagnosis of uterine cancer can be established based on the histologic examination of uterine specimens. The uterine specimens can be obtained through different methods with different accuracy. Table 5 shows the accuracy of different methods used. In addition, some non-invasive methods like transvaginal ultrasound can be used for diagnosis.[27]

Table 5: Accuracy of endometrial histologic methods for diagnosing neoplasia.

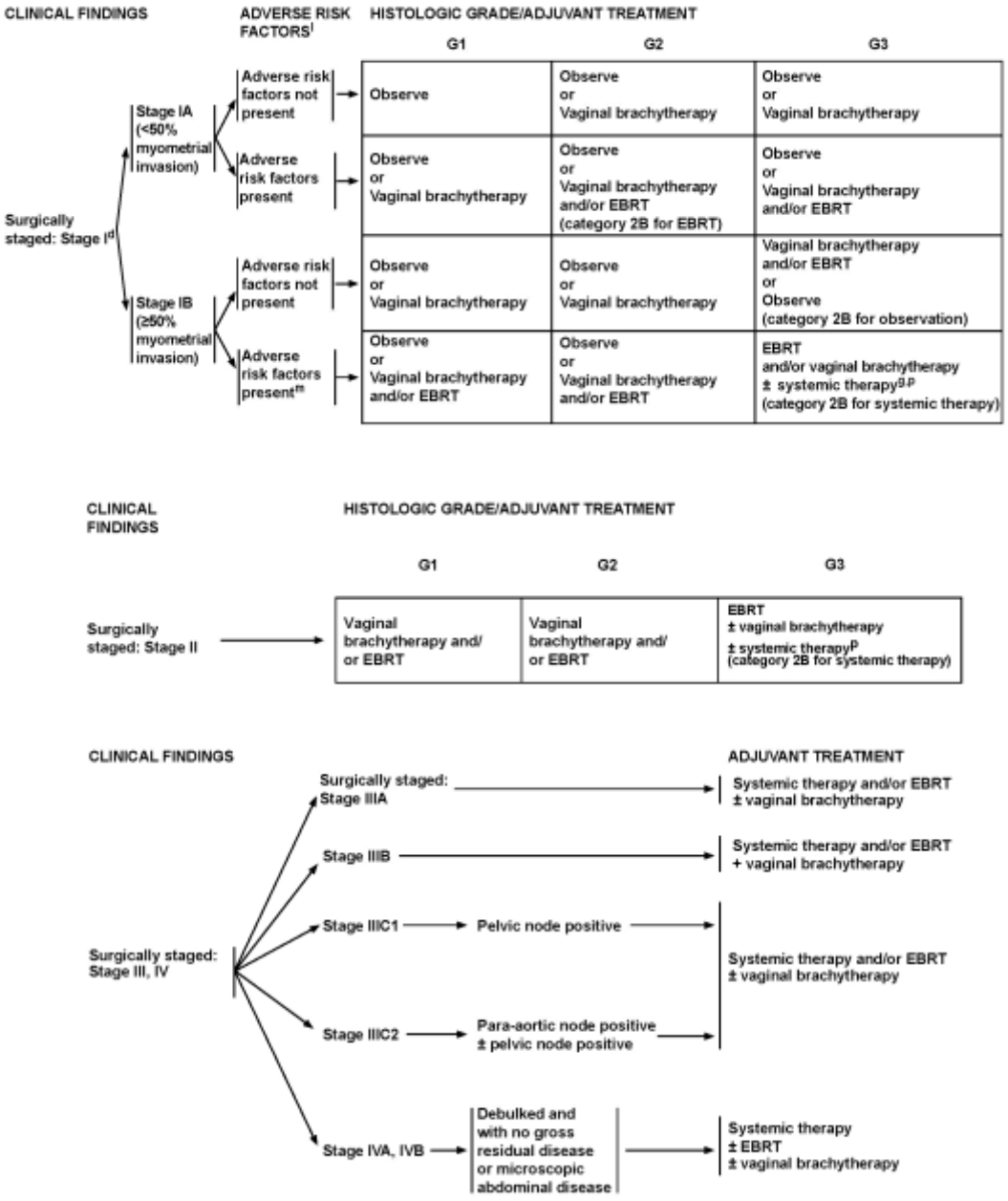
Method	Diagnostic Accuracy (%)	Tissue Insufficient for Diagnosis (%)
Aspiration		
Pipelle	95–98	9
Endocell	95–98	11
Vabra	95–98	26
Isaacs cell sampler	95–98	30
Pistolette	95–98	13
Brushing		
Endoscann	100	36
Biopsy		
Kevorkian	97	10

Accuracy of endometrial histologic methods for diagnosing neoplasia. Adapted from "Endometrial Hyperplasia and Neoplasia: Definition, Diagnosis, and Management Principles," by Mutter, G, Ferenczy, A, 2008, Glob Libr Womens Med, [28]. Reprinted with permission.

Treatment of Uterine Cancer:

Usually the first option of treatment of uterine cancer is surgery. The surgery of removing the uterus is called hysterectomy. The surgery may include some other organs. Hysterectomy with salpingo-oophorectomy will remove the uterus, fallopian tubes, and ovaries. Radical hysterectomy will include the removal of the uterus, fallopian tubes, ovaries, and cervix. The surgery may include removing regional lymph nodes. Based on the cancer type and the condition of the patient surgery may combine with adjuvant therapy to kill the remaining cancer cells in the body. This includes the chemotherapy, radiation therapy and hormonal therapy. Figure1 shows the different modalities that can be used to determine the treatment types for endometrial cancer patients based on National Comprehensive Cancer Network (NCCN) Guideline Version 1.2017.

Figure 1: Treatment options for uterine cancer based on the surgical stages



Adapted from NCCN Clinical Practice Guidelines in Oncology (Uterine Neoplasms), National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2017, (www.nccn.org).

Risk Factors

There are different factors that may play role in increasing the risk of uterine cancer. It includes age, low parity, family history of uterine cancer, obesity, diabetes mellitus, hormone replacement therapy, tamoxifen and age of menarche and menopause.

Age:

Since the majority (approximately 80%) of uterine cancers are diagnosed among postmenopausal women, older age is a risk factor for endometrial cancer. The peak age-specific incidence rate in the U.S. and globally is in the age groups of 50-65 years. [29,30]

Parity:

Women with low parity are known to be at higher risk for uterine cancer compared to women with high parity. A meta-analysis study that included 69,681 patients from ten prospective studies, 35 case control studies and one pooled analysis have confirmed the significant inverse relationship of the parity with uterine cancer (RR= 0.69 and 95% CI 0.65-0.74). Furthermore, it confirms that the risk is decreasing with high number of the parity. Nulliparous carries a strong risk for uterine cancer. [31] However, some factors related to the infertility that associated with the nulliparity may influence the endometrial cancer e.g. (polycystic ovary syndrome). [32] Furthermore, short intervals between pregnancies and until menopause and high parity are associated with reduced risk for uterine cancer. [33-35]

Family History and Genetic Disorder:

Research studies have shown a positive association between family history of uterine cancer and increased risk in unaffected female relatives. The odds ratio has been estimated as 2.1 to 2.8 in different studies. [36,37] However, some studies found that women

with family history of uterine cancer will have only small risk for uterine cancer. [38,39] In addition, hereditary non-polyposis colorectal cancer (HNPCC) syndrome carries higher risk for unaffected female family members. [40,41]

Obesity:

There are different ways to determine the obesity. However, the body mass index (BMI) was recognized and adopted by many accredited agency such as World Health Organization (WHO) and American Heart Association (AHA). [42,43] The adult normal weight considered when (BMI ≥18.5 to 24.9 kg/m^2), overweight when (BMI ≥25 to 29.9 kg/m^2), obesity when (BMI of ≥30 kg/m^2) and severe obesity when BMI ≥40 kg/m^2). [42,43] There has been a consistency among several studies that linked uterine cancer to obesity. The relative risk of uterine cancer associated with the obesity was ranging from 2 to 10 in many studies using different types of measurement e.g. BMI, [44-49] body weight, [38,50-52] waist-to-thigh circumference ratio, [53] and waist-to-hip circumference ratio. [54,55] While the risk found to be high and consistent in the postmenopausal women, some study skeptical about the association of obesity and uterine cancer in premenopausal women.[37]

Obesity and overweight can lead to insulin resistance, ovarian androgen excess, anovulation, and chronic progesterone insufficiency in premenopausal women. [49] In postmenopausal women, conversion of the androgens in the adipose tissue through the aromatization can also lead to higher levels of circulating estrogens. These variations in estrogen levels may affect the cells of breast and endometrium by preventing apoptosis and stimulating angiogenesis by increasing cellular proliferation. [56]

Diabetes Mellitus:

Glycemic load is considered a probable factor that may increase the risk of uterine cancer. [57-59] However, some studies claim that the risk is linked to the comorbidity of obesity. [60,61] Different studies found the risk of diabetes was independent with RR= 2.0, 95% CI (1.1-3.6). [50]

There are different mechanisms that explain the potential effect of hyperglycemia on uterine cancer. The long period of hyperglycemic exposure can lead to increases in insulin-like growth factor 1 (IGF-1). IGF-1 enhances the cells growth, decreases cell death, and stimulates cell duplication of uterine cancers. [59,62] Moreover, oxidative stress can be increased by the glycemic overload which triggers uterine cancer. [56]

Hormone Replacement Therapy (HRT):

HRT is frequently used by women in developed countries to treat menopausal symptoms. It is taken to treat the deficiency in the circulating estrogen and progesterone hormones in postmenopausal women. A meta-analysis study that included 30 studies concluded that the RR was 2.3 (95% CI 2.1-2.5), in women using estrogen compared to the nonusers. In addition, women using estrogen for 10 or more years could increase the relative risk to 9.5. However, the risk of uterine cancer was decreased when estrogen combined with progestin. [63,64] However, the Women's Health Initiative has concluded that the risk of using combined estrogen plus progestin was exceeding the benefit.[65]

The HRT (unopposed estrogen) induces the mitotic stimulation of the endometrium with partial shedding. [66] The adding of the progesterone will alleviate the effect of the estrogen by neutralizing the receptor of estrogen and enhance the process of the estradiol metabolisation. [67]

Tamoxifen:

Tamoxifen is a trans-isomer of a triphenylethylene derivative drug that used to prevent and treat breast cancers that are hormone-receptor positive. It prevents the estrogen to bind with the receptor by attaching with the hormone receptor in the cancer cell. Several studies revealed that the odds ratio of the association of Tamoxifen use and uterine cancer was ranging from 2.5 to 9.5 based on the duration of usage of Tamoxifen. [68-72] However, another study has criticizing the association of Tamoxifen and uterine cancer since the biases may affect their inferences. [73]

Tamoxifen works as anti-estrogen on breast tissue, however it works as an estrogen on the endometrium. [74] Therefore, Tamoxifen enhances the estrogenic effect on the endometrium which leads to growth of the lining layer of uterus and increases the risk of developing cancer. [74]

Age of Menarche and Menopause:

Age of menarche and menopause has been associated with the risk of endometrial cancer in different studies. Girls with early age of menarche i.e. before age 11 or 12 have a high risk of uterine cancer with the RR ranging between 1.5 to 5. [38,44,46,50] Longer periods between menarche and menopause have been associated with a higher risk of endometrial cancer and shorter periods have been associated with reduced risk. [38,44,46,75]

The mechanism of increasing risk have been associated with longer periods of exposure to estrogen and related enhancement of proliferative factor that lead to endometrial cancer.[76]

Protective Factors

Some factors have been found to be protective against uterine cancer. These factors included contraceptive hormones, smoking, physical activates and coffee.

Contraceptive hormones:

Contraceptive hormones are synthetic estrogen and progestin hormones that are used to prevent the pregnancy. They can be administered in different forms e.g. oral pill, skin patch or an implant. [77] They have been reported in several studies including a meta-analysis study involved more than 27,276 women that the using of oral contraceptive drugs showed a decline the uterine cancer by 30%.[37,78-81] The protective effect of these types of drugs were increased simultaneously with the increasing of usage duration.[81] The protective effect of the hormonal contraceptive drugs resulted from the suppression effect of progestin on the endometrial proliferation. [82,83]

Smoking:

Although cigarette smoking is well-known to be harmful to health, it has been linked to reduction in uterine cancer risk that was confirmed by a meta-analysis. [84] However, these benefits were not conclusive since some studies limit the protective effect on the current but not the ex-smokers. [85,86] In contrast, another study claims that the ex-smokers have greater protective effect. [87]

The protective effect is believed to be due to the enhancement effect of smoking on estrogen metabolism in the liver, which reduces the risk of uterine cancer development. [88] In addition, smoking women may reach the age of menopause earlier than non-smokers and consequently have less exposure to estrogen. [89]

Physical activity:

Some studies found that limited physical activity increases the risk of uterine cancer, after adjusting for obesity and caloric intake. [90,91] However, some studies claimed that reduction of uterine cancer risk is not directly attributed to the physical exercise. [92] Physical activity has been suggested as a possible protective factor for uterine cancer since it enhances body oxygen uptake and regulates and maintains body metabolism that could in turn minimize insulin levels and reduce insulin resistance as well. [93] Moreover, physical activity can reduce estradiol levels by increasing sex hormone binding globulin (SHBG) and ultimately reduce uterine cancer risk. [94] Therefore, physical activity reduces estradiol by enhancing estrogen metabolism or indirectly by reducing body fat stores. [95]

Coffee:

A consensus among many studies showed that coffee consumption has a protective effect against uterine cancer. [96-101] A two meta-analysis studies published in 2008 and 2012 concluded a significant protective effect of coffee consumption against uterine cancer. [102,103]

Coffee has strong antioxidant effect through enhancing insulin sensitivity and increasing SHBG levels. [100,103] In addition, promoting estradiol elimination and preventing estradiol-mediated carcinogenesis of uterine cancer cells could result from enhanced liver enzymes as an effect of caffeine and bioactive compounds of the coffee.[100]

These risk and protective factors for uterine cancer have different magnitudes of risk which are presented in Table 6, as adapted from the American Cancer Society Guidelines for Early Uterine Cancer Detection[88,104,105] However, these risk and protective factors

may not be applicable to all populations since all of these studies were conducted in Western and East Asian countries.

Table 6: Relative risk of demographic, hormonal, medical and lifestyle related to uterine cancer

Risk factor	Relative risk (RR)
Aging	Women 50- to 70-years-old have a 1.4 percent risk of endometrial cancer
Unopposed estrogen therapy	2 to 10
Tamoxifen therapy	2
Late menopause (after age 55)	2
Nulliparity	2
Polycystic ovary syndrome (chronic anovulation)	3
Obesity	2 to 4
Diabetes mellitus	2
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	22 to 50 percent lifetime risk
Cowden syndrome	13 to 19 percent lifetime risk
Physical activity	0.73 to 0.75
Coffee	0.64 to 0.87
Reproduced with permission from: Canto MI. Chromoendoscopy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on 01/04/2017.) Copyright © 2017 UpToDate, Inc. For more information visit www.uptodate.com. [88,104]	

Screening of Uterine Cancer:

Unfortunately, there is no efficient or cost-effective way for population screening for uterine cancer. [4] However, transvaginal ultrasonography (TVUS), endometrial aspiration biopsy and endometrial curettage can help in early detection of uterine cancer in women with high risk. [104,106] Because of the periodic variations in endometrium thickness in premenopausal women, screening and early detection of cancer are difficult in this age group. Therefore, TVUS in the premenopausal is not sensitive while it has the same sensitivity of endometrial biopsy in the postmenopausal women. [107,108]

Global Epidemiology of Uterine Cancer:

Global and the U.S Epidemiology of Uterine Cancer

Global Incidence & Mortality

According to 2012 Globocan, uterine cancer was ranked as the fifth most common cancer for women worldwide after breast, colorectum, cervical, and lung cancers. [109] The global average age-standardized incidence and mortality rates of uterine cancer were 8.2 and 1.8 per 100,000, respectively. The uterine cancer has different incidence distribution in different regions of the world. It is the most common gynecologic malignancy in developed countries, whereas it is the second most common gynecologic malignancy in developing countries after cervical cancer. [109] In general, high-income countries show high incidence of uterine cancer while low-income countries have a low incidence of the disease. [110] For example, North America and Central and Eastern Europe have the highest incidence of uterine cancer in the world. [109]In contrast, some regions in Africa show the lowest incidence rates in the world. [110-112] The world mortality ASR was 1.7 in 2012. The mortality ASR of uterine cancer has some variations across the world. The WHO European Region has the highest mortality rate of 2.6 per 100.000 followed by the Americas WHO Regional Office with 2.0 among all six WHO regions, the lowest mortality ASR of 1 per 100.000 was reported in the WHO Region of the South East Asia. [113] The survival rate of uterine cancer in high-income countries is higher than the rate in lower income countries. [112] For example, the five-year survival rate in the U.S was 89% and in all developed countries was 82% compared to 61% in Sub-Saharan Africa and 67% in all developing countries.[112]

The variations in uterine incidence and mortality rates across the world can be explained by differences in exposure to risk factors and different levels of access to health care. For example, low parity and obesity are common in Western women. The use of Tamoxifen and oral estrogen replacement therapy are higher in developed countries compared to developing countries. Early diagnosis of uterine cancer in high-income countries due to better access to healthcare and receiving the appropriate treatment have resulted in a good survival rates. On the contrary, late presentation of the disease with limited access to diagnostic and treatment facilities may explain the poor survival rate of uterine cancer in low-income countries.

U.S. Incidence & Mortality

Uterine cancer is the 4th most common type of female cancer in the United States after breast, lung and colorectal cancers. In 2013, the age-standardized incidence and mortality rates were 26.4 and 4.6 per 100,000, respectively. The uterine cancer incidence rate in the U.S. peaked in 1970 followed by a steady decline through the 1980s. [30] Between 1992 and 2002, the incidence rate was fairly steady (24.4 to 24 per 100,000), but the rate has slightly increased since 2002. The incidence rate trend is similar for both younger (20-49 years) and older (50+ years) population. The incidence rate of uterine cancer is higher among white women compared to African-American and Hispanic women while the mortality rate was lower among white women compared to African-American and Hispanic women.[114-118]

Egypt Overview:

Egypt Health System

Egypt is one of the highest populated countries in North Africa. In 2013, the projected population of Egypt was 86 million, 50% of them were below 25 years of age. About 97% of the populations live in 4% of the total area of Egypt. [119,120] The health care system in Egypt is managed and financed by different sectors. This includes public government sectors which include ministries of health, education, the military, and police. In addition, non-governmental organizations, clinics runs by faith based facilities and private health sectors, play an important role in health services. Egypt has a wide spread infrastructure of primary health care clinics within 3 kilometers of any residential area in the country.[119]

Gharbiah Population Cancer Registry:

In the Gharbiah province a population-based cancer registry was founded in 1998 as a project of the Middle East Cancer Consortium. The registry covers the Gharbiah province in the center of Nile delta, an area of 1,948 Km and a population of 4,011,320. The registry is located in Tanta city. The registry aims to employ an active registration from all the clinics, labs and hospitals of the provinces and from death certificates.

Uterine Cancer in Egypt

In 2012, the age-standardized incidence rate of uterine cancer in Egypt was 3.8 per 100,000 compared to the global incidence of 8.2 per 100,000. [109] Uterine cancer was ranked as the ninth most common cancer of women in Egypt. The initial report of the Middle East Cancer Consortium (MECC) for the period 1996-2001 showed that Egypt has the lowest incidence of uterine cancer in the region. The incidence rate of uterine cancer was lowest in Egypt 3.5 per 100.000 compared to other populations such as Israeli

Jews (13.8 per 100.000), Cypriots (11.8 per 100.000), Israeli Arabs (8.7 per 100.000), and Jordanians (5.8 per 100.000). [121] In addition, the low stage at diagnosis of uterine cancer is high compared to other female cancers in Egypt. With urbanization, life style changes are increasing the risk of various types of cancer including hormonally driven cancers such as uterine cancer. Although the risk of uterine cancer is believed to be relatively low in Egypt, there seem to be considerable geographic variations in the incidence rate of uterine cancer.

According to a study from the Gharbiah Cancer Registry, the incidence of gynecological cancer (ovary, uterine, and cervical) was higher in urban than in rural areas. [122] Uterine cancer showed the highest urban–rural incidence rate ratio (IRR = 6.07, 95% CI = 4.17, 8.85). Also in the advanced age group of urban women the incidence of uterine cancer was high compared to women in rural areas. [122] The significant findings of this study that shows urban areas have a higher incidence of gynecological cancers compared to rural areas would suggest some differences in environmental hormonal compounds across the two different areas. However, there may be some factors that affect the overall estimation of uterine cancer incidence. Consequently, the variation in these factors among different populations would explain the discrepancies in the uterine incidence.

There are some factors that may lead to variations in uterine cancer across different geographic regions or populations. Different risk factors may result in variation of uterine cancer incidence. [123] The availability, affordability and accessibility of the health care may influence the variation in uterine cancer incidence. In addition, the quality of cancer registry plays an important role in the estimation of cancer incidence. The cancer incidence can be underestimated or overestimated by failure to determine the population

at-risk. For example, the population at risk of uterine cancer should not include women with removed uterus (hysterectomy). Hysterectomy is the surgical removal of the uterus. It is considered one of the most frequent surgeries for women. For example, about 88%, 81%, and 78% of all hysterectomy procedures were done for nonmalignant diseases in the US, [124] Germany[125] and Sweden[126] respectively. Leiomyoma, endometriosis and genital prolapse are the most common diseases for which hysterectomy may be used as a treatment. In Egypt, there is no clear data about the prevalence of hysterectomy and the indication of this surgery in the country. However, there is an impression that there has been an overuse and a malpractice of hysterectomy by clinicians and lab workers in Egypt.

There are many studies that show distortions of rate ratios of uterine cancer were changed dramatically by adjusting for hysterectomy. The Black women in the U.S have the highest prevalence of hysterectomy compared to Hispanic and non-Hispanic white women. After adjusting for the hysterectomy effect, the incidence rate of uterine cancer was increased in all racial groups. However, the highest increase after adjustment for hysterectomy were in U.S. Black women which minimized the gap in uterine cancer incidence rates among all groups. [127] Another studies[125], [128] supporting this finding and they found that the hysterectomy correction has different effect on incidence rate of uterine cancer in different geographical regions of the U.S. For example, the hysterectomy correction has high impact on rates in the south compared to other regions of the U.S. [117] Therefore, accounting for hysterectomy is an important measure to have accurate estimate of uterine cancer incidence rate.

Goal of the Dissertation Projects:

Uterine cancer is one of the top-ranking cancers of women with wide international variations in incidence rates. Egypt has a lower incidence of uterine cancer than other countries in the Middle East. In addition to the international incidence variation, there are also wide variations in incidence by rural and urban areas within countries. Women in Egypt are exposed to variable levels of hormones and have variable access to medical care in rural and urban areas. Therefore, this research project focused on the Gharbiah province, the region with the only population-based cancer registry in the country, with the aims of investigating demographic and clinical characteristics of uterine cancer, assessing rural/urban variation in incidence rates, and evaluating the possible role of hysterectomy in under-estimating the disease incidence in this population.

There is gap in knowledge of uterine cancer in Egypt. The low incidence rate of uterine cancer in Gharbiah region compared to the regional countries is an interesting observation to study. It is important to know the characteristics of the uterine cancer in the population of Gharbiah region. This will help us to generate a hypothesis about the low incidence of uterine cancer in this region. It is important to investigate this low incidence rate and examine some factors that may affect the calculation.

Investigating the potential factors that may lead to low presentation/incidence of uterine cancers in Egypt compared to the surrounding countries would help to understand the uterine cancer incidence rate variations. Changes in risk factors of uterine cancer e.g. obesity and fertility rates, may explain some of the disparities in uterine cancer across the regions. There is an impression of an excessive hysterectomy rate in Egypt that may affect the validity of the uterine cancer incidence rate. Therefore, it is worthwhile to study

the impact of hysterectomy prevalence on the uterine cancer incidence rate in this population. This will help to estimate the actual magnitude of the uterine cancer incidence rate.

Project Aims and Hypothesis:

Aim1:

To examine the incidence of uterine cancer over the study period and characterize the demographic and clinical profiles of patients residing in the Gharbiah province of Egypt during the period of 1999-2010.

Hypothesis:

The uterine cancer incidence rate was increasing over the time in Gharbiah.

Aim 2:

To investigate the regional variations (rural vs. urban) of uterine cancer by demographic characteristics, incidence rate and clinical presentations.

Hypothesis:

The urban women in Ghrabiah have high incidence rate of uterine cancer compared to the rural women.

Aim 3:

To quantify the impact of hysterectomy rate on the incidence rate of uterine cancer in Gharbiah province of Egypt.

Hypothesis:

The uterine cancer incidence rate was underestimated by the high prevalence of hysterectomy in Gharbiah.

Chapter 2:

Changes in Uterine Cancer Incidence Rates in Egypt during the Period of 1999-2010

Background:

Globally, uterine cancer is one of the top-ranking cancers that affects women. [109,113] Endometrial cancer arises from the inner layer (endometrium) of the uterus, the origin of approximately 90% of uterine cancers, followed by uterine sarcoma that arises from the outer layer (myometrium) (8%) and less frequent types of cancer (2%).

According to the latest figures of the International Agency for Research on Cancer (Globocan 2012), corpus uteri cancer ranks as the fifth most common women's cancer worldwide after breast, colorectal, cervix uteri and lung cancers. [29,109] Globocan reported the aggregate age-standardized incidence and mortality rates of corpus uteri cancer as 8.2 and 1.8 per 100,000, respectively. [109] Uterine cancer has a different incidence distribution in different regions of the world. It is the most common gynecologic malignancy in developed countries and the second most common gynecologic malignancy in developing countries after cervical cancer. [109,129] North America and Central and Eastern Europe have the highest incidence of corpus uteri cancer in the world. [29,109] In contrast, some regions in Africa show the lowest incidence rate in the world. [110-112]

The variation in uterine cancer incidence rates across the world can be explained by differences in exposure to risk factors and different levels of healthcare in the different regions. [130]

Based on Globocan, corpus uteri cancer is ranked as the tenth most common cancer among women in Egypt. According to the Middle East Cancer Consortium (MECC)

Report of 2006, the incidence rate of uterine cancer in Egypt (3.5/100,000) is the lowest compared to other countries in the Middle East: Israeli Jews (13.8/100,000), Cypriots (11.8/100,000), Israeli Arabs (8.7/100,000) and Jordanians (5.8/100,000). [121] In addition, the low stage at diagnosis of uterine cancer is high compared to other female cancers in Egypt. [121]

This study incorporated the most recent data collected by the Egyptian registry after the published report on the data of 1999-2002. We aimed at verifying the suspected increasing incidence rate of uterine cancer and characterizing the demographic and clinical profiles of patients residing in the Gharbiah province of Egypt during the period of 1999-2010.

Methods:

The Study Population

The study included the primary uterine cancers that were diagnosed in the Gharbiah province and collected by the Gharbiah Population-based Cancer Registry (GPCR) from January, 1999 through December, 2010. Data were abstracted from all uterine cancer cases included in the registry for the study period. The registry was founded in 1998 as a project of the Middle East Cancer Consortium. The Gharbiah Cancer Society is the home of GPCR in Tanta, which is the capital city of Gharbiah Province in the center of the Nile delta region. The registry uses the International Agency for Research on Cancer (IARC)'s software CanReg4 for registry the cases. The data were actively collected from all hospitals and pathologic labs of Gharbiah Province. In addition, patients seeking medical care outside the Gharbiah Province are tracked and their data are abstracted and included in the registry.

The Gharbiah province is about 100 km north of Cairo in the Nile delta region. It is the tenth largest province in Egypt with a total area of 1,948 Km^2. It consists of 8 districts. These include: El-Mahalla El-Kubra, Kafr El-Zayat, Samannoud, Tanta, Zifta, El-Santa, Kotoor and Bassyoun. The total population of Gharbiah Province according to the Egyptian census of 2006 was 4,011,320 individuals that represent 5.5% of Egypt's total population. The study was approved by the Institutional Review Board (IRB) at University Nebraska Medical Center (UNMC) and Gharbiah Cancer Center Ethics Committee.

Data Collection:

Cases were coded in the registry based on the third edition of International Classification of Diseases for oncology, (ICD-O-3) coding systems. Cases included C54.0 – C54.9 (Corpus Uteri Cancer) and C55.9 (Uterus, NOS Cancer). There were 660 cases of uterine cancer reported during the period of 1999 through 2010 in Gharbiah Province. The demographic and clinical characteristics of the cases that were abstracted included registration number of the patients, age, marital status, number of children, place of residence, smoking status, occupational status, date and basis of diagnosis, tumor topography, tumor morphology, tumor stage, tumor grade, and treatment. The population data of the latest Egyptian census of 2006 were obtained from the data of the Central Agency for Public Mobilization and Statistics (CAPMAS). [131]

Data management and statistical analysis:

The histopathologic tumor types were grouped into four types based on the histopathologic grouping of the International Agency for Research on Cancer (WHO) used in Cancer Incidence in Five Continents Volume IX (CI5). [132]

The Uterine cancer morphology codes were grouped into four main subgroups. These are carcinoma (8010-8574, 8576), sarcoma (8800-8811, 8830, 8840- 8921, 8990-8991, 9040-9044, 9120-9133, 9150, 9540-9581), other specified malignant neoplasm and unspecified malignant neoplasm (8000-8005). Carcinoma was divided into adenocarcinoma (8140-8141, 8190-8211, 8230-8231, 8260-8263, 8310, 8380, 8382-8384, 8430, 8440-8490, 8510, 8560, 8570-8574, 8576), other specified carcinoma and unspecified carcinoma (8010-8035).

Tumor grades were classified into four grades: Grade I, for well differentiated, Grade II, for moderately differentiated, Grade III, for poorly differentiated, and Grade IV, for undifferentiated anaplastic tumors and lastly the Unspecified Grade. Tumor stages were grouped into four stages: local, regional, distal and un-staged.

The incidence rate (IR) was calculated by dividing the number of events (E) by the total number in the population at risk (P) per 100,000 women. The 95% confidence interval (CI) was calculated using the following formula: $CI = IR \pm 1.96 \times IR/\sqrt{E}$ and the 95% CI of rate ratio calculated by using $CI = \exp [\ln (IR1/IR2)] \pm 1.96 \times \sqrt{(1/E1 + 1/E2)}$. The Egyptian census of 2006 was used to determine the number of women at risk.

The incidence rate of uterine cancer was calculated for both pre and postmenopausal women. The women with age of 50 years old or older were considered post-menopause and the women younger than 50 years old were considered pre-menopause. Due to the low number of cases, the incidence rates were compared over the three periods: 1999 to 2002, 2003 to 2006 and 2007 to 2010. The crude incidence rate was used to compare the incidence of uterine cancer over the entire time frame of the study to the initial incidence in the period of 1999 to 2002. The person-years at risk was calculated over the 12 year period based on the total population of Gharbiah women in the census of 2006. The world standards population (WHO 2000) was used to calculate the age-standardized rate.

Chi-square tests and t-tests were used to test the associations of categorical and continuous variables respectively. For all the analyses, a two-sided p-value of ≤ 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used in all statistical analysis.

Result:

There were 660 women diagnosed with primary uterine cancer in the Gharbiah province during the period of Jan 1999 through December 2010. Table 7 shows the distribution of demographic and clinical characteristics of the patients included in this study. About 83% of patients were postmenopausal and 54% lived in urban areas. Most patients (93%) were diagnosed based on the histologic diagnosis. However, less than 5% of patients were diagnosed with uterine cancer based on the death records only. About 91% of the patients had corpus uteri cancer and 9% were had the diagnosis of uterus NOS (not otherwise specified). Adenocarcinoma and other carcinomas, comprised 80% of the patients. Sarcoma represented 11% of the tumors and 9% of all tumors were "unspecified malignant neoplasms". Surgery alone was the most offered treatment in 48% of treated cases, followed by surgery and adjuvant radiotherapy in 19% of the patients who had treatment information reported. Treatment data showed that 23% of the patients either did not receive any kind of treatment because they were not fit for the treatment or the treatment was not available or affordable. In addition, 27% of all patients' treatment data was missing because the treatment data was not available in the registry from the beginning, which resulted in "missing" in all of those patients.

The overall crude incidence rate of uterine cancer in Gharbiah was 2.8 per 100,000 with 95% CI (2.6-3.0). The age standardized incidence rate was 4.1 per 100,000 with 95% CI (3.8-4.4). Unsurprisingly, the crude incidence rate of uterine cancer was 15.9 per 100,000 in post-menopausal women with 95% CI (14.6-17.3) whereas the pre-menopausal women were only 0.57 per 100,000 and 95% CI (0.46-0.67). The crude rate

ratio was 28.1 and 95% CI (23.0-34.4). Therefore, the postmenopausal women had 28.1 times the odds to develop uterine cancer compared to premenopausal women.

Table 7: Demographic and Clinical Characteristics of Uterine Cancer patients (n=660) in Gharbiah Province between 1999 and 2010.

Variables		Frequency	Percent	95% CI	
				LL	UL
Menopausal Status	Pre-Menopause	115	17.4	14.5	20.3
	Post-Menopause	545	82.6	79.7	85.5
Residential Status	Urban	355	53.8	50.0	57.6
	Rural	305	46.2	42.4	50.0
Periods	1999-2002	154	23.3	20.1	26.6
	2003-2006	227	34.4	30.8	38.0
	2007-2010	279	42.3	38.5	46.1
Age Groups	<40	23	5.0	3.3	6.7
	40-49	82	12.4	9.9	14.9
	50-59	237	35.9	32.2	39.6
	60-69	217	32.9	29.3	36.5
	>=70	91	13.8	11.2	16.4
Parity(n=351)	nulliparous	171	48.7	43.5	54.0
	Low Parity	21	6.0	3.5	8.5
	High Parity	159	45.3	40.1	50.5
Employment(n=418)	Employed	48	11.5	8.4	14.6
	Housewife	370	88.5	85.4	91.6
Basis of Diagnosis	Death Certificate Only	30	4.5	3.0	6.1
	Histology of Primary	614	93.0	91.1	95.0
Cancer Topography	Other	16	2.4	1.2	3.6
	Corpus Uteri Cancer	599	90.9	88.7	93.1
	NOS Cancer	60	9.1	6.9	11.3
Tumor Grades	Well Diff	94	14.2	11.6	16.9
	Mod Diff	300	45.5	41.6	49.3
	Poorly and Anaplastic	110	16.7	13.8	19.5
	Unspecified	156	23.6	20.4	26.9
Tumor Stage(n=560)	Localized	334	59.6	55.6	63.7
	Regional	19	3.4	1.9	4.9
	Distant	72	12.9	10.1	15.6
	Un staged	135	24.1	20.6	27.7
	Adenocarcinoma	447	68.1	64.6	71.7

Cancer Histology(n=656)	Other carcinoma	78	11.9	9.4	14.4
	Sarcoma	72	11.0	8.6	13.4
	Other, unspecified malignant neoplasm	59	9.0	6.8	11.2
Treatment(n=516)	No Treatment Given	120	23.3	19.6	26.9
	Surgery alone	246	47.7	43.4	52.0
	Surgery + adj RT	98	19.0	15.6	22.4
	Surgery + adj RT and or adj CT	52	10.1	7.5	12.7

Table 8 shows the age specific incidence rate of uterine cancer. Descriptively, the age specific rate peaked at 22 per 100,000 and 95% CI (19.28-25.16) in the age group of 60-69 years while the age specific rate was lower in subsequent age groups.

Table8: Age-Specific Incidence Rate (per 100,000) of 660 Uterine Cancer diagnosed in Gharbiah Population, 1999-2010.

Age at Diagnosis	Number of Cases	Age Specific Incidence Rate /100,000	95% Confidence Interval	
			Lower Limit	Upper Limit
<40	33	0.19	0.13	0.26
40-49	82	2.94	2.35	3.63
50-59	237	12.52	11.00	14.19
60-69	217	22.07	19.28	25.16
>=70	91	16.65	13.49	20.34
Total	660	2.78	2.58	3.00

The crude incidence rate of uterine cancer in Gharbiah province over the period of 1999 through 2002 was 1.95 per 100,000 and 95% CI (1.6-2.3) and for the period of 2003 through 2006 it was 2.9 per 100,000 and 95% CI (2.5-3.2). By 2007 to 2010 the crude rate had increased to 3.5 per 100,000 and 95% CI (3.1-3.9). The crude rate was higher in (2003-2006) and (2007-2010) compared to (1999-2002). The crude rate of uterine cancer in the period of 2007 to 2010 was 1.8 times the rate in the period of 1999 to 2002. Table 9, shows uterine cancer crude rate and the increment in the rate ratio over the time with the significant 95% CI.

Table 9: The crude rate of uterine cancer in Gharbiah province for pre and postmenopausal women with rate ratio (total n= 660) 1999-2010.

Status	1999-2002 (ref)		2003-2006				2007-2010			
	CR	95% CI	CR	95% CI	CRR	95% CI	CR	95% CI	CRR	95% CI
Pre-menopausal	0.44	0.3-0.6	0.5	0.4-0.7	1.2	0.74-1.95	0.7	0.52-0.93	1.6	1.04-2.57
Post-menopause	10.87	8.96-12.78	16.7	14.37-19.12	1.5	1.23-1.95	20.2	17.55-22.77	1.9	1.49-2.31
Total	1.95	1.64-2.25	2.9	2.50-3.24	1.5	1.20-1.81	3.5	3.11-3.94	1.8	1.49-2.21

CR: Crude Rate
CRR: Crude Rate Ratio

Corpus uteri cancer comprises the majority of uterine cancers in both pre- and post-menopausal women with proportions of 83% and 93%, respectively (Table 10). However, the NOS cancer has a higher proportion in pre-menopausal women (17%) than (7%) in post-menopausal women ($p<0.001$).

Carcinomas were the most common type in pre and post-menopausal women, 61% and 84%, respectively. The tumor grades have significant association with the menopausal status ($p< .001$). About 10% and 15% of pre and postmenopausal respectively were well-differentiated tumor grade. Moderately differentiated tumor comprised 38% of premenopausal and 47% of postmenopausal patients. Unspecified tumor grade had the

highest percentage of premenopausal women (41%) whereas only 20% of postmenopausal women had unspecified tumor grade. Poorly and anaplastic tumor grade comprised 11% and 18% of pre and postmenopausal patients respectively.

Although, the nulliparity was relatively high in both premenopausal and post-menopausal (52% and 48%, respectively), the levels of the parity did not show a significant difference by menopausal status (p=0 .35). Moreover, treatment, residential status and employment status did not have any significant association with the menopausal status (Table 10).

Table 10: The association of clinical characteristics and Menopausal Status of the Uterine Cancer Cases (n=660) Gharbiah Province 2010.

		Menopause Status				Pearson /Exact Chi Square
		Pre	Post	Pre	Post	
		N	N	Col %	Col %	
Cancer Site	Missing	0	1			<.001
	Corpus Uteri Cancer	95	504	83%	93%	
	NOS Cancer	20	40	17%	7%	
Basis of Diagnosis	Death Certificate Only	10	20	9%	4%	0.04
	Histology of Primary	101	513	88%	94%	
	Other	4	12	3%	2%	
Histology	Missing	2	2			<.001
	Adenocarcinoma	57	390	50%	72%	
	Other carcinoma	12	66	11%	12%	
	Sarcoma	23	49	20%	9%	
Employment	Missing	38	204			0.04
	Employed	14	34	18%	10%	
	Housewife	63	307	82%	90%	
Parity	Missing	52	257			0.54
	Nulliparous	33	138	52%	48%	
	Low Parity	5	16	8%	6%	
	High Parity	25	134	40%	47%	
Residential Status	Urban	60	295	52%	54%	0.70
	Rural	55	250	48%	46%	
stage	Missing	14	86			0.98
	Localized	62	272	61%	59%	
	Regional	3	16	3%	4%	
	Distant	13	59	13%	13%	
	Unstaged	23	112	23%	24%	
Tumor Grade	Well Diff	11	83	10%	15%	<.001
	Mod Diff	44	256	38%	47%	
	Poorly and Anaplastic	13	97	11%	18%	

	Unspecified	47	109	41%	20%	
Treatment	Missing	32	112			0.04
	No Treatment Given	14	106	17%	25%	
	Surgery alone	37	209	45%	48%	
	Surgery + adj RT	17	81	21%	19%	
	Surgery + adj RT and or adj CT	15	37	18%	9%	

Table 11 displays the association of histology with different clinical characteristics of uterine cancer. About half of the carcinoma patients were diagnosed with moderate tumor grade. Histological types of cancer have significant differences across the levels of tumor grades, 59% of adenocarcinoma were moderately differentiated, 53% of other carcinoma were unspecified tumor grade and 32% of sarcomas were diagnosed with poor and anaplastic tumor grade ($p < 0.001$). All sarcomas (100%) were diagnosed as corpus uteri whereas 75% of other and unspecified malignancies were diagnosed as NOS uterine cancers. The highest proportions of all histological types that were treated with surgery only were sarcoma (63%) followed by adenocarcinoma (48%). Histological types of cancer had significant influence over the treatment options that were given ($p < 0.001$).

Table 11: The association of histology types of cancer and different clinical characteristics, (n=660) Gharbiah, 2010.

		Histology Types				
		Adeno-carcinoma	Other carcinoma	Sarcoma	Other and unspecified malignant neoplasm	*P*
		N %	N %	N %	N %	
Tumor Grade	Well Diff	83 19	2 3	9 13	0 0	<.0001
	Mod Diff	262 59	14 18	22 31	1 2	
	Poorly and Anaplastic	65 15	21 27	23 32	0 0	
	Unspecified	37 8	41 53	18 25	58 98	
Cancer Site	Corpus Uteri Cancer	440 98	69 90	72 100	15 25	<.0001
	NOS Cancer	7 2	8 10	0 0	44 75	
Stage	Missing	72	9	17	2	<.001
	Localized	245 65	42 61	35 64	10 18	
	Regional	13 3	2 3	3 5	1 2	
	Distant	37 10	13 19	14 25	7 12	
	Unstaged	80 21	12 17	3 5	39 68	
Treatment	Missing	102	25	13	22	<.0001
	No Treatment Given	74 21	13 25	6 10	26 70	
	Surgery alone	166 48	23 43	37 63	7 19	
	Surgery + adj RT	68 20	12 23	12 20	0 0	
	Surgery + adj RT and or adj CT	37 11	5 9	4 7	4 11	

Discussion:

This study revealed three findings. First, the uterine cancer ASR in this population was relatively low during the entire study period of 1999-2010, however the crude and ASRs increased significantly by 2010. Second, the peak age-specific incidence rate of uterine cancer was in the age group of 60-69 years. Third, adenocarcinoma and other carcinomas comprised about 80% of all uterine cancers in this population.

There are a limited number of studies examining ASR of uterine cancer in Egypt. The first population-based study, included data from 1999-2001, in the monograph of the Middle East Cancer Consortium (MECC). [121] The MECC report included the period 1999-2001 and showed an ASR of 3.5 per 100,000 in this population in Egypt compared to ASR of 5.8 per 100,000 for Jordan, ASR of 8.7 per 100,000 for Israeli Arabs, ASR of 13.8 per 100,000 for Israeli Jews, ASR of 11.8 per 100,000 for Cyprus, and ASR of 17.6 per 100,000 for SEER, USA. [121]. A more recent study showed a crude incidence rate of uterine cancer of 1.91 per 100,000 for the same population for the period of 1999 to 2002. [122] However, based on the Cancer Incidence in Five Continents Vol. X, [29] other Arab countries have higher ASRs than the Egyptian rates. For example, Saudi Arabia, Kuwait and Qatar had ASRs of 4.7, 6.7, and 8.4 per 100,000, for the 3 countries, respectively. [29] Rates reported from developed countries in Europe or North America were significantly higher than the Egyptian rates (19.5, 17.0, and 13.9 per 100,000 for the US, France, and the U.K., respectively. [113] In addition, the world uterine cancer ASR as reported in Globocan 2012 was 8.2 per 100,000. [113] Therefore, the results of this study clearly show that the Egyptian ASR of uterine cancer is considered one of the lowest uterine cancer incidence rates, globally.

Regarding the trend of increasing uterine cancer crude rates in Egypt, other studies showed increasing trends of uterine cancer incidence in some European countries. For example, the incidence of uterine cancer increased significantly in the period of 1988 to 2008 in Norway, Ireland, the United Kingdom, and the Netherlands. [133] Some Asian countries also showed continuous increase in uterine cancer incidence rates. For example, five out of 6 population-based cancer registries in India showed an increase in uterine cancer trend over the period of 1982 to 2003. [134] In addition, the increment in the uterine cancer trend was noticed also in Japan over the period of 1983 to 2005. [135] In contrast, the rates declined in Austria, Sweden and Germany. [133] In the U.S., the trend showed declining rates for 3 decades until the 1990, stability in the 1900s, then slight increase after 2007.[136]

The significant variations in ASRs across different countries could be explained by the variation in risk factors for uterine cancer or health care factors influencing the diagnosis of the disease. [130] The increasing rates in Gharbiah province of Egypt over the study period could be related to both risk factors and health systems factors. It is unlikely that an improvement in the population-based registries has been a factor, since these have maintained consistently high standards verified by peer review.[137,138]

Early age of menarche, late age of menopause, nulliparity, obesity, and diabetes mellitus are well-documented risk factors for uterine cancer in different countries.

Early age of menarche and late age of menopause are two risk factors related to increased risk for uterine cancer. [38,44,46,50,75] Average age of menarche in high and low SES girls in Egypt was reported in 1978 as 12.59 years and 13.89 years, for the two groups, respectively. [139]. A more recent study showed that the mean age at menarche in Egypt

declined to 12.49 years in the period of 2012-2013. [140] Age of menopause has increased in Egypt over time. In 1986, a study from the Sharkia province in Egypt showed an average age of menopause of 45.2 years. [141] and another study from Alexandria, Egypt showed an average of menopause of 45.8 years. [142] Studies from the rural province of Menoufia showed a lower average age of menopause of 43.1 years. [143] More recent studies showed a higher average of menopause of 46.7 and 50.84 in Alexandria and Assiut respectively.[144-146]

Regarding the relationship between parity and uterine cancer, low parity has been considered a risk factor while high parity was considered a protective factor for the disease [147,148] The fertility rate among Egyptian women (15-49 years) was 3.5 births per woman in 2014. [149] Although, the fertility rate declined from 5.3 to 3.5 births per woman during the period of 1980 to 2014, the rate still is higher than that of developed countries. For example, the fertility rates in the U.S., France, and the U.K. were reported as 1.9, 2.0 and 1.9 respectively in 2011-2015. [150] There were no significant association of parity levels and menopausal status of Gharbiah women. Therefore, both groups of women have maintain the same level of parity.

Obesity is considered an important risk factor for endometrial cancer for both pre- and postmenopausal women. [49,56,88,104,151,152] About 39% of the risk for endometrial cancer can be attributed to overweight and obesity. [153] Egypt has been considered one of the countries with the highest overweight and obesity rates. [154] The Egyptian Demographic and Health Survey (EDHS) showed an increase in obesity from 40.85 to 48.1% during the period of 2000 through 2014. [149,155-157] According to the WHO estimate for 2010-2014, obesity (BMI $\geq$ 30) prevalence among Egyptian females aged 18+ was 37.5%

(95% CI 30.5-44.9). [154] A hospital-based study from Alexandria, Egypt showed abdominal obesity as a significant risk factor for endometrial cancer (OR= 13.58, 95% CI (4.0-46.6). [158] Moreover, diabetes mellitus is a well-known risk factor. [159-161] The prevalence of diabetes mellitus in Egyptian women increased from 8% in 1980 to 18.2% in 2014. [162] Therefore, the increase in some uterine risk factors over the last decades could explain the increasing incidence of uterine cancer in our study.

Egypt is one of the middle-income countries that have been undergoing epidemiologic and nutritional transitions. [163-165] For example, the prevalence of overweight and obesity were 28.2% and 7.6%, respectively, among Egyptian schoolgirls of mean age of 13.2 during the period of 2006-2010. [152] If increasing trends of overweight and obesity continue among Egyptian women, endometrial cancer might be expected to continue to increase in the future.

Although, variations in risk factors may explain differences in incidence of uterine cancer between populations, protective factors may also play a role in variation in rates between countries. For instance, smoking is another risk factor that has been associated with low rates of uterine cancer in postmenopausal women. [84,166,167] However, it should be noted that smoking rate among Egyptian women is extremely low (0.5%), compared to the male population (37.7%).[168,169] However, these studies did not address the possibility of exposure of women to passive smoking.

Oral contraceptive pills and injectable contraceptive methods are considered protective against endometrial cancer. [170,171] The estimated prevalence of using birth control pills of Egyptian women of reproductive age (15-49 years) was 16.6 % in 1980 and declined to 9.5% in 2000 then increased again to 16% in 2014. [172] However, there has been a constant

increase in the use of injectable contraceptive methods from 0.1% in 1988 to 8.5% in 2014. [149] These rates of usage are quite low compared to rates in developed countries that reach 40%.[172]. In addition, the increases in physical activity were found protective against uterine cancer [173-175]. About 57% of women living in rural areas in our study region were engaged in daily activities and work in extensive farm-related physical work, which demanded a considerable amount of physical activity. [131] Moreover, the different exposure to environmental factors may affect uterine cancer incidence. For instance, exposure to xenoestrogens as a component of environmental estrogen may have an influence on increasing uterine cancer rates. [122].

About 36% of the patients included in our registry were in the age group 50-59 years. And the age specific rate was the highest (22.07 per 100,000) among the age group of 60 to 69 years. This result does not differ from uterine cancer data worldwide. [3,176] The decrease in the hormonal imbalance for both exogenous and endogenous hormones may explain the decline in the uterine cancer incidence among elderly women. [177] Use of hormonal replacement therapy (HRT) by menopausal women is linked to increasing rates of uterine cancer. [147,178,179] However, HRT is rarely used in Egypt and is not known to most women in Egypt. [145,180].

Egypt has a wide-spread system of primary health care and access to medical care in primary care, hospitals, and private clinics is not a major barrier to receiving medical care. [131] Also, availability of resources for imaging and pathologic diagnosis of cancer have improved significantly in Egypt. [137,138] Whether these resources are available by physicians in the diagnosis of uterine cancer is unknown and if resources are under-utilized, that could result in under-diagnosis of uterine cancer in this population.

Regarding the histologic types of uterine cancer, the majority of all histologic types of uterine cancer in this study were carcinoma and the adenocarcinomas. The results of this study are in agreement with the classic presentation of adenocarcinoma among uterine cancer patients elsewhere. For example, the adenocarcinoma comprises over 90% of all uterine cancer in the US. [181] However, in Tunisia, which is one of the North African countries, the adenocarcinoma was about 63% of uterine cancer patients. [182]

Most of uterine cancers in this study were among postmenopausal women. This finding is consistent with studies from the U.S. where more than 90% of uterine cancer patients are postmenopausal. [3]

The study has several strengths. The study builds on a track record of a reliable population-based cancer registry with validated data. The relatively long period of the study (12 years) adds to the strengths of the study. The coverage of medical care and accessibility to health care facilities in Egypt minimize the chance of missed cases that had no access to medical care. Whether or not physicians histopathologically confirm the diagnosis of all uterine cancers in this population could be a factor in under-estimating uterine cancer in this population. Also, because of the low incidence of uterine cancer in this population, the relatively-small sample size of this study might be a limitation.

In summary, while the uterine cancer incidence rate is low, but increasing over time in Gharbiah province of Egypt compared to other countries, the postmenopausal Egyptian women comprised the vast majority of uterine cancer as in other countries. Future studies should focus on elucidating the impact of epidemiologic, demographic, and nutritional transitions on the future of uterine cancer in this population. Future studies should also investigate if uterine cancer is under-estimated in this population, although this is

unlikely due to population-wide accessibility to medical care in Egypt. Finally, researchers should explore if the increasing environmental pollution and environmental estrogens may have an impact on regional distribution of the disease in rural and urban regions of this population.

Chapter 3:

Clinical and Demographic Characteristics of Uterine Cancer by Rural-Urban Residence in Gharbiah, Egypt (1999-2010)

Background

Uterine cancer is among the top-ranking cancers affecting women worldwide. [113] There are wide international variations in the disease incidence and by rural-urban place of residence within countries.[183-186]

Incidence rates of cancer, including those for uterine cancer, tend to be higher in urban compared to rural populations. [183,187,188] However, the gap between rural and urban areas in cancer incidence has decreased over time, especially in the developed countries. [189] Limited number of studies exist on uterine cancer distribution by rural and urban areas in developing countries.

Hormonal exposures implicated in uterine cancer etiology and access to health care in disease management varies between rural and urban areas, globally. [184-186,190-193] According to a previous study from the Gharbiah Population-based Cancer Registry (GPCR) for 1999-2002, the incidence of gynecological cancers (ovary, uterine and cervical) was higher in urban compared to rural areas. [122] Uterine cancer showed highest urban–rural incidence rate ratio among the 3 gynecologic cancers (IRR = 6.07, 95% CI = 4.17, 8.85) whereas the ovarian and cervical cancers had 2.57 and 3.11 respectively. Urban areas had higher incidence rates and older age at diagnosis of uterine cancer compared to rural areas and a relatively low rate of uterine cancer in this population compared to the global rates of the disease. [122,194]

The Gharbiah province comprises about 5.5% of Egyptian the population and about 70% of the population lives in rural areas. [131] With the availability of a larger dataset from the registry for the period 1999-2010, and improvement in medical and diagnostic facilities in the region[137], this study aimed at examining the rural-urban difference in uterine cancer in Gharbiah.

Methods:

Data included in this study was obtained by abstracting clinical and demographic information of all 660 patients who resided in the Gharbiah province and diagnosed with uterine cancer during the period of 1999-2010. The Gharbiah Population-based Cancer Registry of (GPCR) province in Egypt was the source of information in this study. The GPCR is a population based cancer registry established based on the Middle East Cancer Consortium (MECC) in 1999. The Cancer Society in Tanta, the capital city of Gharbiah, hosts GPCR. Highly trained staff collected the data actively from across the entire region. Data were obtained by abstracting clinical and demographic information from the GPCR for all 660 patients who resided in the Gharbiah province and were diagnosed with uterine cancer during the period of 1999-2010. Data of all Gharbiah province patients diagnosed with cancer and Gharbiah patients seeking medical advice outside the region were included in the registry.

Uterine cancers included in the registries were classified based on the international code of disease classification (ICD-O-3). [195] Corpus uteri included codes C54.0 – C54.9 and uterus not otherwise specified (NOS) cancer included code C55.9.

Rural-urban residence was based on the classification of the Egyptian Central Agency for Public Mobilization and Statistics (CAPMAS). The Gharbiah province consists of the

following 8 districts: Tanta, Mehalla, Kafr Zayat, Zefta, Samanood, Santa, Kotoor and Basyoon. Each district has a capital city and surrounding villages. The population of the capital cities of each district was considered urban residents while the population of the remaining areas of each district was considered rural residents. [131] Residence was considered rural or urban based on the permanent residence address of patients.

The total population of women in Gharbiah province was 1,977,324 in 2006 (last published census). [131] About 70% of residents were rural and 30% were urban. Data from the Egyptian census of 2006 was used for calculating incidence rates in this study. [131]

Medical care in the province is provided through a large network of public and private clinics and hospitals including 257 primary health care units, 57 integrated hospitals and 2 central hospitals in rural areas and 88 urban hospitals.

The incidence rate of uterine cancer was calculated for rural, urban, and the total population. The world standard population of WHO 2000 was used to calculate the age-standardized rate (ASR). [29] The rate ratio was calculated to compare the rates in rural and urban areas and to examine the incidence trend over time. The study period was divided in to 3 periods; 1999-2002, 2003-2006 and 2007-2010. The first period was used as a reference period in calculating rate ratio; the rate in the last period was compared to second period.

The crude incidence rates (IR) were calculated by dividing the total number of uterine cancers (E) by the total number of women at risk in the same population per 100,000. The formula of $CI = IR \pm 1.96 \times IR/\sqrt{E}$ was utilized to calculate the 95% Confidence Interval (CI). The rate ratio of uterine cancer in urban areas versus rural areas was calculated by

dividing the incidence rate in urban areas (IR1) by the incidence rate in rural areas (IR2). The CI of Rate Ratio = exp [In (IR1/IR2)] ± 1.96 × √ (1/E1 + 1/E2). The Chi-square test was used to compare categorical variables. A two-sided p-value ≤0.05 was considered statistically significant. Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc, Cary,NC).

The study was approved by the IRB committees of the University of Nebraska Medical Center and the Gharbiah Cancer Society in Egypt.

Results:

Slightly more than half the patients (54%) resided in urban areas while 46% of patients resided in rural areas. There were no significant differences between patients residing in rural and urban areas with respect to following menopausal status [rural premenopausal (18%) vs. urban premenopausal (17%)] and parity [rural nulliparous (48%) vs. urban (49%)]. However, occupation was significantly different in rural vs. urban women; only 4% of rural women were employed compared to 19% of urban women ($p< 0.001$).

Tumor morphology had a significant association with the residential status. Adenocarcinoma was the most common type in both rural and urban patients, 66% and 70%, respectively. Sarcoma was found equally (11%) in each of the urban and rural patient groups. About 8% of urban uterine cancers were classified as “other carcinoma” whereas double of that proportion (16%) was found in rural areas. The majority of uterine cancer cases were diagnosed as “localized” in both urban (56%) and rural (64%) areas. About 48% of patients with treatment data had surgery alone, in both rural and urban. Tumor stages, grades, and treatment did not show any significant association with place of residence (Table12).

Table 12: Clinical and demographic characteristics of 660 uterine cancer patients in Gharbiah, Egypt during the period of 1999-2010 by urban and rural status

Characteristic		Place of Residence		
		Rural	Urban	
		N (%)	N (%)	P value
Menopausal Status	Pre-Menopause	55 (18%)	60 (17%)	0.70
	Post-Menopause	250 (82%)	295 (83%)	
Occupation Status (n=418)	Employed	9 (4%)	39 (19%)	<.001
	Housewife	201 (96%)	169 (81%)	
Parity(n=351)	Nulliparous	87 (48%)	84 (49%)	0.86
	Low Parity	12 (7%)	9 (5%)	
	High Parity	81 (45%)	78 (46%)	
Cancer Site	Corpus Uteri Cancer	284 (93%)	315 (89%)	0.07
	NOS Cancer	21 (7%)	39 (11%)	
Tumor Histology	Adenocarcinoma	198 (66%)	249 (70%)	0.01
	Other carcinoma	49 (16%)	29 (8%)	
	Sarcoma	32 (11%)	40 (11%)	
	Other and unspecified	23 (8%)	36 (10%)	
Tumor Stage(n=560)	Localized	166 (64%)	168 (56%)	0.18
	Regional	6 (2%)	13 (4%)	
	Distant	33 (13%)	39 (13%)	
	Unstaged	55 (21%)	80 (27%)	
Tumor Grade	Well differentiated	39 (13%)	55 (16%)	
	Moderately differentiated	136 (45%)	164 (46%)	0.07
	Poorly differentiated	63 (21%)	47 (13%)	
	Undifferentiated anaplastic	67 (22%)	89 (25%)	
Treatment(n=516)	No Treatment Given	59 (23%)	61 (24%)	0.99
	Surgery alone	125 (48%)	121 (48%)	
	Surgery + adj RT*	50 (19%)	48 (19%)	
	Surgery + adj RT and or adj CT**	27 (10%)	25 (10%)	

* Radiotherapy
** Chemotherapy

Urban areas had the highest age-specific rates for all age groups (Table 13). However, rural and urban patients had the same pattern of increasing rates with the increase of women's age up to the age group of 60-69.

Table 13: Age specific rates of 660 uterine cancer patients resided in rural and urban Gharbiah, Egypt 1999-2010

AGE	Rural			Urban		
AGE Group	No. of Cases	Age Specific Rate/100,000	95% CI	No. of Cases	Age Specific Rate/100,000	95% CI
<40	17	0.14	(0.08-0.21)	16	0.32	(0.19-0.50)
40-49	38	2.05	(1.47-2.78)	44	4.71	(3.47-6.26)
50-59	108	8.90	(7.34-10.70)	129	18.98	(15.92-22.48)
60-69	105	16.03	(13.18-19.32)	112	34.14	(28.25-40.92)
>=70	37	9.65	(6.90-13.15)	54	33.12	(25.14-42.87)
Total	305	1.84	(1.64-2.06)	355	4.96	(4.47-5.50)

The crude rates of uterine cancer were consistently higher in urban than rural areas, during the period of 1999 to 2010. The overall crude incidence rate of uterine cancer during the period 1999-2002 was 1.95 per 100,000 with 95% CI of 1.64-2.25. Rural crude incidence rate was 0.78 per 100,000 while the rate was 4.65 per 100,000 in urban areas. The gap between the 2 crude incidence rates of rural and urban areas declined in the last 2 periods (2003-2006 and 2007-2010).

The rural ASR was 2.8 (95% CI: 2.48-3.13) compared to 6.9 (95% CI: 6.13-7.66) per 100,000 in urban areas. The rate ratio showed that the incidence rate of uterine cancer in urban areas was 2.46 times the rate in rural areas (Table 14).

Table 14: Crude and adjusted incidence rates and rate ratio of uterine cancer in rural and urban of Gharbiah, Egypt 1999-2010, (N=660)

	N	CR	95% CI	RR	95% CI	ASR	95% CI	RR	95% CI
Rural	305	1.84	(1.64-2.06)	1.00		2.80	(2.48-3.13)	1.00	
Urban	355	4.96	(4.47-5.50)	2.70	(2.31-3.14)	6.90	(6.13-7.66)	2.46	(2.10-2.88)

N: Number of Cases
CR: Crude Rate per 100,000 population
ASR: Age standardized Rate per 100,000 population based on world standards population (WHO 2000).
RR: Rate Ratio (Rural residence was used as a reference)

Table 15 shows the crude rate of uterine cancer over time for each of the geographic areas of Gharbiah. The crude rate increased over time for both rural and urban areas. The

rate ratio between time periods in rural areas, considering 1999-2002 as a reference period, steadily and significantly increased over time as the crude rate ratio was 2.7 with 95% CI of 1.94-3.89 for 2003-2006 and 3.4 with 95% CI 2.38-4.71 for 2007- 2010, in comparison with reference time period. Although the crude rate was always higher in urban areas, the rate ratio did not show any significant increase over time. Figure 2 shows the steady increase of crude rates in both rural and urban areas all over the time

Table 15: Crude incidence rate of 660 uterine cancers in rural and urban Gharbiah over the period of 1999 to 2010

	Time periods											
Status	1999-2002 (Ref)			2003-2006				2007-2010				
	Cases	Rate*	95% CI	Cases	Rate*	95% CI	RR**	95% CI	Cases	Rate*	95% CI	RR**	95% CI	RR***	95% CI
Rural	43	0.78	0.55-1.01	118	2.1	1.75-2.52	2.7	1.94-3.89	144	2.6	2.2-3.03	3.4	2.38-4.71	1.22	0.96-1.56
Urban	111	4.65	3.79-5.52	109	4.6	3.7-5.4	0.98	0.75-1.28	135	5.7	4.7-6.6	1.2	0.95-1.56	1.24	0.96-1.59
Total	154	1.95	1.64-2.25	227	2.9	2.50-3.24	1.5	1.20-1.81	279	3.5	3.11-3.94	1.8	1.49-2.21	1.23	1.03-1.46

* Rate: Crude rate per 100,000 women.
**RR: Rate ratio (1999-2002 used as a reference)
***RR: Rate ratio (2003-2006 used as a reference)

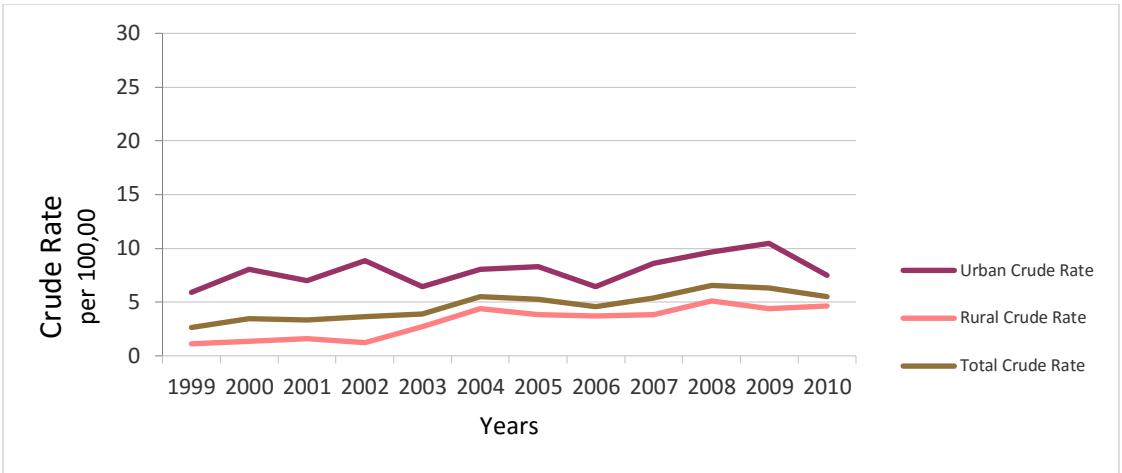


Figure 2: Time trend of uterine cancer crude rate in Gharbiah province, 1999-2010

Discussion:

This study revealed the following interesting observations. First, there were no differences in most clinical and demographic characteristics between patients from rural and urban areas. Second, age-specific rates showed similar patterns of increase with aging for patients from both rural and urban areas. Third, uterine cancer incidence rate was significantly higher in urban areas compared to rural areas. Fourth, uterine cancer incidence rates increased from 1999 to 2010 in rural areas but not in urban areas.

Regarding the lack of difference in clinical and demographic characteristics between patients from rural and urban areas and increasing uterine cancer rates with aging, it is important to note that accessibility and affordability of health care in this population is not an impediment to receiving appropriate cancer management. Health care facilities (health units, primary care centers, private clinics, and private and public hospitals) are available and accessible to both rural and urban populations. For example, there are more than 300 primary health care, integrated hospitals and central hospitals distributed throughout the rural areas. In addition, the distance between remote rural sites of the province and respective capital cities of the districts is no more than 20 kilometers. Also, various methods of transportation are available and affordable if special diagnostic or treatment regimens are needed. Increasing the accessibility to health care has reduced mortality rates in the U.S. by providing early diagnosis and specific treatment for uterine cancer. [196] Furthermore, the impact of improving diagnostic and management facilities in Gharbiah showed a significant impact on diagnostic methods of cancer patients included in the Gharbiah registry in both areas. [137,138]

A systematic review of the literature from 1992 to 2012 that included a total of 366,299 uterine cancer patients in the U.S., revealed an association between socioeconomic status (SES), incidence, stage at diagnosis, and survival rates. [197] Patients with low SES presented more frequently with advanced-stage of uterine cancer that may attributed to the low accessibility of health care. [198-200] Disparities in access to health care may explain the relationship between SES and disparities in incidence rates and stages of diagnosis of uterine cancer in the U.S. However, health care accessibility and affordability were not barriers to receiving care in rural and urban areas of our study population in Egypt. This may explain why tumor grades and stages at diagnosis were not associated with place of residence of patients in our study population in Egypt.

The pattern and increment of age-specific rates among rural and urban women age in this population was consistent with global trends for uterine cancer in both developed and developing countries, as reported in Cancer Incidence in Five Continents.[29]

The higher incidence of uterine cancer in urban than rural areas was observed in previous study. [122] It was conducted in the same population on a shorter time period (1999-2001) and it showed crude incidence rates of 0.74 and 4.52 per 100,000 in rural and urban areas compared to 1.84 and 4.96 per 100,000 in rural and urban areas, respectively. [122] The ratio of urban to rural rates decreased from 6.07 in the first study to 2.70 in the current study. The changes in incidence rate ratios over the study period emphasize the increasing rate in rural areas and stable rates in urban areas, which was reflected on narrowing the gap between rural and urban rates. While the rural ASR in this study (2.8 per 100,000) is significantly low compared to the urban ASR (6.9 per 100,000) that is relatively close to the global average ASR of uterine cancer. [109]

The significant difference between rural and urban rates as well as increasing rural rates revealed in this study might be a reflection of changes in risk factors of uterine cancer in this population over time. Examples of these risk factors include parity, obesity, early age of menarche, contraceptives, and physical activity.

Parity has been inversely associated with uterine cancer in several studies from various countries. [31,37,148,201] In Egypt, higher fertility rates have been reported in rural compared to urban areas, including our study population in Gharbiah. It is important to note that fertility rates have declined in rural areas of Gharbiah from 4.6 per 1000 women in 1988 to 3.6 per 1000 women in 2014 and from 3.8 per 1000 women in 1988 to 3.0 per 1000 women in 2014 in urban areas.[149]

Obesity is a strong risk factor for uterine cancer. [49,56,158,202] The obesity and overweight data that was collected by World Health Organization showed that Egypt has high obesity rate compared to many countries worldwide. [154] During the 1990s, average BMI was higher among urban (29.8 kg/m^2) compared to rural women (26.8 kg/m^2). [203] This gap declined over the time. The average BMI were 31.1 kg/m^2 in urban areas and 31.0 kg/m^2 in rural women in 2014. Therefore, the risk factor of uterine cancer in rural women has increased compared to urban areas.

Early age of menarche has been identified as one of the factors that have lifetime risk for uterine cancer. [15] In Egypt, the urban girls tend to have an earlier age of menarche compared to those in rural areas in 1980s. [139] In addition, age at first marriage in rural areas is younger than in urban areas. The median age at first marriage was 20 and 22.4 years in rural and urban women in Egypt, respectively. [149], Therefore, there was about 10% of young women in the age group of 15 to 19, who had at least one pregnancy. [149]

Therefore, urban women were exposed to high risk of uterine cancer for a longer time during their lifetime compared to rural women.

Oral contraceptive rates were low and with no clear difference among rural and urban women of Egypt. [149] However, previous studies suggested that higher rates of uterine cancer in urban than rural areas might be related to higher xenoestrogenic exposures in urban than rural areas. [122] The stable incidence rate in urban areas compared to rates in rural areas might be related to nutritional and epidemiologic transition. [204] The urbanization of rural areas, dietary factors and food sources and epigenetic factors[205-207] may lead to weaken the estrogenic compounds in both urban and rural population.[208-210]

Physical activity plays a significant role in risk reduction of uterine cancer by lowering the level of serum estradiol, which may help in reduction weight gain. [94,174,175,211] Physical activity of rural women in Egypt is significantly higher than the activity of urban women. Occupational activities in farming, livestock breeding and less technological household environment translate to higher level of activity in rural areas compared to urban areas. [131]

This study has several strengths. The study period spans over 12 years. The population-based nature of the study and the validated quality of the data add to the strength. Comparing the results with previous research from the same region highlights the impacts of the changes in lifestyle, demographic, and environmental factors on the epidemiology of uterine cancer in this population.

However, the study has several limitations. The registry-based nature of the study did not provide information about lifestyle and risk factors. The low number of uterine cancer patients in this population was another limitation.

In summary, this study revealed the increasing rates of uterine cancer in rural areas and stable but much higher rates in urban areas in Gharbiah, Egypt. Future studies should elucidate the etiology of uterine cancer in both urban and rural populations in Gharbiah and other regions in Egypt. The studies should also quantify the impact of nutritional and epidemiologic transitions in this population. While no significant difference existed in stage of presentation or type of treatment, further studies should examine the diagnostic methods, treatment outcomes, and uterine cancer-specific mortality in rural and urban regions.

Chapter 4:

Impact of Hysterectomy on Uterine Cancer Incidence Rates in Egypt

Background:

Uterine cancer is one of the common cancers affecting women worldwide. [109] However, there are significant variations in the incidence globally with highest rates in North America (19.1 per 100,000) and lowest rates in Africa (3.5 per 100,000).[194]

The age-standardized incidence rate of uterine cancer in Egypt was reported in 2012 as 3.8 per 100,000 compared to a global average incidence of 8.2 per 100,000. [194] Uterine cancer is ranked as the tenth most common women's cancer in Egypt. Reports from the Middle East Cancer Consortium (MECC) showed that the incidence rate of uterine cancer in Egypt was the lowest (3.5 per 100,000) compared to rates from other MECC countries in the region: Jordan (5.8 per 100,000), Israeli Arabs (8.7 per 100,000), Cyprus (11.8 per 100,000) and Israeli Jews (13.8 per 100,000).[121]

In addition to the wide range of geographic variation in the uterine cancer incidence rate in the Middle East, underestimation of uterine cancer is suspected in Egypt due to the presumed frequent hysterectomy procedures in the country.[149,212]

Surgical resection of the uterus (hysterectomy) is one of the main lines of surgical treatment of uterine cancer. There are also other medical indications for performing a hysterectomy. [213] These indications include uterine leiomyomas (fibroid), dysfunctional uterine bleeding, endometrial adenomyosis, genital prolapse, chronic pelvic pain, pelvic inflammatory disease, massive postpartum hemorrhages, endometrial hyperplasia and uterine cancers. [214] The majority of hysterectomies are performed for managing non-

malignant conditions and fibroids are considered the most common indication for hysterectomy. [215] Non-malignant conditions that were treated by hysterectomy accounted for 88%, 81%, and 78% of all hysterectomies procedures in the US, [124] Germany[125] and Sweden[126], respectively.

Hysterectomy is one of the most common gynecologic surgical procedures for women worldwide and has been reported in 2009 as the second most common surgery for women in the U.S. (479,814 hysterectomies/year). [216] The incidence rate of hysterectomy varies across the globe, with reporting rates of 510 per 100,000 in the US, [217] a much lower incidence rate in Europe as demonstrated by an incidence rate of 173 per 100,000 in Denmark. [218] Unfortunately, Egypt and most of developing countries have a scarcity of research in hysterectomy.

Some studies have suggested that hysterectomy might be a factor in underestimating the observed incidence of uterine cancer. It has always been believed that white non-Hispanic women have a significantly higher incidence of uterine cancer than the incidence in other racial groups in the U.S. It is interesting to note that the overall age-adjusted endometrial cancer rate increased 66.8% in all race groups after correcting for hysterectomy prevalence. [127] After adjusting for hysterectomy, Blacks had the highest increase in endometrial cancer incidence rate by 95.3%, followed by 65.1% for White non-Hispanics and 57.6% for Hispanics. These adjustments provided a better understanding of the actual incidence rates between the different ethnic groups considering the influence of different hysterectomy rates among them. [127] Therefore, adjustment for hysterectomy was an important factor in documenting the actual uterine cancer rate in the U.S. population. Other studies[125, 128] supporting this finding, reported

that the hysterectomy correction has a different effect on the incidence rate of endometrial cancer in different geographical regions of the U.S. For example, the hysterectomy correction had a high impact on rates in Southern U.S. compared to other U.S. regions. [117]

Adjusting for hysterectomy had different levels of effect on the uterine cancer incidence rate depending on the prevalence of hysterectomy in different countries. For example, after adjusting for the prevalence of hysterectomy, uterine cancer incidence rates increased in England and Wales from 13.4 to 16.2 per 100,000, from 15.9 to 23.0 per 100,000 in Germany and from 14.6 to 18.8 per 100,000 in Finland.[219-221]

In Egypt, there are no clear data about the prevalence of hysterectomy and the indication of this surgery. However, there are clinical impressions about a frequent practice of hysterectomy in the country. Because of the documented low incidence of uterine cancer in Egypt and the presumed high rates of hysterectomy, this is the first study to quantify the impact of hysterectomy rate on the incidence rate of uterine cancer in Gharbiah province of Egypt.

Methods:

The population of the study region:

The Gharbiah province is located in the center of the Nile delta region of Egypt in a space area of 1,948 km^2 and a population of approximately 4,011,320. The province is composed of eight districts: Tanta, Al-Maḥallah al-Kubrā, As-Sanṭah, Basyoun, Kafr az-Zayyāt, Quṭūr, Samannūd, and Zefta. The two main districts that encompass the majority of the Gharbiah population and health care facilities are Tanta (TA) and Al-Mahallah Al-kubra (MK). Approximately 50% of the population lives in TA and MK.

The hysterectomy dataset:

The primary pathology labs that examine all uterine specimens in the province were included in this study. The main pathology labs in Tanta are located at the Tanta University Medical School, the Gharbiah Cancer Society (GCS), the Menshawy hospital and three other private labs. In MK and Kafr az-Zayyāt, there are three private labs that could receive and examine uterine specimens. Patients from the other 6 districts of Gharbiah come to these pathology labs if uterine specimens need histopathologic examination. Based on the Ministry of Health regulations in Egypt, uterine biopsy after every hysterectomy procedure must be sent to a pathology lab for histopathologic examination before treatment.

All logbooks of the above-listed labs in 2013 and 2014 were reviewed. The review was limited to this period since records prior to 2013 were not available because of inadequate storage spaces in the labs. After identifying all uterine biopsies from the logbooks, pathology reports of each case were examined. In the Gharbiah city of Tanta, there were 1055 hysterectomy specimens among 3072 benign uterine lesions. There were 306 hysterectomy specimens identified from 1008 cases of benign uterine lesions in MK. Samples included in this study represented all patients from all districts of Gharbiah aged 18-80 years.

Variables abstracted from pathology reports included lab ID number, age, clinical presentation, type of surgery, date of the procedure, pathologic diagnosis, pathology lab and district referral surgeon.

The incidence rate of uterine cancer for Gharbiah was calculated using the Gharbiah population-based Cancer Registry (GPCR) for uterine cancer cases included in the period

1999-2010 and the population data from the Central Agency for Public Mobilization and Statistics (CAPMAS) census. [131]

Data management and statistical analysis:

The incidence rate (IR) of hysterectomy (E) was calculated for 2013 and 2014 in the Gharbiah region by dividing the number of newly-diagnosed cases of hysterectomy by the population of women in Gharbiah during the same time period. The 95% Confidence Interval (CI) was calculated using the following formula: CI= IR±1.96 × IR/√E.

In order to adjust for the effect of hysterectomy on uterine cancer incidence rates, all women with hysterectomies (prevalent cases) were eliminated from the denominator of at-risk women. Therefore, backward prevalence projection was calculated under the assumption that age has a constant effect pattern and the stability of health care-related factors (e.g. availability, affordability, accessibility). The hysterectomy probability was derived from the hysterectomy rate by using hysterectomy probability, $q(h) = 1 - e^{-5r(h)}$ as used in a previous study from New South Wales of Australia. [222]

Here, r(h) stands for hysterectomy rate by five year age groups. The 95% Confidence Interval (CI) for prevalence (P) was calculated using the following formula: CI=P±1.96 × (√P(1-P)/n) where (n) stands for the population size. The adjusted uterine cancer rate was calculated by removing the hysterectomized women from the population at risk (denominator). The adjusted uterine cancer incidence rate was compared to the pre-adjustment rate using 95% confidence intervals. SAS statistical software was used in the analysis (SAS version 9.4 SAS Institute Inc., Cary, NC).

Details of uterine cancer incidence rate calculations are included in our previous chapters.

Result:

There were 1040 hysterectomy cases in the Gharbiah region during the period of 2013 and 2014. The total crude incidence rate of hysterectomy was 26.3 per 100,000 women [95% CI (24.7-27.9)]. The age-specific rate of hysterectomy was highest in the age groups (40-49) and (50-59) by rates of 112.2 and 109.7 per 100,000 women, respectively, (Table 16). The age-standardized rate (ASR) of hysterectomy was 30.4 and 95% CI was (28.5-32.2) per 100,000.

Table 16: Crude Incidence Rate of hysterectomy by age group (/100,000), Gharbiah 2013-2014

AGE	Hysterectomy Cases	Incidence Rate per 100,000	95% CI	
<40	115	3.94	3.27	4.71
40-49	522	112.25	102.93	122.19
50-59	346	109.67	98.56	121.68
60-69	47	28.69	21.34	37.80
>=70	10	10.98	5.64	19.48
Total	1040	26.30	24.74	27.93

The estimated prevalence of hysterectomy was 13.1 per 10,000 women and 95% CI was (12.65-13.66). The age group of 45-49 had the highest prevalence of 74.8 per 10,000 women. The prevalence of hysterectomy among women in Gharbiah increased with age to the peak in the age group of 45 to 49 years then gradually decreased in older women (Table 17).

Table 17: The projected prevalence of Hysterectomy in the women population of Gharbiah, Egypt 1999-2010

Age groups	Hysterectomy prevalence per 10,000	95% CI	
15-19	0.1	0.03	0.36
20-24	0.1	0.04	0.37
25-29	2.1	1.54	2.92
30-34	4.6	3.54	5.87
35-39	13.8	11.95	15.94
40-44	39.3	36.00	42.98
45-49	74.8	69.89	80.13
50-54	67.7	62.67	73.17
55-59	32	27.92	36.70
60-64	16.1	12.91	20.13
65-69	18.4	14.39	23.59
70-74	6.4	3.88	10.58
75+	4.5	2.45	8.31
Total	13.1	12.65	13.66

After adjusting for the hysterectomy cases in the population at risk, the uterine cancer incidence rate was not affected significantly in all age groups. The total crude rate of uterine cancer after adjustment for hysterectomy was 2.79 and 95% CI (2.58-300) per 100,000 compared to almost the same rate (2.78 per 100,000 women) before the adjustment (Table 18).

Table 18: Uterine cancer incidence rate before and after adjustment for hysterectomy by age group Gharbiah, 1999-2010

		Before Adjustment			After Adjustment		
AGE	Cases	Crude Rate per 100,000	95% CI		Crude Rate per 100,000	95% CI	
<40	33	0.19	0.13	0.26	0.19	0.13	0.26
40-49	82	2.94	2.35	3.63	2.96	2.37	3.65
50-59	237	12.52	11.00	14.19	12.59	11.06	14.27
60-69	217	22.07	19.28	25.16	22.11	19.31	25.20
>=70	91	16.65	13.49	20.34	16.66	13.50	20.36
Total	660	2.78	2.58	3.00	2.79	2.58	3.00

Moreover, no significant differences were seen for pre- or post-menopausal women regarding crude incidence rates of uterine cancer after adjustment for hysterectomy, (Table 19).

Table 19: Uterine cancer crude incidence rate before and after adjustment for hysterectomy by menopausal status, Gharbiah, 1999-2010

		Before Adjustment			After Adjustment		
Menopause	Cases	Crude Rate	LL	UL	Crude Rate	LL	UL
Pre-menopause	115	0.57	0.47	0.68	0.57	0.47	0.68
Post-menopause	545	15.92	14.63	17.30	15.98	14.68	17.36
Total	660	2.78	2.58	3.00	2.79	2.58	3.00

The incidence rate of uterine cancer did not change significantly after adjusting for the projected hysterectomy prevalence [pre-adjustment IR= 2.78, 95% CI (2.85-3.00), post-adjustment IR=2.79 95% CI (2.58-3.00)]. The incidence rate of uterine cancer could be significantly impacted to become IR=3.25 95% CI (3.01-3.51) if the current observed prevalence would increase by 110 times.

Discussion:

This study has revealed interesting findings. First, women in Gharbiah have a low incidence rate of hysterectomy. Second, uterine cancer incidence rates did not change after adjusting for hysterectomy in this population. Third, based on the uterine cancer incidence, the observed uterine hysterectomy prevalence would need to be 110 times the current number of hysterectomy cases to have a significant impact on the uterine cancer incidence.

This study showed that the crude and ASR of hysterectomy rates in Gharbiah were significantly lower than the respective rates reported from other countries. For example, in the U.S. the ASR of hysterectomy was 500 per 100,000 women in 2000-2004. [217] In Germany, the ASR of hysterectomy was reported as 362.9 per 100,000-person year in 2005-2006. [125] However, other developed countries showed hysterectomy incidence rates of 370 and 120 per 100,000 women in Italy and Norway, respectively. [223,224] Based on the available data from Africa, the hysterectomy rate was very low compared to rates in developed countries. For example, the hysterectomy incidence rate was 5 per 100,000 women in rural areas of Kenya in 1996. [225] while the ASR of hysterectomy in our study from Egypt is 30.4 per 100,000. The difference between hysterectomy ASRs in developed and developing countries could be attributed to differences in fertility rates as well as variation in availability of health care services and reliability of medical records and diseases registries. The highest age-specific rates of hysterectomy in this population were observed in the same age groups of high age-specific rates in developed countries [(40-49) and (50-59)]. [226]

These findings and observations regarding the low incidence of hysterectomy in this population in Egypt were confirmed by the results of our calculation of the prevalence rate to estimate the denominator of at-risk women. For example, the prevalence rate of hysterectomy in this population was 0.13% compared to prevalence of 6.9% in rural areas of India and 16.9% in the U.S. [227,228] A hospital-based study from Ain Shams University hospital in Cairo showed an increment in admissions numbers of patients requiring hysterectomy surgery by comparing hospital admission rates of 1995-1996 to the rate in 2000. [212] Unfortunately, there is a scarcity of studies of hysterectomy prevalence and incidence in Africa and developing countries in general. Therefore, it is difficult to document changes in hysterectomy trends over time.

Regarding the second observation of the insignificant impact of hysterectomy on uterine cancer incidence in this study, previous studies from the U.S. showed that adjustment for hysterectomy prevalence increased the overall age-adjusted endometrial cancer incidence rate from 29.2 per 100,000 to 48.7 per 100,000 i.e. increase in rate by 66.8% during the period 1992-2000. [127] Furthermore, several studies found that failure to adjust for hysterectomy prevalence resulted in distortion of uterine cancer rates based on age, race, and place of residence in the United State. [125,128,229] In Germany, corrected uterine cancer incidence rate after adjusting for hysterectomy prevalence led to a 20% increase in incidence. [230] Moreover, hysterectomy prevalence has different impacts on uterine cancer incidence rates among different countries. For example, the relative change in uterine cancer incidence rates after adjustment for hysterectomy prevalence was higher in the U.S. compared to some European countries. [230] Our study showed that the low prevalence

of hysterectomy in the study had no significant impact on the uterine cancer incidence rate in Gharbiah, Egypt.

The results of our study revealed that hysterectomy procedures are not as common as presumed based on clinical impressions. The hysterectomy prevalence in our study population was not high enough to influence uterine cancer incidence rates. There are multiple factors that might have contributed to the results. There is a possibility that not all cases of hysterectomy were recorded or reported due to poor reporting, inadequate record storage, or illegal undocumented practices. However, the significant impact of hysterectomy on uterine cancer incidence rate in this population did not appear until the observed prevalence was multiplied by 110. Therefore, it is highly unlikely that even with underreporting of hysterectomy that uterine cancer rate is underestimated in this population.

In addition, there are certain factors that could influence hysterectomy rates, such as availability and affordability of health care facilities and levels of socioeconomic status. [231,232] Furthermore, knowledge and attitude about hysterectomy influence decision-making regarding hysterectomy. A Swiss study found that patients' knowledge about hysterectomy and different alternative treatments could help in reducing the choice of hysterectomy. [233] Cultural factors may also lead to acceptance or rejection of hysterectomy as a line of treatment. For example, in the Middle East, the uterus is considered an important organ for femininity and reproduction even in multiparous women. [234,235] The beliefs about the importance of the uterus may affect the utilization of hysterectomy among women and may also influence their consideration of other alternative non-surgical lines of treatments such as hormonal manipulation and laser

ablation. It is important to note that while hysterectomy rates were shown to be low in this study, the increasing rates of obesity in this population could result in increasing rates of gynecological diseases that will require a hysterectomy for treatment. [149,236,237]

The study has several strengths. The study was the first population-based investigation of the influence of hysterectomy on uterine cancer rates in Egypt. The availability of reliable data from the population-based cancer registry of Egypt on uterine cancer adds to the validity of the information. The study also provided useful information about the low rate of hysterectomy in this population in Egypt. The low rate of hysterectomy in this population can be extrapolated to the population of women in Egypt, as Gharbiah is representative of the country in terms of the population age structures, socioeconomic and geographic living status. The inclusion of the limited number of pathology labs in this study increased the opportunity for capturing the vast majority of the resected hysterectomy specimens during the study period. However, the study has a few limitations. The limited storage capacity of the pathology labs restricted the duration of the study period. Therefore, there was a potential that some cases were missing. Also, the limited demographic and clinical variables in the pathology reports hindered the clinical investigation of the gynecological diseases involved in the study.

In conclusion, this study highlights the low prevalence of hysterectomy among women in the Gharbiah region of Egypt and confirms the low incidence of uterine cancer in this population, eliminating the clinical impression that the low incidence of uterine cancer is due to high rate of hysterectomy. Future studies should investigate the clinical and demographic factors related to hysterectomy in this population for optimizing medical care and setting guidelines for practice. Additional research is needed to compare the

indication of hysterectomy in this population to populations in other developing countries. With the high and increasing rates of obesity in this population, investigating the potential increase in hysterectomy would be an interesting research topic.

Chapter 5:

Discussion:

Main finding of the dissertation:

This project included three studies. The first study included in chapter two of the dissertation focused on investigating the epidemiologic and clinical characteristics of uterine cancer in Gharbiah and the changes in incidence rates and trend over the period 1999-2010. This study revealed that the uterine cancer ASR was relatively low during the study period. However, the trend of uterine cancer increased significantly over time. The second study in chapter three of the dissertation focused on the similarities and differences of uterine cancer incidence in rural and urban populations of Gharbiah. The results of this study showed that urban population of Gharbiah region has a significantly higher incidence rate of uterine cancer compared to the urban population of the region. However, the incidence rate of uterine cancer showed a significant increment in rural areas during the period 1999-2010. Interestingly, there were no differences in most clinical and demographic characteristics between the patients by place or residence (i.e. rural and urban Gharbiah). The third study in chapter four of the dissertation aimed at quantifying the impact of rate of hysterectomy on the incidence rate of uterine cancer in Gharbiah. The results of this study showed that the prevalence of hysterectomy was low in Gharbiah and that adjusting for the prevalence of hysterectomy did not impact the uterine incidence rate in the region.

Cancer incidence rates vary across the world. It has been found that developed countries have higher incidence rates compared to the rates in developing countries. The variations among the cancer risk factors across different countries may have influence on the

variations of uterine cancer incidence rates. The known risk factors of uterine cancer have a prominent distribution among women in developed countries compared to developing countries. Cancer patients are traditionally exposed to the risk factors for long time (lag period) and the period ranges between 15-more than 25 years. For example, the high incidence of lung cancer in developed countries in the 1980s and 1990s resulted from high smoking rates in the 1950s and 1960s. Therefore, the higher rates of uterine cancer in the western countries after decades of exposure to risk factors could be repeated in developed countries in the near future with the current epidemiologic and nutritional transitions there and the emergence of risk factors. The rising and high rates of obesity among Egyptian women may increase the incidence of uterine cancer in Egypt in the next several years. Therefore, the analysis of the Gharbiah cancer registry data in the future can confirm or refute this hypothesis. However, it should be noted that the anticipated increase in uterine cancer rates in this population in the future, because of the high and increasing rates of obesity, may not lead to rates similar to the rates in developed countries. The reason is that the current and near future cohorts of postmenopausal women in this and other similar middle-income populations in developing have experienced protective effects of high parity and other protective reproductive factors.[238]However, this protective effect during the premenopausal period may not last for long as young women in Egypt and other similar countries are experiencing later age of first childbirth, lower parity, and Western lifestyles. Moreover, some policies might be initiated to limit the exposure to risk factors. For instance the harmful effect of Tamoxifen and HRT may encourage healthcare policy makers in Egypt to adopt some

initiative to limit their use. Therefore, the increment in uterine cancer in Gharbiah may be reduced by limiting the exposure to possible risk factors.

Urban women in Gharbiah have higher incidence of uterine cancer compared to the rural women. The variation in rates is consistent with the variation in risk factors across the two populations. The protective factors that help minimize the risk of uterine cancer in urban women were less prevalent in rural women. Therefore, the variations in the uterine cancer incidence across the two different populations of Gharbiah (rural vs urban) could provide stronger evidence about the association between uterine cancer and the mentioned risk factors for uterine cancer.

Since the Gharbiah region has a low prevalence of hysterectomy, there was no impact on the estimation of the uterine cancer incidence rate. This study documented this finding and refuted the clinical impression and claims that the lower incidence of uterine cancer is due to hysterectomy.

Future Directions and Conclusion:

The future directions and recommendations of the research studies included in the dissertation could be formulated into the following directions:

Research Studies:

Future studies could be focused on epidemiologic, behavioral, environmental, and genetic research.

It will be important to investigate the effect of nutritional and epidemiologic transitions in Egypt on the future of uterine cancer in this population. It will be especially important to track the changes in reproductive factors related to endometrial cancer (e.g. parity and

contraceptive pills) among the population of Gharbiah in the future. Comparing the decline in parity with the changes in incidence of uterine cancer in the rural and urban populations in Egypt may help estimate the role of parity as a risk factor in association of the changing incidence rates.

The pattern of uterine cancer observed in urban Gharbiah could also be investigated in urban populations in Cairo with much higher exposure to uterine cancer risk factors to further understand the risk factors in Egypt. Higher rates of obesity, more Western diets, later age of first childbirth, and lower parity are more prevalent among women in Cairo than urban Gharbiah, warrants further research in Cairo.

Investigating the socio-behavioral factors related to seeking medical care for uterine cancer may provide clues to the predominance of early-stage presentation of this disease in this population and how to utilize the results of such research for early diagnosis of other cancers.

The external environmental xenoestrogens could impact uterine cancer development.[239] Therefore, it is important to explore the potential hazards of environmental factors that may contribute to increasing the uterine cancer rates in the future in both urban and rural populations.

It will also important to investigate the possible protective genetic factors that reduce the incidence of uterine cancer in this population. Tracking the genomic classifications of uterine cancer in Gharbiah could help the understanding of disease pathways, carcinogenesis, and ultimately treatment of the different genomic subtypes of uterine cancer.

The previous research studies will help in understanding the nature of the uterine cancer in details based on the local characteristics of Gharbiah population. Therefore, implementing a tailored program and interventions will help to limit and prevent uterine cancer in Gharbiah region.

Cancer Registration:

The Population-based cancer registry in Gharbiah can play an important role in the future measurement of uterine cancer in the region. In order to observe the trend of uterine cancer, the cancer registry should maintain their regular process of registration to collect the cancer data from the entire Gharbiah region. It will be very interesting to observe the trend of uterine cancer after 2010 and compare it to the current study period.

The completeness of the cancer registry records would help explore in detail the different important aspects of uterine cancer. Fortunately, many women with uterine cancer present in the early stages, however the survival rate could not predicted. Although, the mortality records of Gharbiah are available, linking the mortality records to the data of cancer registry will be essential in tracking patient survivorship.

Improving the quality of hospital cancer registries in Gharbiah can also help improve the quality and completeness of the data of the population-based cancer registry. Moreover, the hospital cancer registries can help track patients' records to monitor the time required for the diagnostic investigations and treatment.

Medical care

The population of Gharbiah has the potential for future increase in uterine cancer incidence rate. The future increase in uterine cancer incidence will definitely impose a

burden on the healthcare system of the region. Therefore, policy makers and healthcare stakeholders should closely observe the uterine cancer incidence and plan accordingly. Appropriate measures should be implemented to minimize the consequences of the high load of uterine cancer patients. Healthcare facilities should also be prepared for the potential increase in the volume of uterine cancer patients. It is recommended to establish a patient navigation system that could facilitate provision of optimal care to patients. Patients diagnosed at the early stages should be tracked to receive the appropriate treatment within reasonable time. Patients diagnosed in the rural areas should also be tracked for quick referral and initiation of treatment in the advanced oncology centers.

Developing uterine cancer management protocols could help to deal with different types of uterine lesions. These protocols can minimize missed cases and can help in early detection.

Education

Educational efforts should be channeled into professional, patient and public education. Healthcare professionals should receive a continuous medical education through scientific programs that can keep them updated on the latest updates in managing uterine cancer. The survival data of uterine cancer is presently missing, so the relative efficacy of treatments cannot be assessed. Therefore, patients may require an appropriate health education in regard the uterine cancer and maintaining treatments. Moreover, conducting a public health awareness campaign to maintain the high level of physical activities in the daily life of the public might be beneficial. Highlighting the hazards of the risk factors of uterine cancer that could have a positive impact on women's health. For example, obesity and diabetes mellitus were considered a major health problem in Gharbiah region.

Therefore, it is essential to promote healthy life style to reduce the risk of chronic diseases that influences uterine cancer.

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