Gallbladder disease: A review of cholecystectomy specimens in South Africa

Zafar Ahmed Khan

Student number 1053865

Supervisor: Martin Brand

A research report submitted to the Department of Surgery, School of Medicine, Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine.

Johannesburg, 2018

Candidate's declaration

I, Zafar Ahmed Khan, declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

This study has been submitted to the journal "Lancet Public Health" for consideration

A copy of the receipt of study for consideration is included in the appendix

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Zafar Ahmed Khan

Signed on this 3rd day of June 2019 in Leeds, United Kingdom

Dedication

This dissertation is dedicated to my parents, my wife Sumayya, daughter Hannah and the rest of my family

Abstract

Background

Studies suggest that the rate gallstone disease in Africa is low. Our hypothesis is that gallstone disease in Africa has increased due to urbanization and its associated increases in body mass index (BMI).

Methods

An audit of cholecystectomies done in South Africa by reviewing gallbladder specimens processed by the South African National Health Laboratory Service (NHLS) from 2004 and 2014 was done. The NHLS services 82.5% of SA's population. Descriptive analysis was performed with comparison done. Urbanization ratios were obtained from Statistics South Africa and BMI data from previously published studies.

Results

33467 cholecystectomy specimens were analysed. There was a 92% absolute increase in cholecystectomies during the study period (Pearson r 0.94; $p < 0.01$) with the overall cholecystectomy rate increasing by 65% from 8·36 to 13·81 per 100000 population. 85% of cholecystectomies were in females, who were significantly younger than males. The data was divided into two equal time periods and compared. During period 2 there was 28·8% increase in cholecystectomies and patients were significantly younger (46·9 vs 48·2 years; $p = < 0.0001$). The Northern Cape was the only province to show a decline in the cholecystectomy rate in period 2 and was also the only province to record a decline in urbanization ratios. Population based studies in SA have demonstrated a clear association between urbanization and increases in BMI.

Interpretation

This nationwide African study demonstrates a significant increase in cholecystectomies for younger patients with gallstone disease. A positive relationship between urbanization and

cholecystectomy rates has been demonstrated. As urbanization is associated with increases in BMI, this risk factor may be a significant factor in the aetiology of gallstone disease in an apparently low risk population.

Acknowledgements

I would like to acknowledge Sue Candy and the NHLS who was supportive of this effort and facilitated the acquisition of the data

Contents

List of abbreviations

BMI – Body mass index

CC – Cholecystectomy

NHLS – National Health Laboratory Service

SA – South Africa

SD – Standard Deviation

EC – Eastern Cape

FS – Free State

GP – Gauteng

Lim – Limpopo

MP – Mpumalanga

NW – North West

NC – Northern Cape

WC – Western Cape

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Chapter 1

Introduction

Gallbladder disease is a common and costly pathology. The development of gallstones varies among population groups around the world.[1] In developed societies the rate of gallstone disease averages between 10 and 15%. The risk of developing symptomatic disease is approximately 2-3% per year and 10% five years after the development of stones.[1] There is a causal association between changes in dietary intake, increases in body mass index (BMI) and symptomatic cholelithiasis.[2]

In the last thirty years the burden of disease has increased by 30% and population based studies have identified an increased BMI as a risk factor for subsequent cholecystectomy.[3] As a result the number of procedures for gallstone disease has risen with cholecystectomy becoming the most common elective surgical procedure in the United States.[1]

Epidemiological studies from African countries, including South Africa suggest a low rate of gallstone disease in the African population.[4] Two South African studies completed during the 1980's suggested that the rates of gallstone disease in the black "urban" African population was low. These studies did note an increasing trend of gallstone disease, citing increasing exposure to a Western lifestyle as the possible causal association.[4,5]

We hypothesized that urbanization and its association with increased BMI has resulted in an increase in gallstone disease and thus cholecystectomy rates for gallstone related disease in South Africa.

Chapter 2

Methods

Data Source

The South African National Health Laboratory Service (NHLS) was established by legislation in 2001, enabling the amalgamation of all laboratories in the public health service. The public sector hospitals service 82·5% of the South African population and thus provide a cross sectional study of the South African population.[6] Paid medical insurance allows for access to private healthcare in South Africa. Due to inequity in South Africa, 89·4% of black South Africans have no medical insurance. In contrast, 73·3% of the white population are members of medical insurance schemes. It is standard practice for all cholecystectomy specimens to be sent for histological analysis in South Africa. Cholecystectomy (CC) data was obtained from the NHLS prospective histological database for the period 2004 to 2014. South Africa has nine provinces and data was collected and categorised according to the province in which the CC was performed. Kwa-Zulu Natal province was excluded for comparative statistics due to data only being available after 2010. In 2014 Kwa-Zulu Natal had a population of 10 million people accounting for 19·6% of the South African population.[6] The data obtained was analyzed for errors and duplicates were removed. Data on urbanization were obtained from Statistics South Africa. Ethics approval for the study was granted by the University of Witwatersrand Human Research Ethics Committee and the NHLS (Reference M140935).

Inclusion and exclusion criteria

All patients over 12 years of age with gallstone related disease were included in the analysis. Any cholecystectomy performed during the course of another operation and where gallstone related disease was not the cause of the primary pathology were excluded (e.g. liver surgery, biliary bypass procedures, pancreatic surgery, and trauma).

Statistics

The objectives of this study were descriptive and the database was very large, hence no sample size estimation was necessary. Descriptive analysis of the data was carried out as

follows: Categorical variables were summarised by frequency and percentage tabulation. Continuous variables were summarised by the mean, standard deviation, median and interquartile range. Comparison of categorical variables were carried out using Fisher's exact test and continuous variables using independent samples t-test. Calculation of cholecystectomy rates was per 100000 population. This was done by excluding the 17·5% patients with medical insurance that are not treated by public service hospitals. Medical insurance data was obtained from Statistics South Africa.[6] Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

Chapter 3

Results

A total of 34294 cholecystectomy specimens were processed during the study period. Following exclusions, 33467 were analyzed. The proportion of female patients in this series was 85% with a female to male ratio of 5·7. The mean age of the study population was 47·3years (SD 15 years), male patients had a mean age of 52·2 years (SD 15·2 years) and were significantly older than the female patients with a mean age of 46·4 years (SD 14·7 years) ($p < 0.0001$). There was an absolute increase of 92% in the number of CC during the study period (Pearson r 0·94; $p < 0·01$), and the CC rate increased by 65% from 8·36 to 13·81 per 100 000 population. The greatest proportion of CC were performed in the two provinces that have the highest rates of urbanisation, namely Gauteng and the Western Cape provinces.

The data was divided into two equal time periods, period 1 (2004-2008) and period 2 (2009-2013). Kwa-Zulu Natal province was excluded due to data only being available after 2010. Overall there was a 28·8% increase in the number of cholecystectomies during period 2 compared to period 1 (Figure 3·1). Seven of the eight studied provinces recorded increases in cholecystectomy rates. The Northern Cape was the only province to show a decrease in the cholecystectomy rate. There were 29% fewer cholecystectomies in the Northern Cape in period 2. Overall, during period 2, the patients undergoing cholecystectomy were significantly younger than during period 1 (48·2 vs 46·9 years; $p = < 0.0001$). This was true for both female (47·4 vs 46·1 years; $p = < 0.0001$) and male patients (52·6 vs 51·5 years; $p = 0·0362$). There was no significant change in the male to female ratio ($p = 0·4156$). At the beginning of the study there were only three hospitals in the country that performed more than 100 cholecystectomies in a calendar year and all were affiliated to a university or located in large metropolitan areas. At the end of the period 2 fifteen hospitals were consistently performing more than 100 cholecystectomies in a year, with all but three university affiliated hospitals or in major metropolitan areas.

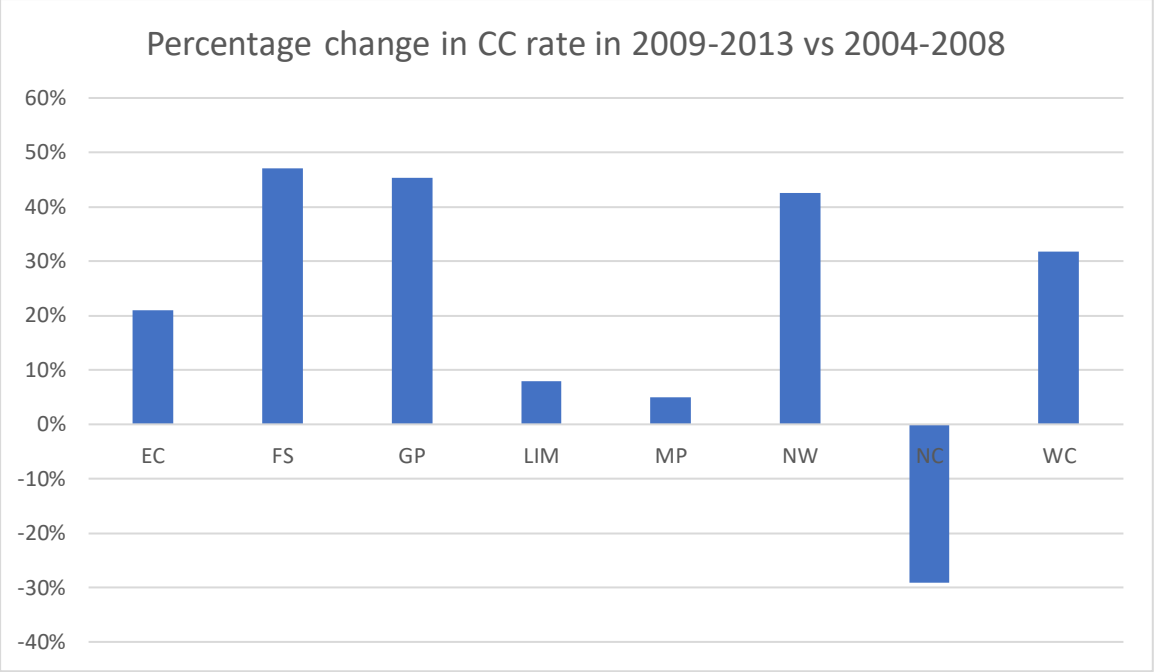

Figure 3.1 – Percentage change in cholecystectomy rates in the last decade per province

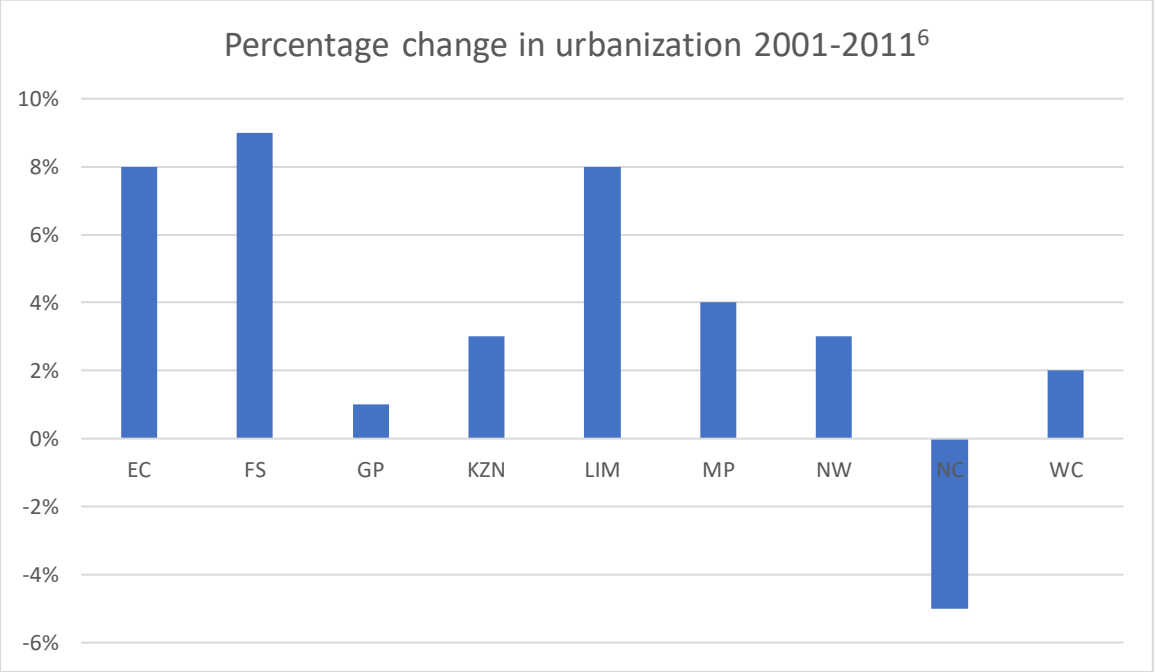

Figure 3.2 – Percentage change in urbanization in the nine South African provinces

Chapter 4

Discussion

The rate of gallstone disease among women is is reported to 2-3 times higher than men.[7] Our finding of a 1:6 male to female ratio is in keeping with the literature albeit at a higher rate. Male patients were significantly older than female patients in this study which has also been consistent with other cholecystectomy studies.[8] In period 2 of the study there was a significant trend for younger patients to have a cholecystectomy. This is an unusual finding as the incidence of cholelithiasis increases with age[9], and suggests that other risk factors may be more prevalent in the study population.

This study, the largest from Africa, demonstrates an increase in the number of cholecystectomies for gallstone related disease in South Africa over the last 10 years. Cholecystectomy studies from the early 1990's have attributed the increased rate of cholecystectomies to a lower threshold for surgery and enthusiasm associated with the advent of less morbid and better tolerated laparoscopic surgical procedures.[8,10–12] The increases from studies on cholecystectomy has ranged from 20% to 53%. [8,10,12,13] A continued and sustained increase in cholecystectomy rates are ascribed to changes in risk factors; specifically dietary changes and increasing body mass index.[2,8,14] The overall absolute increase of 92% in the CC rate is not commensurate with the annual 1·5% population growth in South Africa during the years of the study and more so when 30% of the growth was in the age group 0 to 14 years old. This increased rate is also supported by the increases demonstrated per 100 000 population. However, when comparing the first half of the study to the second there was an increase of 28·8%, suggesting that although the annual rate continues to increase, the rates of increase are slowing down.

Two studies conducted in Soweto, South Africa, during the 1980s suggested that although the rate of cholelithiasis in the black "urban" African population was low, there was an increasing incidence together with increases in cholecystectomy rates.[4,5] It was suggested that an increased exposure to a Western lifestyle, namely increased saturated fat with a decreased fiber intake, was a possible risk factor for this. A similar study from Japan also suggests that westernization of the Japanese diet after World War 2 has resulted in an increase in

symptomatic gallstone disease.[15] These suggestions seem to be substantiated by this study where the two most urbanized provinces had the most cholecystectomies performed.

An increased body mass index is a well-established risk factor for the development of gallstones.[16] South Africa has the highest prevalence of obesity in Sub-Saharan Africa with the highest incidence among black South African women.[17] Cois et al. conducted a study investigating obesity trends and risks factors in South Africa between 2008 and 2012.[18] The investigators reported an increasing trend in BMI among South African adults, however, rural dwellers had a lower baseline BMI compared to their urban counterparts. An increase in BMI was suggested to be due to the adoption of "urban lifestyles". Figure 3·2 depicts the change in the percentage of the population residing in urban versus rural areas between the 2001 and 2011 census with a positive value indicating an increase in the number of people residing in urban areas and a negative value a decrease in the number residing in urban areas. Urbanization trends in South Africa over the last decade show that all but one province had an increase in rural to urban migration.[19] The Northern Cape experienced a 5% decline in urbanization. It was also the only province in our series to show a decline in the cholecystectomy rate (Figure 3·1). The urbanization and BMI data lend support to previous data suggesting urbanization together with increases in BMI are associated with an increase in symptomatic cholelithiasis.[4] This together with the decreasing age of cholecystectomy patients all appear to support our primary hypothesis.

During the last 30 years the burden of gallstone disease has increased by 30% resulting in an estimated annual expenditure of approximately $6.5 billion in the United States.[2] The South African health system is plagued by four concurrent epidemics, namely infectious diseases, specifically HIV, maternal death, malnutrition and an increasing burden of other non-communicable diseases[20]. The almost doubling in the number of cholecystectomies during the last decade represents a significant increased burden on an already strained system. This data provides a platform from which the population may be educated regarding the risks of gallstone disease and the plausibility for the implementation of risk reduction strategies, specifically community education and weight loss programs.

Low hospital volume for surgical cases has been associated with morbidity and mortality[21]. Several studies exploring cholecystectomy outcomes in relation to hospital volume suggest that high volume centers are associated with reduced morbidity and costs.[22,23] However, in patients with average operative risk, the clinical outcomes are not different between low and high volume centres.[24] In South Africa, most high-risk patients are referred to tertiary hospitals. This study suggests that most tertiary institutions are now high-volume centers and would be able to adequately manage these patients, thus reducing morbidity and costs.

A limitation of this study is that clinicodemographic data obtained is limited to that provided by surgeon and pathologist. A second limitation may be related to the introduction of laparoscopic cholecystectomy. Our findings of a 92% increase is higher than international trends and thus cannot be accounted for simply by the introduction of laparoscopy alone. Furthermore, the introduction of laparoscopic cholecystectomy in South Africa occurred in the early 1990's, more than 10 years prior to this study. Although the increase in cholecystectomy rates may suggest an increase in the prevalence of symptomatic cholelithiasis, cholecystectomy rates alone are subject to several sources of bias and may therefore be a crude indication of the prevalence of gallstone disease. These include variations in surgical rates as suggested above and variations over time.[25] Several methods including ultrasound, autopsy studies and oral cholecystography have been used to estimate prevalence with all having their specific drawbacks.[25] Although it is practice for all cholecystectomies done at public hospitals are submitted to the NHLS, there is a possibility that some may not have been sent. Furthermore, although the NHLS provided all of the electronic data available, there may be gaps in the system as some data may have been logged manually and not inserted electronically into the database. An estimate of number of these cases was not available. The large number of patients included in this study may mitigate against the incomplete data.

In conclusion we have demonstrated through analysis of 33467 gallbladder specimens for gallstone related disease in South Africa over a 10-year period that the number of cholecystectomies have increased significantly. The results of this study suggest a change in the disease pattern in South Africa. As urbanization is associated with increases in BMI, this may a significant risk factor in the aetiology of gallstone disease. This is particularly

worrisome as the population under study has generally been regarded as being at low risk for the development of gallstone disease. The increasing trend in cholecystectomies has implications of increased cost and burden of disease and is thus likely to become a public health problem in a system that is already plagued by other concurrent epidemics (infectious disease, malnutrition).

Chapter 5

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Appendix 1: Copy of ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Zafar Ahmed Khan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140935

NAME: (Principal Investigator)	Dr Zafar Ahmed Khan
DEPARTMENT:	Surgery NHLS,Lancet, Ampath, Pathcare, Gritzman and Thatcher and Wits Laboratory
PROJECT TITLE:	Gallbladder Disease: A review of Cholecystectomy Specimens in South Africa
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Martin Brand
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/07/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 14 July 2018

Appendix 2: Submission of paper to Lancet Public Health

Gmail

Zafar Khan <zafcee@gmail.com>

Manuscript Reference Number For Your Submission to The Lancet Public Health

The Lancet Public Health <eesserver@eesmail.elsevier.com> Mon, Jul 30, 2018 at 11:09 AM
Reply-To: The Lancet Public Health <publichealth@lancet.com>
To: zafcee@gmail.com, zafar@webmail.co.za

*** Automated email sent by the system ***

Dear Dr. Khan,

Your submission, Cholecystectomy rates mirror urbanization trends and highlight consequences of urban living in an African cohort, has been assigned to an editor and now has the following manuscript reference number: THELANCETPUBLICHEALTH-D-18-00415.

Please quote this number in any correspondence you have with us as it will enable us to efficiently handle any queries you may have.

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Appendix 3: Approved research protocol

Title: Gallbladder disease: A review of cholecystectomy specimens in South Africa

MMed Candidate: Zafar Ahmed Khan

Contact details:

Tel: 011 646 6453, 082 420 8243

Email: zafar@webmail.co.za

Supervisor: Dr. M Brand

Summary

Gallbladder disease is a common and costly pathology worldwide**.** Little has been written about the disease in the South African context. The last study done with specific focus on gallbladder disease was in the 1980s. Furthermore, the rate of gallbladder carcinoma appears to be increasing. This study aims to use cholecystectomy specimens to estimate the prevalence of gallbladder disease, the prevalence of incidental gallbladder malignancy in routine cholecystectomy specimens and specifics with regard to pathological findings in cholecystectomy specimens. This will be done by approaching several laboratories across South Africa for data with regards to demographics and histology from cholecystectomy specimens processed over the last 20 years.

Gallbladder disease: A review of cholecystectomy specimens in South Africa

Introduction and background

Gallbladder disease is a common and costly pathology worldwide. The spectrum of disease ranges from asymptomatic gallstone disease to gallbladder carcinoma. Very little has been written about gallbladder pathology in the South African context.

The development of gallstone disease varies among population groups around the world with an average of 10-15% in developed societies with an annual incidence of approximately 1 in 200. However, the vast majority will not experience pain nor complicate merely by the presence of stones in the gallbladder. [1] The risk of developing symptomatic disease is approximately 2-3% per year and 10% at five years.[1] As a result the number of procedures for gallstone disease has risen with cholecystectomy becoming the most common elective surgical procedure in the United States with over 750000 cholecystectomies performed per year.[1] In the last thirty years the burden of disease has increased by 30% resulting in an estimated annual expenditure of approximately $6.5 billion in the United States.[2]

Epidemiological studies from African countries, including South Africa, Nigeria, Kenya and Uganda suggest that the rate of gallstone disease is low in the African population.[3] However these studies used methods including cholecystectomy rates which is a crude indication of prevalence and autopsy studies which are subject to bias as only bodies that underwent autopsies were included. Two studies conducted at Baragwanath hospital in the 1980s suggest that although the rates of gallstone disease in the black “urban” African population may be low, the trend was that of an increasing one citing increasing exposure to a Western lifestyle as a possible risk factor.[3,4] This included mainly changes in dietary intake, with an increase in fat and decreased fibre intake. The authors hypothesized that a continuing exposure would lead to an increase in prevalence on gallstones. Additional studies looking at investigating the epidemiology of gallstone disease are thus needed.

Risk factors for the development of gallstone disease are divided into non-modifiable and modifiable factors.[2]

Non-modifiable factors include a family history of gallstone disease, genetic predisposition, ethnic background, increasing age and female gender. Cholelithiasis probably requires the inheritance of multiple genetic aberrations as evidenced by the five times increased risk in family members of affected individuals without any obvious Mendelian pattern of inheritance. Ethnicity may play a significant role in gallstone formation. International literature quotes North American Indians as having the highest reported rates of cholelithiasis with approximately 64% of the female population affected, closely followed by the indigenous populations of South America with almost 50% of women affected.[1] Despite the lack of data, sub Saharan Africans appear to have the lowest incidence of cholelithiasis at less than 5%. With regard to increasing age, a 4-10 fold increase risk of developing gallstone disease is observed after the age of 40. Females have been found to have an increased of forming gallstones, more so during the reproductive years due to an increase in female sex hormones. Following menopause the risk of developing gallstones is similar to men of the same age.

Modifiable factors include obesity, specifically centripetal obesity, rapid weight loss, drugs including ceftriaxone, thiazide diuretics and octreotide, total parenteral nutrition and pregnancy. Black pigment stones occur most commonly in the East. They may be caused by ileal Crohn’s disease, cirrhosis, haemolysis or parasitic infection.

Gallbladder carcinoma is an uncommon malignancy. However when it does present it is associated with a short life expectancy. The incidence of gallbladder malignancy increases with age reaching a maximum in the seventh decade. It is approximately five times more common in females. There is a significant variation amongst different geographical regions and ethnic groups and is an uncommon disease in developed populations. The highest incidences are described in East Asia, North India, Pakistan, Eastern Europe and South America.[1] Other risk factors for gallbladder malignancy include cholelithiasis, chronic inflammatory conditions of the gallbladder, biliary tract abnormalities and diagnostic confusion caused by gallbladder polyps.[1]

Approximately 10-30% of patients presenting with gallbladder carcinoma are resectable. In 1978 Piehler and Crichlow reported a 5 year survival rate of 4.1% with a median survival of 5-8 months in more than 5000 patients diagnosed with gallbladder cancer.[5] Most survivors in this report came from a group of patients who had a gallbladder resection in which the malignancy was not apparent to the surgeon as well as those who had a papillary gallbladder cancer variant with minimal invasion. In an analysis of the patients who underwent a resection for cure of malignancy, only 16.5% of that subgroup survived at 5 years. Results from a French Surgical Association Survey found similar 5 year survival rates and median survival of 5% and 3 months respectively.[6] They found that simple cholecystectomy for Tis, T1 and T2 yielded a projected 5 year survival of 93%, 18% and 10% respectively with no difference in survival for patients with T3 and T4 disease irrespective of the surgical procedure adopted. These large studies illustrate that advanced disease is associated with a uniformly poor outcome but early disease treated appropriately may result in prolonged survival. However, a pre-operative diagnosis of early disease is made in less than 20%.[7] This is largely due to the fact that patients are often asymptomatic and even if they do have symptoms, these often mimic those of chronic cholecystis.[7] Furthermore, it is believed that chronic inflammation is responsible for the development of gallbladder cancer and up to 92% of patients with gallbladder carcinoma will have concomitant stone disease. Conversely the lifetime risk for the development of carcinoma in stone disease is only 0.5%. The only recognized premalignant condition is that of a porcelain gallbladder and this has been challenged in various reviews of the subject.[10] Furthermore the diagnosis of gallbladder carcinoma may also be missed intra-operatively with early disease. This has been shown even when the specimen was examined by the surgeon.

Incidental gallbladder malignancies are found in approximately 0.3-1.5% of cholecystectomy specimens.[11] These patients tend to have a better prognosis than those diagnosed pre-operatively. The routine pathological examination of cholecystectomy specimens in patients with symptomatic cholelithiaisis has come into question in the last 15 to 20 years.

Routine evaluation of specimens has been suggested by several studies. These studies suggest that despite careful clinical evaluation, radiological evaluation and macroscopic examination by the operating surgeon a number of malignancies would go unrecognized.[11] Furthermore up to 40% of patients, in some series', with abnormalities on pathological evaluation will require further treatment. The question of medicolegal consequences has also not been taken into account by proponents of selective evaluation. Hence routine evaluation gives one a certain diagnosis, may prognosticate and suggest further treatment as necessary.

Selective evaluation has also been suggested in several studies.[11] The studies failed to demonstrate the presence of a truly incidental gallbladder malignancy i.e. not suspected by either pre- or intra-operative evaluation. However this has been refuted by studies supporting routine evaluation. They go on to suggest that it would be unlikely to have a

gallbladder malignancy in a completely normal appearing gallbladder specimen and suggest histopathological examination for any macroscopic abnormality. Furthermore, in patients with symptomatic cholelithiasis it would be unlikely to find a histologically normal specimen, especially in the presence of acute or chronic cholecystitis. Lastly, a selective evaluation process would reduce both costs and the burden on already overburdened pathology system.

Currently there is not enough evidence to support selective histological evaluation of cholecystectomy specimens in patients with symptomatic cholelithiasis.

Two models for the carcinogenesis in the development of gallbladder carcinoma have been theorized: the metaplasia-dysplasia-carcinoma sequence and the adenoma-carcinoma sequence.[8] These represent two distinct models. It is frequently found that severe dysplasia and carcinoma in situ flank invasive carcinoma. However, actual polypoid masses akin to colorectal carcinoma are infrequent. Thus, the majority of studies have favoured the metaplasia-dysplasia sequence with relatively few studies describing a carcinogenic sequence from an adenoma. Further research is required.

Hypothesis

The prevalence of gallstone disease and incidental gallbladder cancer in the South African population is higher than previous estimates.

Study objectives

- To determine the number of cholecystectomy specimens processed by the various laboratories included in the study
    - To determine the change in the number of cholecystectomies performed, including those for malignancies over the last 10 years versus the preceding 10 years

- To determine the prevalence of incidental gallbladder malignancy in both public and private health care settings in South Africa, and how this has changed over the last 20 years.

- The determine the incidence of adenomas, dysplasia and calcification in gallbladder specimens.

Methods

A retrospective audit of cholecystectomy specimens processed by the major histopathological laboratories in South Africa over the last 20 years. These laboratories include NHLS, Lancet, Ampath, Pathcare, Gritzman and Thatcher and WITS Laboratory.

Inclusion criteria

All cholecystectomy specimens processed over the last 20 years (January 1994 to December 2013)

Exclusion criteria

Patients under the age of 18 will be excluded

Data that will be requested from the pathology laboratories

All data will be anonymous without individual identifiers.

- Date of specimen collection
- Hospital where cholecystectomy was performed
- Age of patient
- Gender
- Race
- Surgical information if supplied
    - Indication for procedure
    - Surgical method
- Gall bladder histology information
    - Acute or chronic inflammation
    - Presence of polyps, type of polyps, number and size
    - Presence of calcification, type of calcification
    - Presence of Rokitansky Aschoff sinuses
    - Presence of gallstones
    - Presence of cystic duct lymph node, especially in the presence of carcinoma
    - Presence of cancer
        - TNM classification
        - Flat or polypoid, size of the lesion, site in the gallbladder
        - Presence of associated adenoma, dysplasia, polyps, BIN

Statistical analysis

Data will be entered into an excel spreadsheet. Statistica will be used to calculate relationships between variables. A student t-test will be used to determine statistical differences between various parameters; such as age, underlying pathology, presence of polyps, malignancy etc.; in the cholecystectomy specimens in the two ten year periods. A p value of <0.05 will be considered significant. Univariate analysis will be carried out to determine predictors of malignancy.

Authorship

All participating laboratories may nominate one person for acknowledgement or co-authorship. This will be at the discretion of the investigator or supervisors and will be

included into the publication. The primary investigator will be the first author, and the study supervisor will be the last author.

Ethical Approval

Conditional ethics approval has been obtained from the University of Witwatersrand HREC committee. Ethics number M140935. The certificate is attached at the end of this protocol.

Budget/Funding

None/Not applicable

Limitations

It is unlikely that this study will be able to establish true prevalence of gallbladder disease among the South African population as cholecystectomy rates suffer from problems including access to healthcare and threshold for surgery. However, true prevalence is a difficult objective to achieve. Autopsy studies suffer from inherent biases in the fact that they only include patients subjected to autopsy and may represent a younger population who do not represent a true prevalence of disease. Furthermore, at autopsy the gallbladder may not be examined and incidental early cancer, adenomas, etc. may be missed. The best possible measure for prevalence would probably be a very large ultrasound study in an asymptomatic cohort, something which would be difficult to attain in our circumstance.

Potential Outcomes and Benefits

This study will add significant data with regards to indications and numbers of cholecystectomies performed. Extrapolation of data may suggest prevalence rates of gallbladder disease and incidental gallbladder malignancies which are not currently known. Furthermore, information attained from incidental gallbladder malignancies will further add facts to the debate on routine versus selective evaluation of cholecystectomy specimens. Lastly, a contribution with regard to the pathogenesis of gallbladder malignancy may be obtained by carefully evaluating the presence of adenomas and metaplasia/dysplasia in specimens which may have invasive or in situ carcinoma.

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Appendix 4: Plagiarism report (Turn-it-in)

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by Pascaline Fru-Fonteh

Submission date: 21-Sep-2018 10:17AM (UTC+0200)
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Gallbladder disease: A review of cholecystectomy specimens in South Africa

Abstract

Background

Studies suggest that the rate gallstone disease in Africa is low. Our hypothesis is that gallstone disease in Africa has increased due to urbanization and its associated increases in body mass index (BMI).

Methods

An audit of cholecystectomies done in South Africa by reviewing gallbladder specimens processed by the South African National Health Laboratory Service (NHLS) from 2004 and 2014 was done. The NHLS services 82.5% of SA's population. Descriptive analysis was performed with comparison done. Urbanization ratios were obtained from Statistics South Africa and BMI data from previously published studies.

Results

33467 cholecystectomy specimens were analysed. There was a 92% absolute increase in cholecystectomies during the study period (Pearson r 0.94; $p < 0.01$) with the overall cholecystectomy rate increasing by 65% from 8.36 to 13.81 per 100000 population. 85% of cholecystectomies were in females, who were significantly younger than males. The data was divided into two equal time periods and compared. During period 2 there was 28.8% increase in cholecystectomies and patients were significantly younger (46.9 vs 48.2 years; $p = < 0.0001$). The Northern Cape was the only province to show a decline in the cholecystectomy rate in period 2 and was also the only province to record a decline in urbanization ratios. Population based studies in SA have demonstrated a clear association between urbanization and increases in BMI.

Interpretation

This nationwide African study demonstrates a significant increase in cholecystectomies for younger patients with gallstone disease. A positive relationship between urbanization and cholecystectomy rates has been demonstrated. Urbanization associated increases in BMI is the likely cause for gallstone disease in this low risk population.

Chapter 1

Introduction

Gallbladder disease is a common and costly pathology. The development of gallstones varies among population groups around the world.[1] In developed societies the rate of gallstone disease averages between 10 and 15%. The risk of developing symptomatic disease is approximately 2-3% per year and 10% five years after the development of stones.[1] There is a causal association between changes in dietary intake, increases in body mass index (BMI) and symptomatic cholelithiasis.[2]

In the last thirty years the burden of disease has increased by 30% and population based studies have identified an increased BMI as a risk factor for subsequent cholecystectomy.[3] As a result the number of procedures for gallstone disease has risen with cholecystectomy becoming the most common elective surgical procedure in the United States.[1]

Epidemiological studies from African countries, including South Africa suggest a low rate of gallstone disease in the African population.[4] Two South African studies completed during the 1980's suggested that the rates of gallstone disease in the black "urban" African population was low. These studies did note an increasing trend of gallstone disease, citing increasing exposure to a Western lifestyle as the possible causal association.[4,5]

We hypothesized that urbanization and its association with increased BMI has resulted in an increase in gallstone disease and thus cholecystectomy rates for gallstone related disease in South Africa.

Chapter 2

Methods

Data Source

The South African National Health Laboratory Service (NHLS) was established by legislation in 2001, enabling the amalgamation of all laboratories in the public health service. The public sector hospitals service 82·5% of the South African population and thus provide a cross sectional study of the South African population.[6] It is standard practice for all cholecystectomy specimens to be sent for histological analysis in South Africa. Cholecystectomy (CC) data was obtained from the NHLS prospective histological database for the period 2004 to 2014. South Africa has nine provinces and data was collected and categorised according to the province in which the CC was performed. The data obtained was analyzed for errors and duplicates were removed. Data on urbanization trends were obtained from Statistics South Africa. Ethics approval for the study was granted by the University of Witwatersrand Human Research Ethics Committee and the NHLS (Reference M140935).

Inclusion and exclusion criteria

All patients over 12 years of age with gallstone related disease were included in the analysis. Any cholecystectomy performed during the course of another operation and where gallstone related disease was not the cause of the primary pathology were excluded (e.g. liver surgery, biliary bypass procedures, pancreatic surgery, and trauma).

Statistics

The objectives of this study were descriptive and the database was very large, hence no sample size estimation was necessary. Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation. Continuous variables were summarised by the mean, standard deviation, median and interquartile range. Comparison of categorical variables were carried out using Fisher's exact test and continuous variables using independent samples t-test. Calculation of cholecystectomy rates was per 100000 population. This was done by excluding the 17·5% patients with medical insurance that are not treated by public service hospitals. Medical

insurance data was obtained from Statistics South Africa.[6] Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

Chapter 3

Results

A total of 34294 cholecystectomy specimens were processed during the study period. Following exclusions, 33467 were analyzed. The proportion of female patients in this series was 85% with a male to female ratio of 1:5·7. The mean age of the study population was 47·3years (SD 15 years), male patients had a mean age of 52·2 years (SD 15·2 years) and were significantly older than the female patients with a mean age of 46·4 years (SD 14·7 years) ($p < 0.0001$). There was an absolute increase of 92% in the number of CC during the study period (Pearson r 0·94; $p < 0·01$), and the CC rate increased by 65% from 8·36 to 13·81 per 100000 population. The greatest proportion of CC were performed in the two provinces that have the highest rates of urbanisation, namely Gauteng and the Western Cape provinces.

The data was divided into two equal time periods, period 1 (2004-2008) and period 2 (2009-2013). Kwa-Zulu Natal province was excluded due to data only being available after 2010. Overall there was a 28·8% increase in the number of cholecystectomies during period 2 compared to period 1 (Figure 1). Seven of the eight studied provinces recorded increases in cholecystectomy rates. The Northern Cape was the only province to show a decrease in the cholecystectomy rate. There were 29% fewer cholecystectomies in the Northern Cape in period 2. Overall, during period 2, the patients undergoing cholecystectomy were significantly younger than during period 1 (48·2 vs 46·9 years; $p = < 0.0001$). This was true for both female (47·4 vs 46·1 years; $p = < 0.0001$) and male patients (52·6 vs 51·5 years; $p = 0·0362$). There was no significant change in the male to female ratio ($p = 0·4156$). At the beginning of the study there were only three hospitals in the country that performed more than 100 cholecystectomies in a calendar year and all were affiliated to a university or located in large metropolitan areas. At the end of the period 2 fifteen hospitals were consistently performing more than 100 cholecystectomies in a year, with all but three university affiliated hospitals or in major metropolitan areas.

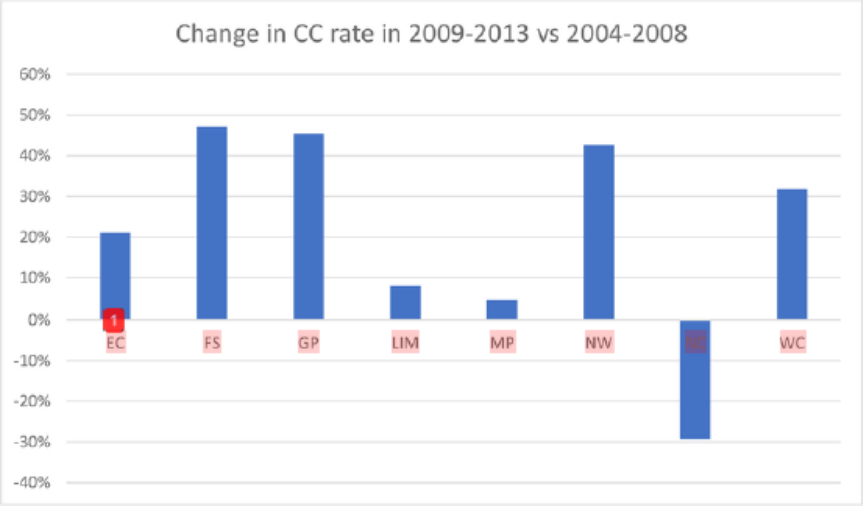

Figure 3.1 – Change in cholecystectomy rates in the last decade

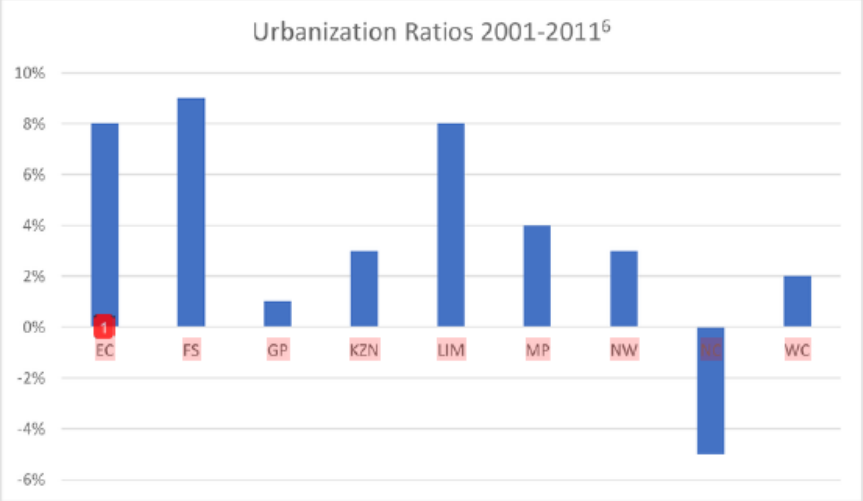

Figure 3.2 – Rate of urbanization of the nine provinces. The Northern Cape experienced a negative urbanization rate.

6

Chapter 4

Discussion

The rate of gallstone disease among women is 2 to 3 times higher than men.[7] Our finding of a 1:5 male to female ratio is in keeping with the literature albeit at a higher rate. Male patients were significantly older than female patients in this study which has also been consistent with other cholecystectomy studies.[8] In period 2 of the study there was a significant trend for younger patients to have a cholecystectomy. This is an unusual finding as the incidence of cholelithiasis increases with age[9], and suggests that other risk factors may be more prevalent in the study population.

This study, the largest from Africa, demonstrates an increase in the number of cholecystectomies for gallstone related disease in South Africa over the last 12 years. Cholecystectomy studies from the early 1990's have attributed the increased rate of cholecystectomies to a lower threshold for surgery and enthusiasm associated with the advent of less morbid and better tolerated laparoscopic surgical procedures.[8,10–12] However, continued and sustained increases in cholecystectomy rates are ascribed to changes in risk factors; specifically dietary changes and increasing body mass index.[2,8,13] The overall absolute increase of 92% in the CC rate is not commensurate with the annual 1·48% population growth in South Africa during the years of the study and more so when 30% of the growth was in the age group 0 to 14 years old. This increased rate is also supported by the increases demonstrated per 100000 population. However, when comparing the first half of the study to the second there was an increase of 28·8%, suggesting that although the annual rate continues to increase, the rates of increase are slowing down.

Two studies conducted in Soweto, South Africa, during the 1980s suggested that although the rate of cholelithiasis in the black "urban" African population was low, there was an increasing incidence together with increases in cholecystectomy rates.[4,5] It was suggested that an increased exposure to a Western lifestyle, namely increased saturated fat with a decreased fiber intake, was a possible risk factor for this. A similar study from Japan also suggests that westernization of the Japanese diet after World War 2 has resulted in an increase in

symptomatic gallstone disease.[14] These suggestions seem to be substantiated by this study where the two most urbanized provinces had the most cholecystectomies performed.

An increased body mass index is a well-established risk factor for the development of gallstones.[15] South Africa has the highest prevalence of obesity in Sub-Saharan Africa with the highest incidence among black South African women.[16] Cois et al. conducted a study investigating obesity trends and risks factors in South Africa between 2008 and 2012.[17] The investigators reported an increasing trend in BMI among South African adults, however, rural dwellers had a lower baseline BMI compared to their urban counterparts. An increase in BMI was suggested to be due to the adoption of "urban lifestyles". Urbanization ratios in South Africa over the last decade show that all but one province had an increase in rural to urban migration[6], with the Northern Cape experiencing a 5% decline in urbanization (Figure 2). It was also the only province in our series to show a decline in the cholecystectomy rate (Figure 1). The urbanization and BMI data lend support to previous data suggesting urbanization together with increases in BMI are associated with an increase in symptomatic cholelithiasis.[4] This together with the decreasing age of cholecystectomy patients all appear to support our primary hypothesis.

During the last 30 years the burden of gallstone disease has increased by 30% resulting in an estimated annual expenditure of approximately $6.5 billion in the United States.[2] The South African health system is plagued by four concurrent epidemics, namely infectious diseases, specifically HIV, maternal death, malnutrition and an increasing burden of other non-communicable diseases[18]. The almost doubling in the number of cholecystectomies during the last decade represents a significant increased burden on an already strained system. This data provides a platform from which the population may be educated regarding the risks of gallstone disease and the plausibility for the implementation of risk reduction strategies, specifically community education and weight loss programs.

Low hospital volume for surgical cases has been associated with morbidity and mortality[19]. Several studies exploring cholecystectomy outcomes in relation to hospital volume suggest that high volume centers are associated with reduced morbidity and costs.[20,21] However, in

patients with average operative risk, the clinical outcomes are not different between low and high volume centres.[22] In South Africa, most high-risk patients are referred to tertiary hospitals. This study suggests that most tertiary institutions are now high-volume centers and would be able to adequately manage these patients, thus reducing morbidity and costs.

A limitation of this study is that clinicodemographic data obtained is limited to that provided by surgeon and pathologist. A second limitation may be related to the introduction of laparoscopic cholecystectomy. In other countries there has been a sustained increase in the cholecystectomy rate which may be due to broadened indications for cholecystectomy. However, the increases from these studies ranged from 20% to 53%. [8,10,12,23] Our findings of a 92% increase is higher than international trends and thus cannot be accounted for simply by the introduction of laparoscopy alone. Furthermore, the introduction of laparoscopic cholecystectomy in South Africa occurred in the early 1990's, more than 10 years prior to this study. Although the increase in cholecystectomy rates may suggest an increase in the prevalence of symptomatic cholelithiasis, cholecystectomy rates alone are subject to several sources of bias and thus may provide a crude indication of the prevalence of gallstone disease. Although it is practice for all cholecystectomies done at public hospitals are submitted to the NHLS, there is a possibility that some may not have been sent. The large number of patients included in this study may mitigate against the incomplete data.

In conclusion we have demonstrated through analysis of 33467 gallbladder specimens for gallstone related disease over a 12-year period that cholecystectomy could be used as a surrogate marker of urbanization in a developing country as well as a marker of increased risk factors, predominantly an increased body mass index. The results of this study suggest a change in the disease pattern in South Africa, in particular an increase in gallstone related disease in younger patients which is associated with urbanization and increases in body mass index. This is particularly worrisome as the population under study has generally been regarded as being at low risk for the development of gallstone disease. The increasing trend in cholecystectomies has implications of increased cost and burden of disease and is thus likely to become a public health problem in a system that is already plagued by other concurrent epidemics (infectious disease, malnutrition).

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