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SciVerse ScienceDirect
EJSO 38 (2012) 407–412
EJSO the Journal of Cancer Surgery
www.ejso.com

Predictors of re-operation due to post-surgical bleeding in breast cancer patients: A Danish population-based cohort study

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Accepted 27 February 2012
Available online 17 March 2012

Abstract

Aim: To assess the risk of re-operation due to post-surgical bleeding after initial breast cancer surgery and to identify predictors of re-operation.
Methods: We conducted a population-based study in Denmark. Patients were categorized according to age group, surgery type, and glucocorticoid use before surgery: never, current (0–90 days), and former (>90 days). We calculated the risk of re-operation due to post-surgical bleeding within 14 days after surgery, risk differences, and risk ratios of re-operation associated with age group, surgery type, and glucocorticoid use.
Results: 19,919 women were studied; 508 were re-operated. 3573 of the 19,919 women ever used glucocorticoids. Older age and mastectomy increased the risk of post-surgical bleeding compared with breast conserving surgery and younger age among both ever and never users of glucocorticoids. The crude risk of re-operation was 2.5% among never users of glucocorticoids, 2.6% among ever users and 4.0% among current users. Women aged ≥80 who were ever users of glucocorticoids and who had a mastectomy had 8.1% risk of re-operation due to post-surgical bleeding, whereas women <80 years old who never used glucocorticoids and who had breast conserving surgery had a 1.7% risk of re-operation.
Conclusions: Older age, mastectomy, and – in some women – glucocorticoid use add an extra risk of re-operation due to bleeding. Clinicians and their patients can use this information to evaluate the patient-specific risk of this complication.

Keywords: Epidemiology; Breast neoplasms; Glucocorticoid; Post-surgical bleeding; Aging; Denmark

Introduction

Breast cancer is the most common cancer among women in industrialized countries.[1] Almost all breast cancer patients undergo surgery, either breast conserving surgery or mastectomy. Although re-operation due to post-surgical bleeding is a rare complication, it delays hospital discharge, usually requires general anesthesia, and therefore is associated with substantial costs to both the patient and healthcare system. Predictors of re-operation due to bleeding after breast cancer surgery have not previously been identified.

Synthetic glucocorticoids are among the most frequently used drugs to lower the general immune response to inflammation.[2,3] Some of the side effects associated with use of synthetic glucocorticoids include delayed wound healing, upper gastrointestinal bleeding, skin atrophy, striae cutis and masked and increased activation of microbial infections. These can result in substantial post-operative complications in patients.[2–4] Animal models have shown that even a single dose of dexamethasone, a highly potent glucocorticoid, can delay wound healing.[5] Despite this, few population-based studies, with conflicting results, have investigated the impact of glucocorticoid use on post-operative complications.[6–9]

Despite the high incidence rate of breast cancer and the risk of post-operative bleeding, no study has investigated

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0748-7983/$ - see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.ejso.2012.02.184

predictors of the risk of post-surgical bleeding. We therefore conducted a large population-based cohort study with prospectively collected data to examine predictors of post-surgical bleeding – with special focus on age, surgery type, and glucocorticoid use – in a population-based cohort of Danish breast cancer patients.

Methods

Study population

Following a design we used earlier to study the association between selective serotonin reuptake inhibitor (SSRI) anti-depressant prescriptions and re-operation due to bleeding,[10] we conducted this population-based cohort study among residents of the North and Central Denmark Regions, which have a total population of 1.8 million inhabitants. A unique civil personal registration (CPR) number has been assigned to all Danish citizens and immigrants since 1968 by the Danish Civil Registration System.[11] This number encodes sex and date of birth, the latter allowing calculation of age at the date of breast cancer surgery. The CPR number also facilitates precise linkage between population-based registries. All non-psychiatric hospitalizations are registered to individual patients in the Danish National Patient Registry (DNPR).[12,13] The DNPR has registered all inpatient procedures in Danish public hospitals since 1977 and all outpatient procedures since 1995. Information is recorded in the DNPR immediately after discharge or outpatient visit and includes CPR number, dates of admission and discharge, and up to 20 diagnostic codes categorized according to the International Classification of Disease (ICD). Using the DNPR, we identified 19,919 women who had surgery for a first diagnosis of breast cancer (ICD-10 codes C50.0–50.6, C50.8 & C50.9) from 1 January 1996 through 31 December 2009, the time period during which we could link to complete prescription history by the methods described below. From the DNPR we also collected data on the type of primary breast cancer-directed surgery in accordance with the Danish Classification of Surgical Procedures and Therapy[14] – mastectomy (code KHAC) or breast conserving surgery (BCS) (code KHAB). All breast cancer patients were treated initially with either mastectomy or BCS.

Prescription data

All pharmacies in the North and Central Denmark Regions use computerized accounting systems connected with the National Health Service to record for each prescription the patient's CPR number, type and quantity of medication dispensed (tablet and package size), and prescription data according to the drug's Anatomical Therapeutic Classification (ATC).[15] Information on prescriptions for refundable drugs is forwarded electronically to the National Health Service and to a research database at Aarhus University, with complete coverage in the region since 1998.[12] The National Health Service refunds a proportion of the cost of prescribed drugs. Our target drug class was systemically absorbed glucocorticoids. We therefore limited the definition of exposure to the following classes of glucocorticoids: systemic hormones (ATC code H02AB and H02BX), glucocorticoids for rectal application (ATC codes A07EA and C05AA), and inhalation glucocorticoids (ATC code R03AD and R03BA). A complete list of individual drug types can be found in Appendix Table 1.

Data on potential predictors

To account for factors that may be associated with a prescription for systemic glucocorticoids and with post-surgical bleeding, we acquired data on age at breast cancer surgery and on any (ever) preoperative use of platelet inhibitors, vitamin K antagonists, oral anti-coagulants, non-steroidal anti-inflammatory drugs (NSAIDS) (non-aspirin NSAID, excluding selective Cox-2 inhibitors, as these have prothrombotic side effects[16]), SSRI anti-depressants, and non-SSRI anti-depressants (tri-cyclic anti-depressants (TCA), tetracyclical anti-depressants) (see Appendix for specific ATC codes).

We obtained information on specific precedent comorbidities from the DNPR including liver disease, uremia, other cancers, renal disease, autoimmune diseases, thrombocytopenia, and vasculitis; all of which can cause bleeding.

To obtain information on stage of breast cancer we used data from the Danish Cancer Registry (DCR) and linked to DNPR data. The DCR has existed since 1943 and from 1987 reporting became mandatory for all Danish doctors. The reporting delay in DCR is approximately 2 years and at the time of our data retrieval we could collect information up to 31 December 2008. TNM staging was registered beginning 1 January 2004.[12] With the DNPR data as the underlying basis to identify breast cancer diagnoses, we searched for matching CPR numbers on women who had stage information in the DCR and only one breast cancer diagnosis since 2004. By this strategy, we identified 5037 women. This subpopulation was used to perform the statistical analysis examining the effect of confounding by disease stage.

Post-operative bleeding outcomes

Information on re-operation due to post-surgical bleeding within 14 days of primary breast cancer-directed surgery was retrieved from the DNPR (codes: KHWD00, KHWE00).

Variable definition

Consistent with earlier definitions of older women with breast cancer we stratified the study population by age into two categories: women <80 years and women 80 years or older.[16] Surgery type was dichotomized as mastectomy or breast conserving surgery. Patients were categorized according to their use of glucocorticoids (never/ever use)