Scandinavian Surgical Outcomes Research Group
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# PHYSSURG

## PHYSICAL ACTIVITY IN RELATION TO SURGICAL OPERATIONS

A PROSPECTIVE STUDY OF THE LEVEL OF PHYSICAL ACTIVITY AND ITS RELATIONSHIP TO COMPLICATIONS AFTER SURGERY

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Project plan

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# 1.0 STUDY ORGANISATION

## *1.1 PLANNING GROUP AND STEERING COMMITTEE*

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## *1.2 PRINCIPAL INVESTIGATOR*

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## *1.3 DEPUTY PRINCIPAL INVESTIGATOR*

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## *1.4 STUDY SECRETARIAT*

SSORG/Göteborg at Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg.

## *1.5 SCIENTIFIC FRAMEWORK*

The study is organised and performed within the framework of Scandinavian Surgical Outcomes Research Group SSORG together with collaborators with expert knowledge in the field of physical activity and sports medicine.

The Scandinavian Surgical Outcomes Research Group SSORG is a network of surgeon-scientists in hospitals in Sweden, Denmark and Norway. This network collaborates since 2008 in the formulation of scientific questions or hypotheses, writing of protocols and in all parts of running trials. The first secretariat is situated in Göteborg. The website is www.ssorg.net.

## *1.6 ORGANISATION*

In each participating hospital a local investigator will be responsible for the inclusion, the control of the internal validity, the data collection and participate in the steering committee.

There will be no publication, apart from presentation of the protocol and number of inclusions, during the inclusion part of the trial. The steering committee decides if an

interim analysis should be made. The PI and deputy PI will decide regarding any analyses of results prior to full inclusion.

All analyses, results and conclusions will be discussed in the steering committee, as will any publication issues.

### *1.7 WRITING COMMITTEE*

In agreement with the internationally accepted guidelines for authorship ("the Vancouver criteria") the members in the planning group who are active in planning, running, analysis and writing will be part of the writing committee.

Publication of results is planned to be in international "peer review" scientific journal.

## 2. PROTOCOL

### *2.1 BACKGROUND*

Over the last decades different life style factors have been established as risk factors for various diseases. The obesity pandemic displays a good example of a disease where great effort is undertaken to characterize risk factors associated with obesity {Nguyen, 2010 #1373}. Smoking is another life style risk factor established since several decades, and where primary prevention has been increasingly successful {, 2011 #1371;Callinan, 2010 #1372}. Cardiovascular epidemiologic research at the University of Gothenburg recognized PA as a factor of importance early on and thus included PA related questions in the work up of studies with large cohorts {Rosengren, 2011 #1245;Berg, 2005 #1244;Jonsdottir, 2010 #1246}. A 4-level scale was introduced in the late 1960:s by Saltin and Grimby {Saltin, 1968 #1222} and has been used extensively since then.

Physical activity (PA) has been in focus over the last two decades as a life style factor of importance. A review summarizing nearly 170 studies states that the scientific evidence for the association between lack of physical activity and cancer is convincing regarding breast and colon cancer and probable for prostate cancer and possible for lung and endometrial cancer {Friedenreich, 2010 #1166}. Regarding postoperative rehabilitation the benefits from preoperative physical exercise together with a postoperative early rehabilitation schedule has been reported for spinal surgery {Nielsen, 2010 #2288}. In colorectal surgery the benefits of enhanced recovery programs have been clearly demonstrated {Adamina, 2011 #2282}. The impact of preoperative prehabilitation has been evaluated and seems beneficial {Carli, 2010 #2285;Jack, 2011 #2290}, however most studies have not used clinically important outcome measures such as complications or postoperative morbidity. The evidence for prehabilitation as a measure to reduce postoperative morbidity is scarce {Jack, 2011 #2290}. To evaluate the recovery after a surgical procedure in a broader sense is difficult. Several scales have been tried to assess recovery {Allvin, 2011 #2220;Herrera, 2007 #2310;Paddison, 2011 #2318;Kluivers, 2008 #2317}.

The simple instrument for self-reported PA introduced by Saltin and Grimby has been shown to discriminate between sedentary and active counterparts regarding maximum oxygen uptake {Saltin, 1997 #1227} and has been validated against biological measures {Aires, 2003 #1223}. Indeed, studies have indicated that such single self-reported

approximation of the level of PA, may predict risk for morbidity and cardiovascular as well as total mortality {Apullan, 2008 #1224;Byberg, 2009 #1226;Wilsgaard, 2007 #1225}. The self-assessed PA-level concurs well with the actual physical fitness of the individual {Wanderley, 2011 #2294;Cousins, 1997 #2293;Knapik, 1992 #2292}. This is also important, since cardiorespiratory fitness may also predict cardiovascular risk and mortality {Berry, 2011 #1370}.

There are also studies indicating that other life-style factors such as alcohol consumption has a negative impact on outcome after surgery as well as outcome after health-care associated infections {de Wit, 2011 #2606;Rubinsky, 2012 #2596}. To screen for excessive alcohol consumption the Alcohol Use Disorders Identification Test–Consumption (AUDIT) test has been used. Several recent studies have indicated that a shorter survey with the top three questions in the AUDIT questionnaire (AUDIT-C) is sufficient to provide information on alcohol use {Meneses-Gaya, 2010 #2603;Bush, 1998 #2609}.

Smoking is also a life-style factor that affects surgical outcome {Gourgiotis, 2011 #2607}. It has been shown to increase the risk for complications and studies indicate that smoking cessation prior to the surgical procedure to reduce the risk for complications {Thomsen, 2009 #2610}. Self-reported assessment of smoking seems to be accurate and reflect the actual nicotine use of the individual {Yeager, 2010 #2722}.

Length of hospital stay is of importance both to patients and the society. A surgical procedure that shortens hospital stay may be cost-effective even in cases with higher operation room costs {Braga, 2005 #2578}. It is also of importance to consider time to work/sick leave; a cost for patients and society that can affect the cost analysis of a surgical procedure {Janson, 2004 #781}.

With this background it is of interest to record physical activity one year and one month prior to certain types of elective surgery and to study the relationship of PA to surgical complications and recovery is of interest.

## *2.2 DETAILS ON THE SURGICAL PROCEDURES STUDIED*

### *2.2.1 The incidence of cholecystectomies in Sweden*

A common surgical procedure is gallbladder surgery (cholecystectomy). The gallbladder associated diseases are much more common in women as illustrated by the data on cholecystectomies in Sweden 2010: 7686 cholecystectomies were performed on women (mean age 48 yrs) compared to 3534 cholecystecomies in men (mean age 54 yrs) (Source: The National Gallbladder Surgery Registry) {, 2010 #2200}. Relative incidence for gallbladder surgery regardless of indication is displayed in Figure III.

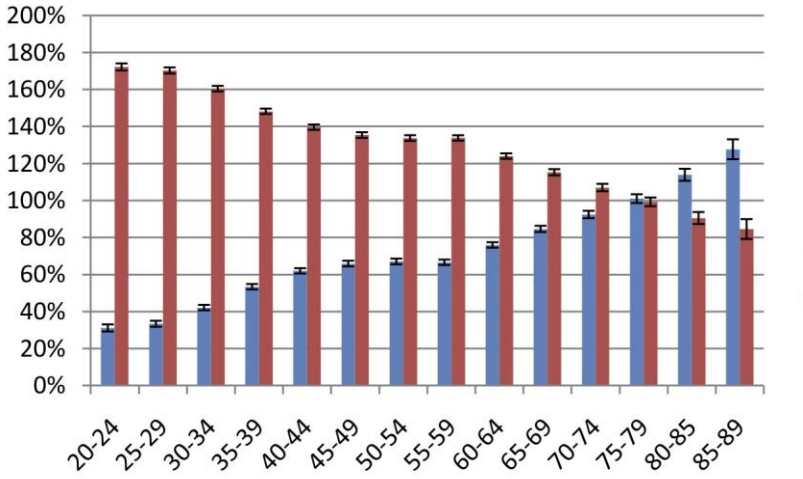


*Figure III. Relative incidence for gallbladder surgery regardless of indication. Source: The National Gallbladder Surgery Registry {, 2010 #2200}.*

### *2.2.2 The incidence of breast cancer in Sweden*

Breast cancer incidence as well as surgery for breast cancer has increased annually the last 20 years and is the most common cancer among women (Figure IV displays age specific incidence). Source: The national registry {, 2011 #2197}.

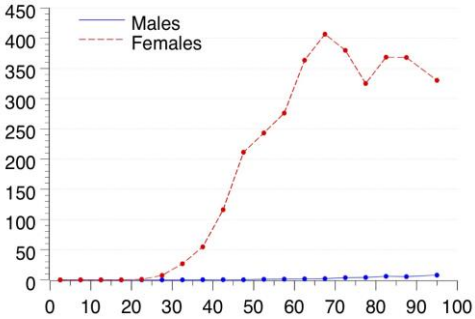


*Figure IV. Age specific incidence per 100 000 for breast cancer in Sweden (data based on the diagnostic years 2005-2009) {S.O.S., 2010 #1374}*

### *2.2.3 The incidence of colon and rectal cancer in Sweden*

Colon and rectal cancer has had a rather stable trend, but colon cancer is slightly increasing among women (Figure VI and VII displays age specific incidence) {, 2011 #2204;, 2011 #2205}. Surgery remains the curative treatment for colon and rectal cancer, although additive treatments such as radiotherapy and chemotherapy are becoming increasingly common {Valentini, 2009 #1148}.

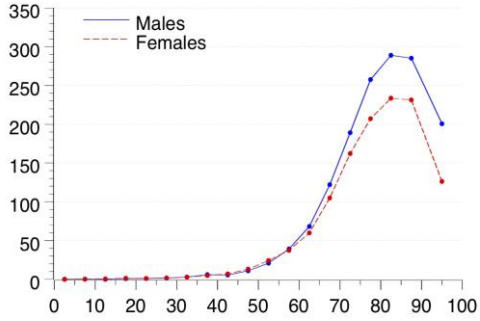


*Figure VI. Age specific incidence per 100 000 for colon cancer in Sweden (data based on the diagnostic years 2005-2009) {S.O.S., 2010 #1374}*

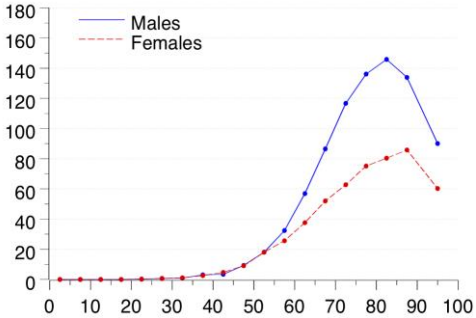


*Figure VII. Age specific incidence per 100 000 for rectal cancer in Sweden (data based on the diagnostic years 2005-2009) {S.O.S., 2010 #1374}*

## *2.3 RECOVERY AFTER A SURGICAL PROCEDURE*

All surgical procedures are followed by a phase of postoperative recovery. It can be measured in many ways and the description of recovery varies. In the recovery room there is short-term recovery, the more surgery-related recovery occurs within 4-6 weeks and then there is recovery more related to resumption of Quality of Life (QoL) and return to normal function {Kluivers, 2008 #2317}.

In recent years the demand for efficacy has brought forth recovery protocols to enhance recovery, such as for colorectal surgery {Adamina, 2011 #2282}, without an increased morbidity but without any reported difference in QoL {Gouvas, 2009 #2716}. More patient-centred self-assessing evaluations regarding recovery have been developed, mainly to address the surgery-related recovery within 4-6 weeks postoperatively {Kluivers, 2008 #2317;Allvin, 2009 #2312}. There are no validated questionnaires that have been used in a large number of studies {Kluivers, 2008 #2317}, and there is no consensus on what areas of recovery that are important. Most questionnaires regarding the surgery-related recovery address physical aspect, some emotional aspects and daily activities. Allvin et al {Allvin, 2011 #2220} has developed an instrument and identified five important domains to consider during the recovery phase: physical symptoms, physical function, the physiological area, social area and activity {Allvin, 2009 #2312}. There are no thoroughly validated questionnaires that address resumption of Quality of Life and return to normal function after surgery.

### *2.3.1 Recovery, hospital stay and complications after a cholecystectomy*

The National Gallbladder Surgery Registry has a high external validity with a registration of more than 90% in many centres compared with the Inpatient Registry {, 2010 #2200}. The frequency of severe complications such as major bile duct injuries are 0,3-0,4% and the total frequency of complications is estimated to be approximately 6% for non-emergency surgery.

Recovery after cholecystectomy has improved in the last decades. Hospital stay ranges from 0-2 days for laparoscopic surgery and 2-7 days for open surgery. According to the national guidelines from the Swedish National Board of Health and Welfare patients operated with laparoscopic surgery are on sick leave for about 1 week. Open surgery often requires up to 2-3 weeks sick leave.

### *2.3.2 Recovery, hospital stay and complications after surgery for breast cancer*

For breast cancer the registry has short-term outcome registered for reoperations within 4 weeks due to surgical complications {, 2011 #2197}. A longer follow-up is performed after at least six months then focusing on lymph-oedema, local symptoms, neurological symptoms. The recovery after breast cancer surgery is related to the long-term symptoms and psychological factors {Montazeri, 2008 #2316;Taira, 2011 #2315} and many patients have symptoms more than six months after surgery.

Hospital stay is approximately 2 days and the Swedish National Board of Health and Welfare recommends 3-6 weeks of sick leave after uncomplicated breast cancer surgery not requiring post-operative chemotherapy or radiotherapy.

### *2.3.3 Recovery and complications after surgery for colorectal cancer*

The National Registry for Colon and Rectal cancer has a history of high validity {Pahlman, 2007 #444}, and is currently undergoing an external review to be able to present accurate figures regarding external validity. In total the last report from 2009 the total incidence of complications for colon cancer was 26% and the corresponding figures for rectal cancer were 41%. Data from a randomized trial comparing open and laparoscopic surgery revealed a return to baseline for most activity related scores after at least four weeks, and at 12 weeks patients score higher than their baseline levels preoperatively {Janson, 2007 #782}.

Hospital stay is in median 7 days for colon cancer and 10 days for rectal cancer. The recommendations from the Swedish National Board of Health and Welfare estimates that without complications most colon cancer patients have returned to normal function after 4-6 weeks, whereas rectal cancer patients may require a longer time to recover, up to 6-8 weeks.

## *2.4 AIM OF THE STUDY*

The aim of this study is to investigate whether a higher physical activity prior to a surgical procedure reduces hospital stay, sick leave and the complication rate.

A secondary aim is to investigate the effect of preoperative physical activity on the rate of resumption of QoL and normal physical function.

## *2.5 THE HYPOTHESIS*

- Physically active persons have shorter lengths of hospital stay, shorter sick-leave, fewer re-hospitalizations and fewer re-operations, fewer complications as well as a faster recovery after a surgical procedure

## *2.6 STUDY DESIGN*

In order to explore the importance of PA for the outcome after a surgical procedure due to gallbladder disease, breast cancer and colorectal cancer we will ask all patients operated for any of the three above mentioned conditions to answer a short questionnaire (Appendix I) including the Saltin and Grimby {Saltin, 1968 #1222} questions to study of the effects of the level of PA immediately before surgical operations. The patients will be asked to estimate their physical activity four weeks prior to the surgical procedure.

1. Mostly sedentary
2. Light PA (such as gardening or walking or bicycling to work) at least two hours a week
3. Moderate PA such as aerobics, dancing, swimming, playing football or heavy gardening) at least two hours a week
4. Vigorous PA (high intensity) at least five hours daily several times a week.

They will also be asked to report weight, length, smoking habits, alcohol consumption, socioeconomic situation, diabetes, hypertension, hyperlipidaemia and BMI as well as certain questions with relation to Quality of Life and their postoperative recovery (Appendix I). The questions are to some extent validated through previous research {Skoogh, 2010 #2492;Steineck, 2002 #1123;Bush, 1998 #2609;Meneses-Gaya, 2010

#2603;Yeager, 2010 #2722} but some questions are newly constructed. The new questions have been constructed by an expert panel consisting of colorectal and general surgeons, cardiologist and specialized nurses. The domains chosen have been related to previous research regarding recovery {Allvin, 2009 #2312}. The questionnaire has been face-to face validated by patients with gall bladder surgery planned or a previous cholecystectomy performed, patients with breast cancer both prior and after surgery and colorectal cancer patients prior and after surgery using the same validation methods previously described for prostate cancer {Steineck, 2002 #1123}.

All patients will be contacted by telephone and a subsequently receive a mailed questionnaire (similar to the pre-operative questionnaire) (Appendix II) regarding their self-assessed QoL post-operatively and postoperative recovery, the timing of this will be related to the estimated time for recovery as follows:

- 3 weeks after gallbladder surgery
- 3 and 6 weeks after surgery for breast cancer
- 3 and 6 weeks after surgery for colorectal cancer

### *2.6.1 Primary endpoint*

For cholecystectomy and breast cancer:

- Length of sick-leave/time to work

For colon and rectal cancer:

- Length of hospital stay

### *2.6.2 Secondary endpoint*

- for colon and rectal cancer: length of sick leave/time to work
- for cholecystectomy and breast cancer: length of hospital stay
- re-operations and re-admittances within the first 6 postoperative weeks after primary surgery
- Recovery measured as resumption of Quality of Life and return to normal function after surgery according to the patient's self-reported assessment in the postoperative questionnaire and measured as return to pre-operative levels.
- Health economic analysis of resource consumption

### *2.6.3 Inclusion criteria*

All patients at including hospitals scheduled for any of the following procedures will be asked to participate:

- cholecystectomy
- breast cancer surgery
- colorectal cancer surgery

### *2.6.4 Exclusion criteria*

Inability to give informed consent.

### *2.6.5 External validity*

All patients operated at the including hospitals will be registered and non-participation and the reason for this will be registered.

### *2.6.6 Patient information and informed consent*

All patients will be asked to participate after receiving written information and a possibility to ask questions. Written consent is obtained from each patient (Appendix III and IV).

## *2.7 WORK PLAN*

Application to the Ethical Committee will be made in the spring of 2012, and after approval the printing of the short questionnaire will take place. The study is planned to begin at including hospitals in the middle of 2012. There are well established processes of care for the three different diseases chosen for this study, and as explained previously time points for information and inclusion have been identified.

## *2.8 STATISTICAL METHODS*

Regarding the surgery for gallbladder disease and surgery for breast cancer, patients are hospitalized in average two days after surgery. To be able to detect a difference of in average 1 day of hospitalization, between the physically active vs. the non-active group, 150 patients must be enrolled. The patients operated for colorectal cancer have a post-surgery hospitalization of around eight days in average. To be able to detect a difference of in average 2.5 days between the two groups, a sample of 150 enrolled patients is demanded. A difference of two days in average, demands a sample size of 220.

The calculations above are based on a power of 80%, 5% significance level and that around 30% of all patients are physically active (grade 3-4 on a four graded scale, Grimby-Saltin). Furthermore an independent t-test is used with standard deviations two for surgery for gallbladder disease and surgery for breast cancer and five for surgery for colorectal cancer. These estimates are based on 11 months historical data (2011) within Sahlgrenska University hospital.

## *2.9 DATA RETRIEVAL AND REGISTRATION*

The database will include personal identity as well as a study specific code. The database is placed on a hospital server at Sahlgrenska University Hospital with username and code for entry. Data from questionnaires will be entered manually. Length of hospital stay will be acquired from the hospital registries and then entered manually into the database. This will be retrieved 60 days postoperatively.

In all a high security standard with automatic back up of server data is present as well as firewalls against external violation. A data manager, employed by the SSORG unit will be responsible for the database.

For the various analyses described, a copy of the original database is made, without personal identification numbers, only with the study specific code. The study is registered at ClinicalTrials.gov. Application to ”Personuppgiftsombudet” at Sahlgrenska University Hospital for the database has been made, number 29882.

### *2.10 HEALTH ECONOMY*

If significant differences in outcome measures after surgery is discovered, a health economy analysis will be performed, using modelling, focusing on the societal perspective and analysing the effects of regular PA for resource consumption.

### *2.11 ETHICAL CONSIDERATION*

The study is approved by the Ethical Committee (Etiska Prövnings Nämnden) in Göteborg with DNR 180-12, date: 2012-04-05.

## 3.0 FINANCING

The study is supported by ALF- grants at Sahlgrenska University Hospital (Eva Haglind, ALFGBG-138751 and Eva Angenete, ALFGBG-136151).

## 4.0 BIBLIOGRAPHY