# *Renal cancer and pregnancy in two different female cohorts*

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***Purpose:*** *Although human renal cell carcinoma (RCC) is considered refractive to hormone therapy, this lesion can be induced in the Syrian hamster by exogenous estrogen. Human RCC also has been demonstrated to contain estrogen receptors. Since there are significant changes of estrogen levels during pregnancy, we wanted to investigate if there were any associations between the hormonal variations of pregnancy and renal cancer in women using two distinct cohorts.*

***Materials and methods:*** *We reviewed the charts of 57 females who presented for treatment of renal cancer. We assessed the size of each tumor radiologically and pathologically, the tumor stage, the number of pregnancies and/or abortions/miscarriages, age at menarche, and use of oral contraceptives. We compared this cohort to a sample of 985 nuns, and then reviewed the literature on the association of pregnancy, contraceptives and renal cell carcinoma. We used analysis of multiple variables (ANOVA) and the student's t test to determine any significance ($p<0.05$).*

***Results:*** *Our age range was 39 to 67 years, with a mean of 51. The tumor volumes ranged from 9 $cm^3$ to 1500 $cm^3$, and the number of pregnancies ranged from 1 to 14. Menarche ranged from 8 to 14. We did not find any significant correlation between menarche or the number of pregnancies and the size or stage of renal cancers. However, our nun population did not reveal any incidence or illness from renal cell carcinoma over a 20 year review.*

***Conclusions:*** *Although our first cohort did not demonstrate any significant associations between the number of pregnancies or age at menarche and RCC, our second cohort and a review of the literature supports the notion that pregnancy is a risk factor for renal cell carcinoma.*

**Key Words:** renal cancer, parity, hormones, neoplasia

## Introduction

With the routine use of ultrasound during the monitoring of pregnancy, numerous other incidental findings have been detected, such as gallstones, cysts, and intra-abdominal solid masses. Renal cell carcinoma (RCC) is the most common renal neoplasm found during pregnancy.[1] Due to the high levels of estrogen and progesterone during pregnancy, one can speculate that these hormones may play a role in the etiology and/or progression of renal cell cancer.[2] This may be further supported by the report that renal tumors can be induced in the Syrian hamster by exogenous estrogen.[3] Interestingly, although human renal cancer is considered refractive to hormone therapy, it has also been demonstrated to contain estrogen receptors.[4]

Since there are significant changes of estrogen levels during pregnancy, we wanted to investigate if there were any associations between the hormonal variations of pregnancy, age at menarche, age at menopause, oral contraceptives and renal cancer in women. We compared this cohort to another cohort consisting of several hundred nuns from local

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monasteries and convents in the states of New York and Pennsylvania. We also reviewed the literature and speculate on possible etiologies or mechanisms which may be involved.

## Materials and methods

We reviewed the charts of 57 females who presented for treatment of renal cancer from 1989 to 1999 at our institution. We assessed the size of each tumor radiologically and pathologically, the tumor stage, the number of pregnancies and/or abortions/miscarriages, age at menarche, and use of oral contraceptives.

We compared this cohort of patients to another cohort of patients who were presumed to never have a pregnancy or use oral contraceptives, namely nuns. We contacted the medical directors of several monasteries and convents in the states of New York and Pennsylvania to review the medical records and death certificates of nuns affiliated with these organizations over a 20 year period.

We used analysis of multiple variables (ANOVA) and the student's t test to determine significance ($p<0.05$) of these findings in the two samples.

We also used MEDLINE to review the literature to assess what other factors or parameters may play a role in the incidence of this disease.

## Results

For our first cohort of patients, our age range was 39 to 67 years, with a mean of 51. The tumor volumes ranged from 9 $cm^3$ to 1500 $cm^3$, and the number of pregnancies ranged from 1 to 14. Menarche ranged from 8 to 14. We also tried to assess dietary factors, oral contraceptives, and smoking history during the evaluation of each female. However, this latter assessment was very difficult due to incomplete history taking. In this retrospective analysis, though, we did not find any significant correlation between menarche or the number of pregnancies and the incidence, size or stage of renal cancers.

In our second cohort of 985 nuns, we had an age range of 43 to 82, with a mean of 62. Our review of the medical records did not reveal a single case of renal tumor involved in any morbidity, mortality, or routine autopsy finding over a 20 year period. Although we assume that there were no oral contraceptives or history of smoking, there were several women who became nuns after being married and/or having a family. These nuns were excluded from our study. However, many of the heights and weights of the nuns were not recorded, and therefore we could not assess their body mass index in this study.

Our MEDLINE review revealed several reports with very large samples of patients which demonstrated an increased risk of RCC with pregnancy, and that non-parity and no oral contraceptives decreased the risk. In addition, there were several studies which demonstrated a risk of RCC associated with obesity, smoking, and high fat intake. Lastly, there were several case reports of spontaneous hemorrhage from angiomyolipoma and/or renal cell carcinoma duringpregnancy, which suggests that there may have been rapid growth of this lesions during hormonal stimulation, leading to vascular or urinary invasion.[5-7]

## Discussion

The incidence of renal cancer is about 1 in 10 000. The incidence of detecting renal masses is increasing, especially in North America, due to the prevalent use of sonography, CT scanning and MRI for other non-related illnesses. Furthermore, the decision making process as to what to do with some of these smaller, questionable solid masses that are found incidentally is beyond the scope of this paper.[1] However, since the incidence is two-fold in males to females, one could speculate that factors other than estrogen and/or progesterone play a role in this tumor.[3]

The finding that obesity is a risk factor for RCC in women, and that increased adipose tissue stores increase the estrogen environment, further suggests that estrogens may play a role in the tumor biology of RCC.[8] Obese women sometimes achieve an ovulation due to increased estrogen levels, both pre and post menopausally. This suggests that estrogen may stimulate RCC and progesterone may inhibit it.

Although our first cohort did not demonstrate an association between the incidence of RCC, or the stage or size of the tumor and pregnancy, this was a small cohort, and it was difficult to stratify among other significant factors such as body mass index, smoking, and complete dietary fat intake because we did not have the complete histories of each patient. Although our second cohort consisted of nuns, we can only presume that there were no pregnancies, oral contraceptives or smoking involved in those nuns who were not previously married or had children. However, that may not have necessarily been the case. Furthermore, we also did not have the body mass index or dietary history of each nun. This was similarly difficult to obtain due to the confidentiality of the medical records or incomplete histories. Lastly, many renal tumors are now being detected during the routine use of ultrasound. The

absence of finding any renal tumors in this nun cohort may be due to the decreased use of routine ultrasonography than any other factor.

Numerous factors play a role in the etiology of cancer formation. Hormones, growth factors, aging, immunosuppression, free radicals and other parameters all play a part in the complex interaction which causes tumor formation.[3] Pregnancy is associated with an increased glomerular filtration rate. The speculation of renal tumor etiology during pregnancy suggests that because of the 40% increase of GFR, glomerular hyperfiltration may play a role in the pathogenesis of glomerulosclerosis, which is ultimately damaging to kidneys.[2,3,8,9] Furthermore, hormones have also been shown to enhance the activity of certain angiogenic growth factors, which can stimulate neoplastic transformation.[9] Therefore, the increased levels of estrogen and progesterone, combined with the increase in blood flow seen during pregnancy, can act as a "fertile soil" for the induction of renal neoplasia. However, it probably is a much more multifactorial, complex process that is evolving.

Chow et al reported a population based, case control study which examined reproductive variables and the use of exogenous hormones in the incidence of renal cell carcinoma. They reported a two fold risk in those patients that had five or more births compared to those women with one or two births. Furthermore, they found that hypertension and increased body mass index were other important variables. However, the risk of RCC was reduced among long term oral contraceptive users but elevated among women who had a hysterectomy or used menopausal hormones.[10]

Lindblad et al reported data from five centers in the United States, Australia, Denmark, Germany, and Sweden. They found a significant trend in risk associated with an increased parity as well as with a decreased age at menarche. They also found an increased risk among those women who had a hysterectomy. However, the use of oral contraceptives reduced the risk, and no association was observed for estrogen replacement therapy.[11]

Lastly, there have been a small series of papers that have described the sudden rupture and/or gross hematuria from otherwise asymptomatic angiomyolipomas and renal cell carcinomas during pregnancy. This suggests that there may be rapid growth of the lesions during this phase.[5,6,12,13] Other papers have described that some of these lesions are detected during routine sonography for pregnancy. However, whether asymptomatic or not, most authors agree that nephrectomy should be done regardless of the trimester of pregnancy.[1,2,4,7]

However, this is the first report, to our knowledge, that has examined the incidence of RCC in a nun population, and current studies are underway to examine larger numbers of these nun organizations to either corroborate or refute these initial findings.

## Conclusions

Our study did not demonstrate any significant associations between the number of pregnancies or age at menarche and the size, stage or incidence of renal cell carcinoma in the first cohort of patients in examined. However, we did not find any reported cases of renal cell carcinoma in a larger cohort of nuns, which would suggest that parity may indeed increase the risk of RCC. Although our sample of nuns is still too small to make a statistically significant correlation to the current incidence of 1 in 10 000, our present findings have been corroborated by other larger studies. However, this is the first study, to our knowledge, which has examined the incidence of renal cell carcinoma in a sample of nuns. □

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