ANESTHESIOLOGY

Volatile *versus* Propofol General Anesthesia and Long-term Survival after Breast Cancer Surgery: A National Registry Retrospective Cohort Study

Mats Enlund, M.D., Ph.D., Anders Berglund, Ph.D., Anna Enlund, M.D., Leif Bergkvist, M.D., Ph.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In patients undergoing breast cancer surgery, biomarker studies demonstrate that propofol *versus* inhaled volatile general anesthesia are associated with distinct immune, vascular growth, and cellular apoptosis profiles
- A randomized controlled trial of regional anesthesia combined with propofol sedation *versus* inhaled volatile general anesthesia combined with opioid analgesia for breast cancer surgery did not demonstrate a difference in cancer recurrence
- The association between propofol *versus* inhaled general anesthesia for breast cancer surgery and cancer recurrence and long-term survival remains unclear

What This Article Tells Us That Is New

- Using data combining two national Swedish clinical registries from 2013 to 2019 for 18,674 breast cancer surgery patients, the authors observed that 13,873 (74.3%) received propofol general anesthesia and 4,801 (25.7%) received inhaled volatile general anesthesia
- In a propensity score–matched cohort of 9,316 patients, there was no difference in overall survival between patients receiving propofol general anesthesia (4,284 of 4,658; 92.0%) *versus* inhaled volatile general anesthesia (4,288 of 4,658; 92.1%)

ABSTRACT

Background: Several retrospective studies using administrative or single-center data have failed to show any difference between general anesthesia using propofol *versus* inhaled volatiles on long-term survival after breast cancer surgery. Although randomized controlled trials are ongoing, validated data from national clinical registries may advance the reliability of existing knowledge.

Methods: Data on breast cancer surgery performed under general anesthesia between 2013 and 2019 from the Swedish PeriOperative Registry and the National Quality Registry for Breast Cancer were record-linked. Overall survival was compared between patients receiving propofol and patients receiving inhaled volatile for anesthesia maintenance.

Results: Of 18,674 subjects, 13,873 patients (74.3%) received propofol and 4,801 (25.7%) received an inhaled volatile for general anesthesia maintenance. The two cohorts differed in most respects. Patients receiving inhaled volatile were older (67 yr *vs.* 65 yr), sicker (888 [19.0%] American Society of Anesthesiologists status 3 to 5 *vs.* 1,742 [12.8%]), and the breast cancer to be more advanced. Median follow-up was 33 months (interquartile range, 19 to 48). In the full, unmatched cohort, there was a statistically significantly higher overall survival among patients receiving propofol (13,489 of 13,873 [97.2%]) *versus* inhaled volatile (4,039 of 4,801 [84.1%]; hazard ratio, 0.80; 95% CI, 0.70 to 0.90; $P < 0.001$). After 1:1 propensity score matching (4,658 matched pairs), there was no statistically significant difference in overall survival (propofol 4,284 of 4,658 [92.0%]) *versus* inhaled volatile (4,288 of 4,658 [92.1%]; hazard ratio, 0.98; 95% CI, 0.85 to 1.13; $P = 0.756$).

Conclusions: Among patients undergoing breast cancer surgery under general anesthesia, no association was observed between the choice of propofol or an inhaled volatile maintenance and overall survival.

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Retrospective cohort studies have shown that choice of a general anesthetic may be associated with survival after cancer surgery.[1–14] Biologically reasonable explanations are available.[15–22] The absolute magnitude of differences in long-term survival in these retrospective studies are comparable to the effects of chemotherapy, approximately five percentage points. However, there are three studies that focused on breast cancer alone, whereby no difference in survival could be observed between the agents.[23–25] Moreover, in the first two published retrospective studies, breast cancer was an exception from the overall results that indicated an association between the choice of anesthetic for cancer surgery and long-term survival (Timothy

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Mats Enlund, M.D., Ph.D.: Center for Clinical Research, Uppsala University, Västerås, Sweden; Department of Anesthesia and Intensive Care, Västmanland Hospital, Västerås, Sweden; European Society of Anaesthesiology and Intensive Care Onco Anesthesiology Research Group, EuroPeriscope, Brussels, Belgium.

Anders Berglund, Ph.D.: Epistat AB, Uppsala, Sweden.

Anna Enlund, M.D.: Center for Clinical Research, Uppsala University, Västerås, Sweden; Department of Anesthesia and Intensive Care, Västmanland Hospital, Västerås, Sweden.

Leif Bergkvist, M.D., Ph.D.: Center for Clinical Research, Uppsala University, Västerås, Sweden.

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Wigmore, B.M., B.Ch., F.R.C.A., F.F.I.C.M., F.C.I.C.M., Department of Anesthesiology and Critical Care Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom, December 2019, written communication).[1,2] It is thus important to clarify the effects of anesthetics on long-term survival for patients with breast cancer. If there is no difference between anesthetic options, there would be no need to "switch" from the globally dominating volatile anesthetic technique to propofol and thereby no requirements for investment in infrastructure and staff training. If, on the other hand, a clinically significant difference between the techniques can be established for breast cancer, it may have major implications for the patients. A difference of five percentage points in survival, as indicated in retrospective studies, means that life is extended every year globally for about 80,000 patients.

A prospective, randomized, controlled trial, the "CAN Study," is underway.[26] Early follow-up data for breast cancer were recently presented, indicating no difference in survival between propofol and sevoflurane groups for patients with a minimum 1-yr follow-up (median follow-up, 2.7 yr).[27] As expected, mortality was low during this short period of time, which calls for caution in interpreting the results. Large retrospective studies offer a complementary evidence base to the very few randomized, controlled trials registered so far. We have recently conducted a relatively large retrospective study with data from seven Swedish hospitals on the association between survival after breast cancer surgery and choice of anesthetics.[28] A total of 6,305 patients with breast cancer were included. However, the main finding was an illustration of the weakness of retrospective design. The interpretation of the results was influenced by the methods for analysis. In the current article, we therefore used two Swedish national registries to incorporate more stable data on population level to reduce both sampling bias and selection bias. By merging these two population registries, we expected to get a data set with both low bias and, in addition, important demographic, anesthetic, surgical, and oncologic data to statistically adjust for known factors affecting survival. Based on some of the results analyzed,[1,2] we conservatively hypothesize that propofol-based anesthesia in patients undergoing breast cancer surgery is associated with five percentage points higher absolute survival rate compared with inhaled volatile-based anesthesia.

Materials and Methods

This is a cohort study based on national registry data in the Swedish PeriOperative Registry and the National Quality Registry for Breast Cancer. The Swedish PeriOperative Registry contains information of the individual surgical procedures, covering the entire perioperative process from preoperative workup to discharge from the postanesthesia care unit, including the anesthetics used (coverage rate, 93.5%). The National Quality Registry for Breast Cancer also contains important supplementary information (*e.g.*, cancer stage and adjuvant treatments with a coverage rate of 99%) in addition to survival data. Both registries are prospectively maintained with several built-in data validation processes. Incorrect and/or inconsistent posts are returned to the user for correction before inclusion in the database. Both registries use the unique social security numbers given to all Swedish citizens. The designation "quality registry," which is necessary to obtain government funding, has been given to both registries (Supplemental Digital Content 1, http://links.lww.com/ALN/C875). A data analysis and statistical plan was written and filed (https://www.medfarm.uu.se/ckfvasteras/forskning/studieprotokoll; accessed February 21, 2020) before the data were accessed (October 2, 2020).

After ethics approval (Ethics Review Board, Uppsala, Sweden; approval no. 2020-00573), with individual written informed consent waived, all patients with breast cancer who were operated on between 2013 and 2019 were identified in the National Quality Registry for Breast Cancer, and all variables of interest (explained in subsequent paragraphs) were extracted. This data set from the National Quality Registry for Breast Cancer was sent to Uppsala Clinical Research Center, which is responsible for the Swedish PeriOperative Registry. Uppsala Clinical Research Center added its data to the file from the National Quality Registry for Breast Cancer and deidentified the final file (with a key) before it was sent encrypted to the first author (Dr. Enlund).

The independent/causal variable was the drug given for maintenance of general anesthesia, *i.e.*, propofol or a volatile (desflurane, isoflurane, or sevoflurane). Of the dependent/control variables, age at surgery, body mass index, and American Society of Anesthesiologists (ASA) status were regarded as true confounders, since they were expected to be associated with both the choice of anesthesia and overall survival. The hospitals were aggregated into three groups depending on their volume of surgery (less than 100, 100 to 500, or more than 500 surgeries annually) to minimize the confounding effect of surgical volumes on outcomes. Finally, cancer classification (according to tumor/metastasis/node staging), neoadjuvant and/or adjuvant therapy (chemotherapy, radiotherapy, endocrine therapy, and/or antibody therapy), type of procedure (total or partial mastectomy, with or without axillary clearance, complementary breast procedure), and progesterone receptor, estrogen receptor, antigen KI67, and human epidermal growth factor receptor 2 status are all known to be associated with prognosis, but not necessarily with the choice of anesthetics; therefore, these data are included as effect modifiers in the model for propensity score matching.

Statistical Analysis

Continuous variables were expressed as medians with interquartile range, while categorical variables were presented as absolute numbers and percentages. Standardized mean differences were presented between the propofol- and volatile-based anesthesia groups.

Table 1. Patient and Clinical Characteristics by Choice of Anesthetic in the Unmatched Cohort

	Unmatched Cohort		
Characteristics	**Inhaled Volatiles, n (%)**	**Propofol, n (%)**	**Standardized Mean Difference**
Total number of subjects	4,801 (100.0)	13,873 (100.0)	
Body mass index, median (interquartile range)	26.4 (23.4–30.5)	26.0 (23.2–29.4)	0.137
Missing	1,953	3,696	
Age at surgery, median (interquartile range)	67 (55–74)	65 (54–72)	0.119
Missing	0	0	
Sex, female	4,759 (99.1)	13,784 (99.4)	0.027
Missing	0	0	
ASA classification			0.173
ASA status I	1,206 (25.8)	3,978 (29.2)	
ASA status II	2,585 (55.2)	7,919 (58.1)	
ASA status III to V	888 (19.0)	1,742 (12.8)	
Missing	122	234	
Local/regional anesthesia			0.005
Regional block	41 (0.9)	112 (0.8)	
Wound infiltration	4,760 (99.1)	13,761 (99.2)	
Missing	0	0	
Year of surgery, median (interquartile range)	2017 (2016–2018)	2018 (2017–2019)	0.416
Missing	0	0	
Median blood loss, ml (interquartile range)	20 (0–50)	20 (5–50)	0.109
Missing	1,485	6,903	
Surgery volume at hospitals			0.173
Less than 100 surgeries	151 (3.1)	180 (1.3)	
100 to 500 surgeries	664 (13.8)	2,566 (18.5)	
More than 500 surgeries	3,986 (83.0)	11,127 (80.2)	
Missing	0	0	
Median follow-up time, days* (interquartile range)	1,062 (618–1,493)	815 (478–1,270)	
Missing	0	0	
Vital status, alive	4,417 (92.0)	13,111 (94.5)	
Missing	0	0	
Diagnosed at screening	2,228 (46.5)	7,182 (51.8)	0.106
Missing	12	17	
Tumor/metastasis/node staging			0.084
T1	2,879 (60.0)	8,771 (63.2)	
T2	1,555 (32.4)	4,209 (30.3)	
T3	291 (6.1)	764 (5.5)	
T4	76 (1.6)	129 (0.9)	
Missing	0	0	
Node stage			0.054
N0	4,030 (83.9)	11,896 (85.7)	
N1 to N3	745 (15.5)	1,926 (13.9)	
Cannot be measured	26 (0.5)	51 (0.4)	
Missing	0	0	
Metastasis stage			0.039
M0	4,757 (99.1)	13,792 (99.4)	
M1	43 (0.9)	80 (0.6)	
Cannot be measured	1 (0.0)	1 (0.0)	
Missing	0	0	
Estrogen receptor status			0.132
Postive	3,735 (78.6)	11,399 (83.5)	
Negative	983 (20.7)	2,181 (16.0)	
Not performed	32 (0.7)	73 (0.5)	
Missing	51	220	
Progesterone receptor status			0.089
Positive	3,125 (65.8)	9,491 (69.5)	
Negative	1,592 (33.5)	4,081 (29.9)	
Not performed	31 (0.7)	80 (0.6)	
Missing	53	221	
Nuclear antigen, marker of proliferation			0.13
Low	2,126 (44.3)	6,115 (44.1)	
Intermediate	414 (8.6)	1,536 (11.1)	
High	1,768 (36.8)	5,220 (37.6)	
Not performed	493 (10.3)	1,002 (7.2)	

(*Continued*)

Table 1. (Continued)

Characteristics	Unmatched Cohort		
	Inhaled Volatiles, n (%)	Propofol, n (%)	Standardized Mean Difference
Missing	0	0	
Human epidermal growth factor receptor 2 status			0.148
0 to 1+	2,786 (61.5)	8,611 (66.5)	
2+	913 (20.2)	2,492 (19.2)	
3+	321 (7.1)	906 (7.0)	
Not performed	511 (11.3)	939 (7.3)	
Missing	0	0	
Triple-negative subjects	345 (7.6)	919 (7.1)	0.02
Missing			
Adjuvant treatment			
Chemotherapy	487 (10.1)	1,231 (8.9)	0.043
Radiotherapy	9 (0.2)	56 (0.4)	0.04
Endocrine therapy	77 (1.6)	256 (1.8)	0.019
Antibodies	187 (3.9)	443 (3.2)	0.038
Missing	0	0	
Main reason for surgery			0.112
Breast conserving therapy	2,977 (62.0)	9,321 (67.2)	
Mastectomy	1,364 (28.4)	3,411 (24.6)	
Modified radical mastectomy	454 (9.5)	1,112 (8.0)	
Surgery of relapses	6 (0.1)	29 (0.2)	
Missing	0	0	
Postsurgery treatment			
Chemotherapy	1,398 (29.1)	4,029 (29.0)	0.002
Radiotherapy	3,234 (67.4)	9,319 (67.2)	0.004
Endocrine therapy	3,144 (65.5)	9,160 (66.0)	0.011
Antibodies	494 (10.3)	1,406 (10.1)	0.005
Missing	0	0	

*Follow-up time in days in patients with no events.
ASA, American Society of Anesthesiologists.

Propensity score matching is a method to minimize selection bias between interventional groups when estimating causal intervention effects in nonrandomized studies.[29] The treatment groups (propofol- or volatile-maintained anesthesia) were matched on a propensity score. The propensity score is the probability of intervention assignment conditional on the current baseline characteristics. Once the sample was created, the treatment effect could be estimated by directly comparing outcomes between the groups.

We created two propensity score–matched cohorts. In the first propensity score–matched cohort, the propensity scores were developed accounting for all demographical and clinical characteristics summarized in tables 1 and 2, except from body mass index and blood loss (due to high proportion of missing values), while in the second propensity score–matched cohort, only variables with a standardized mean difference higher than 0.1 were included (sensitivity analysis). All individual propensity scores were calculated through logistic regression models,[29] and then a 1:1 nearest-neighbor propensity score matching[30] with a caliper size of 0.1 was used.

The primary outcome was overall survival between subjects who underwent propofol- or volatile-maintained anesthesia. All analyses of overall survival included only patients with no missing information. Overall survival was defined as from the date of surgery to death from any cause or the end of follow-up (September 15, 2020, defined as censored), whichever came first. Any subject lost to follow-up was excluded from the study population. Overall survival was presented by using the Kaplan–Meier approach with the corresponding log-rank test. In addition, overall mortality was estimated, expressed as hazard ratios with 95% CI between the two groups using Cox regression models. We tested the proportional hazards assumption for all the Cox regressions using the tests based on weighted residuals.

In a first step, the overall survival and mortality in the unmatched cohort were described. In a second step, after the 1:1 propensity score matching, the outcomes were presented. No imputation of missing data was planned, and all analyses were performed on patients who had information on all variables selected for the propensity score matching. Thus, we excluded patients with missing information on any of the variables. We also changed the caliper size (from 0.1 to 0.5) to see the robustness of the findings for the propensity score–matched cohort. As an exploratory analysis, overall survival and mortality was presented between subjects who underwent propofol or volatile anesthesia in the subgroup of triple-negative breast cancer patients.

Table 2. Patient and Clinical Characteristics by Choice of Anesthetic in the Propensity Score–matched Cohort

	Propensity Score–matched Cohort		
Characteristics	**Inhaled Volatiles, n (%)**	**Propofol, n (%)**	**Standardized Mean Difference**
Total number of subjects	4,658 (100.0)	4,658 (100.0)	
Age at surgery, median (interquartile range)	67 (55–74)	66 (56–73)	0.008
Sex, female	4,615 (99.1)	4,610 (99.0)	0.011
ASA classification			0.013
ASA I	1,203 (25.8)	1,183 (25.4)	
ASA II	2,575 (55.3)	2,604 (55.9)	
ASA III to V	879 (18.9)	870 (18.7)	
Local/regional anesthesia			< 0.001
Regional block	37 (0.8)	37 (0.8)	
Wound infiltration	4,620 (99.2)	4,620 (99.2)	
Year of surgery, median (interquartile range)	2017 (2016–2018)	2017 (2016–2018)	0.018
Surgery volume			0.029
Less than 100 surgeries	137 (2.9)	117 (2.5)	
100 to 500 surgeries	198 (4.3)	188 (4.0)	
More than 500 surgeries	4,322 (92.8)	4,352 (93.5)	
Diagnosed at screening	2,158 (46.3)	2,338 (50.2)	0.077
Tumor/metastasis/node staging			0.027
T1	2,798 (60.1)	2,853 (61.3)	
T2	1,503 (32.3)	1,473 (31.6)	
T3	282 (6.1)	263 (5.6)	
T4	74 (1.6)	68 (1.5)	
Node stage			0.017
N0	3,914 (84.0)	3,941 (84.6)	
N1 to N3	718 (15.4)	690 (14.8)	
Cannot be measured	25 (0.5)	26 (0.6)	
Metastasis stage			0.017
M0	4,616 (99.1)	4,623 (99.3)	
M1	40 (0.9)	33 (0.7)	
Cannot be measured	1 (0.0)	1 (0.0)	
Estrogen receptor status			0.035
Positive	3,630 (77.9)	3,685 (79.1)	
Negative	946 (20.3)	902 (19.4)	
Not performed	31 (0.7)	31 (0.7)	
Missing	50 (1.1)	39 (0.8)	
Progesterone receptor status			0.043
Positive	3,036 (65.2)	3,115 (66.9)	
Negative	1,539 (33.0)	1,474 (31.7)	
Not performed	31 (0.7)	30 (0.6)	
Missing	51 (1.1)	38 (0.8)	
Nuclear antigen, marker of proliferation			0.034
Low	2,051 (44.0)	2,127 (45.7)	
Intermediate	412 (8.8)	389 (8.4)	
High	1,726 (37.1)	1,689 (36.3)	
Not performed	468 (10.0)	452 (9.7)	
Human epidermal growth factor receptor 2 status			0.016
0 to 1+	2,719 (58.4)	2,756 (59.2)	
2+	887 (19.0)	870 (18.7)	
3+	311 (6.7)	302 (6.5)	
Not performed	740 (15.9)	729 (15.7)	
Adjuvant treatment			
Chemotherapy	466 (10.0)	438 (9.4)	0.02
Radiotherapy	9 (0.2)	6 (0.1)	0.016
Endocrine therapy	74 (1.6)	54 (1.2)	0.037
Antibodies	177 (3.8)	164 (3.5)	0.015
Main reason for surgery			0.028
Breast-conserving therapy	2,901 (62.3)	2,953 (63.4)	
Mastectomy	1,308 (28.1)	1,288 (27.7)	
Modified radical mastectomy	442 (9.5)	410 (8.8)	
Surgery of relapses	6 (0.1)	6 (0.1)	
Postsurgery treatment			
Chemotherapy	1,356 (29.1)	1,342 (28.8)	0.007
Radiotherapy	3,149 (67.6)	3,207 (68.9)	0.027
Endocrine therapy	3,049 (65.5)	3,087 (66.3)	0.017
Antibodies	477 (10.2)	460 (9.9)	0.012

ASA, American Society of Anesthesiologists.

All tests were two-sided, and statistical significance was considered with a *P* value less than 0.05. The statistical analyses were performed using R version 3.6.1 (R basis for statistical calculation; Vienna University of Economics and Business, Vienna, Austria) using the packages cobalt, tableone, survival, and MatchIt.

Results

A total of 23,545 subjects were included in the encrypted file from the Swedish PeriOperative Registry. We excluded duplicate subjects (n = 2,041), subjects with incorrect anesthesia codes (n = 2,134), subjects missing follow-up time (n = 2), subjects with no evidence of cancer in the breast (n = 226), subjects with cancer *in situ* (n = 370), subjects whose primary tumors could not be evaluated (n = 96), and subjects with missing tumor staging information (n = 2; fig. 1). The final study population consisted of 18,674 subjects. A majority, 13,873 patients, were anesthetized with propofol, and 4,801 were exposed to an inhalational agent. None of the patients were given both propofol and a volatile for anesthesia maintenance. The anesthesia registry coverage increased during the first years of the time frame and reached 93.5% coverage at the end of the period.

The two groups differed in several characteristics (table 1). The propofol group was younger and its average body mass index was lower; these patients had lower ASA classifications; and their tumor status was unevenly distributed between the groups, with generally lower grading for the propofol patients. The proportions of triple-negative cancer did not differ statistically between the groups. The median follow-up time was 33 months (interquartile range, 19 to 48 months).

In the full, unmatched cohort, there was a statistically significantly higher overall survival among patients receiving propofol (13,489 of 13,873 [97.2%]) *versus* inhaled volatile (4,039 of 4,801 [84.1%]; hazard ratio, 0.80; 95% CI, 0.70 to 0.90; $P < 0.001$; fig. 2; table 3). After propensity score matching for all of the variables summarized in table 1, except for body mass index and blood loss due to high level of missing data, there was no statistically significant difference between the propofol and volatile groups (propofol, 4,284 of 4,658 [92.0%]; inhaled volatiles, 4,288 of 4,658 [92.1%]; $P = 0.756$; fig. 3) with a hazard ratio of 0.98 (95% CI, 0.85 to 1.13; table 3). The same pattern was also seen in the second propensity score–matched cohort, in which only variables with a standardized mean difference higher than 0.1 were included and in which no statistically significant differences were observed (Supplemental Digital Content 2 [http://links.lww.com/ALN/C876], tables S1 and S2; Supplemental Digital Content 3, fig. S1 [http://links.lww.com/ALN/C877]). In addition, findings in this cohort were not altered by changing the size of the caliper or when body mass index (caliper size, 0.1; $P = 0.397$; data not shown) and blood loss (caliper size, 0.1; $P = 0.510$; data not shown) were included in the propensity score matching.

The assumption of proportional hazards did not hold in the unmatched cohort ($P < 0.001$) but did hold for the full propensity score–matched ($P = 0.370$) and restricted matched cohorts ($P = 0.340$), respectively. Triple-negative breast cancer propensity score–matched patients indicated no meaningful survival benefit for propofol (hazard ratio, 1.17; 95% CI, 0.79 to 1.72; $P = 0.443$; table S3, Supplemental Digital Content 3, fig. S2, http://links.lww.com/ALN/C877). The 3- and 5-yr survival rates were calculated as a complement (table 3).

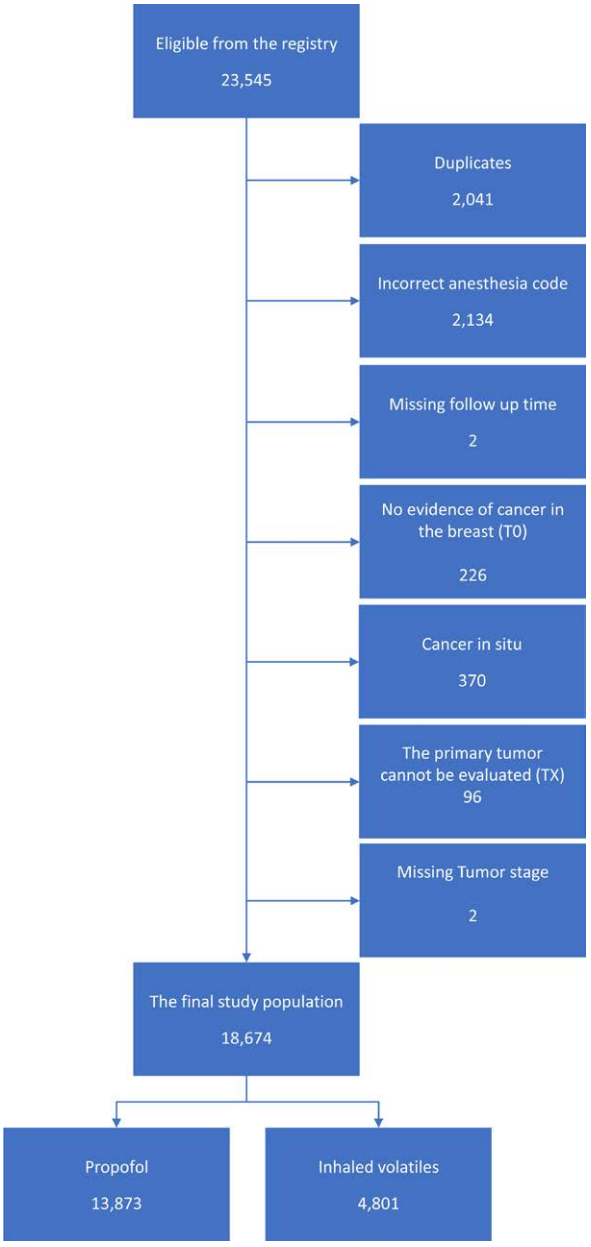

Fig. 1. Flow chart describing the study population.

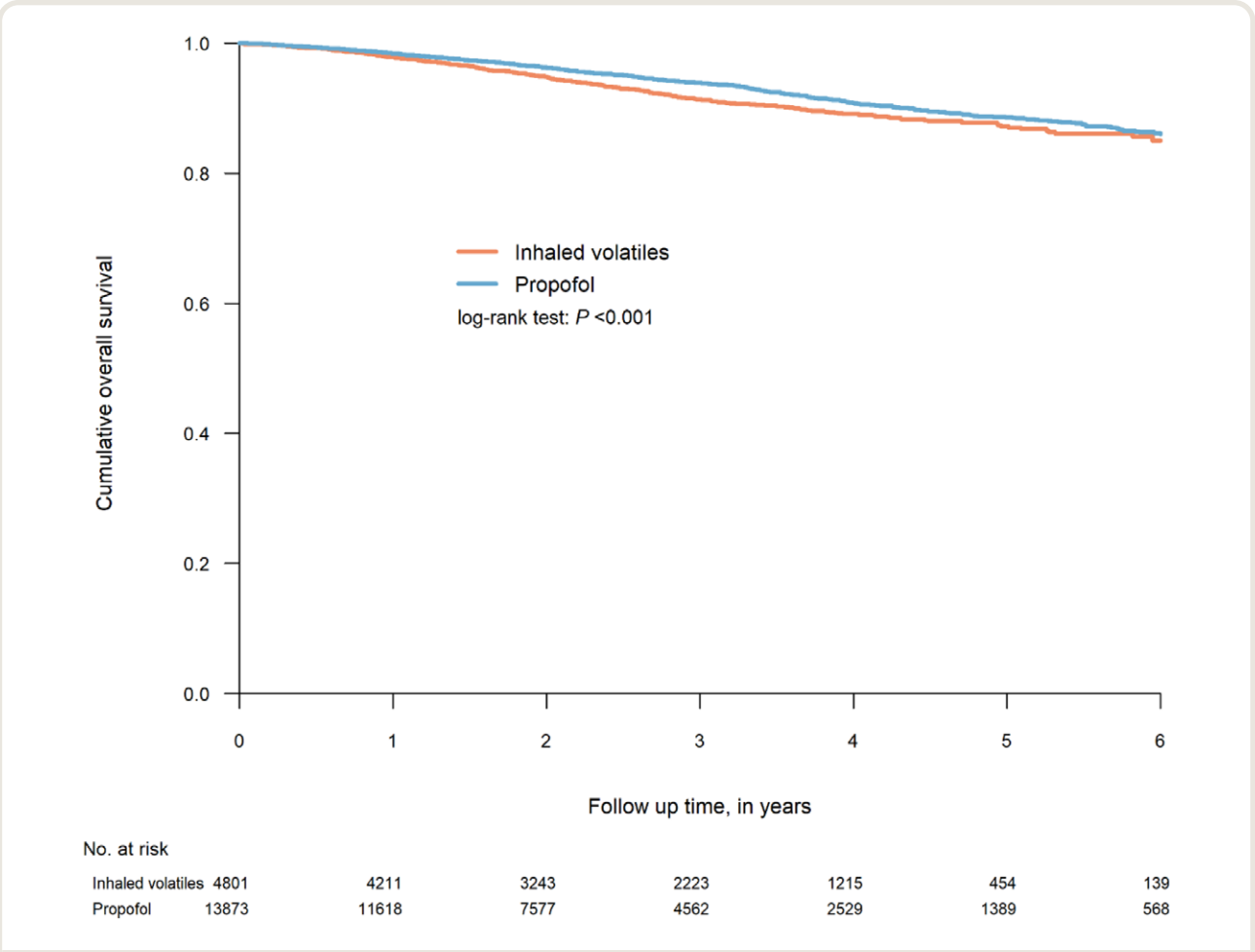

Fig. 2. Overall survival by type of anesthesia in the unmatched cohort, in which 4,801 subjects received inhaled volatiles and 13,873 subjects received propofol, respectively.

Discussion

In this national registry–based, propensity score match study with prospectively gathered data from 9,316 patients, the previous findings of several retrospective studies were confirmed. Neither a statistically significant difference nor a clinically meaningful difference could be found between administration of general anesthesia using propofol *versus* inhaled volatile in long-term survival for patients with breast cancer.

Clinical Findings Giving a Rationale for Our Hypothesis

The current results are not consistent with findings from biomarker studies. The results indicate that: (1) propofol, compared with sevoflurane, has a more favorable inhibiting effect on vascular endothelial growth factor C and transforming growth factor β in women undergoing breast cancer surgery[31]; (2) the activity of natural killer cells is higher in blood sampled from women anesthetized with propofol (and receiving a paravertebral block instead of parenteral opioids) for breast cancer surgery in comparison with women given a sevoflurane or opioid anesthetic[32]; and (3) cancer cell apoptosis is higher in a propofol or paravertebral group, compared with a group given sevoflurane or opioid for breast cancer surgery.[33] Furthermore, the transcription factor hypoxia-inducible factor, which improves the cancer cells' adaptation to hypoxia, acidosis, and starvation in a solid cancer, will be upregulated when exposed to a volatile, while the opposite appears to be the case when it is exposed to propofol.[17,34–36] These biomarker studies suggested that an inhaled volatile general anesthetic may increase the risk of a local recurrence or metastasis, while propofol general anesthesia may be neutral or even protective.

Comparison of Breast Cancer Recurrence Rate in a Randomized Controlled Trial

The combined effects of propofol and a paravertebral block compared with sevoflurane and opioids were

Table 3. Survival and Mortality Rates of Breast Cancer Patients by Choice of Anesthetic

	3-yr Survival					5-yr Survival					Overall Mortality	
Anesthetics	**Events**	**At Risk**	**3 yr**	**95% CI**	***P* Value**	**Events**	**At Risk**	**5 yr**	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**
Unmatched cohort												
Inhaled volatiles	191	2,223	91.4	90.4–92.3	< 0.001	58	454	87.2	85.8–88.7	< 0.001	1.00	Reference
Propofol	278	4,562	93.9	93.4–94.4		158	1,389	88.6	87.6–89.6		0.80	0.70–0.90
Propensity score–matched cohort												
Inhaled volatiles	187	2,154	91.3	90.4–92.3	0.202	57	449	87.2	85.8–88.7	0.716	1.00	Reference
Propofol	157	2,041	92.3	91.4–93.2		81	617	86.8	85.3–88.3		0.98	0.85–1.13
Triple-negative breast cancer in unmatched cohort												
Inhaled volatiles	10	119	81.9	77.3–86.7	0.040	3	13	80.1	75.0– 85.5	0.183	1.00	Reference
Propofol	29	223	86.9	84.2–89.7		11	47	77.2	71.5–83.4		0.81	0.58–1.13
Triple-negative breast cancer in propensity score–matched cohort												
Inhaled volatiles	46	106	81.7	76.9–86.8	0.837	1	12	80.5	75.2–86.1	0.443	1.00	Reference
Propofol	44	106	82.9	62.5–79.6		11	22	70.5	62.5–79.6		1.17	0.79–1.72

The table shows the 3- and 5-yr overall survival and mortality rates expressed as hazard ratios with 95% CI by choice of anesthetic for the unmatched cohort, the propensity score–matched cohort, and the subgroup of triple-negative breast cancer patients.

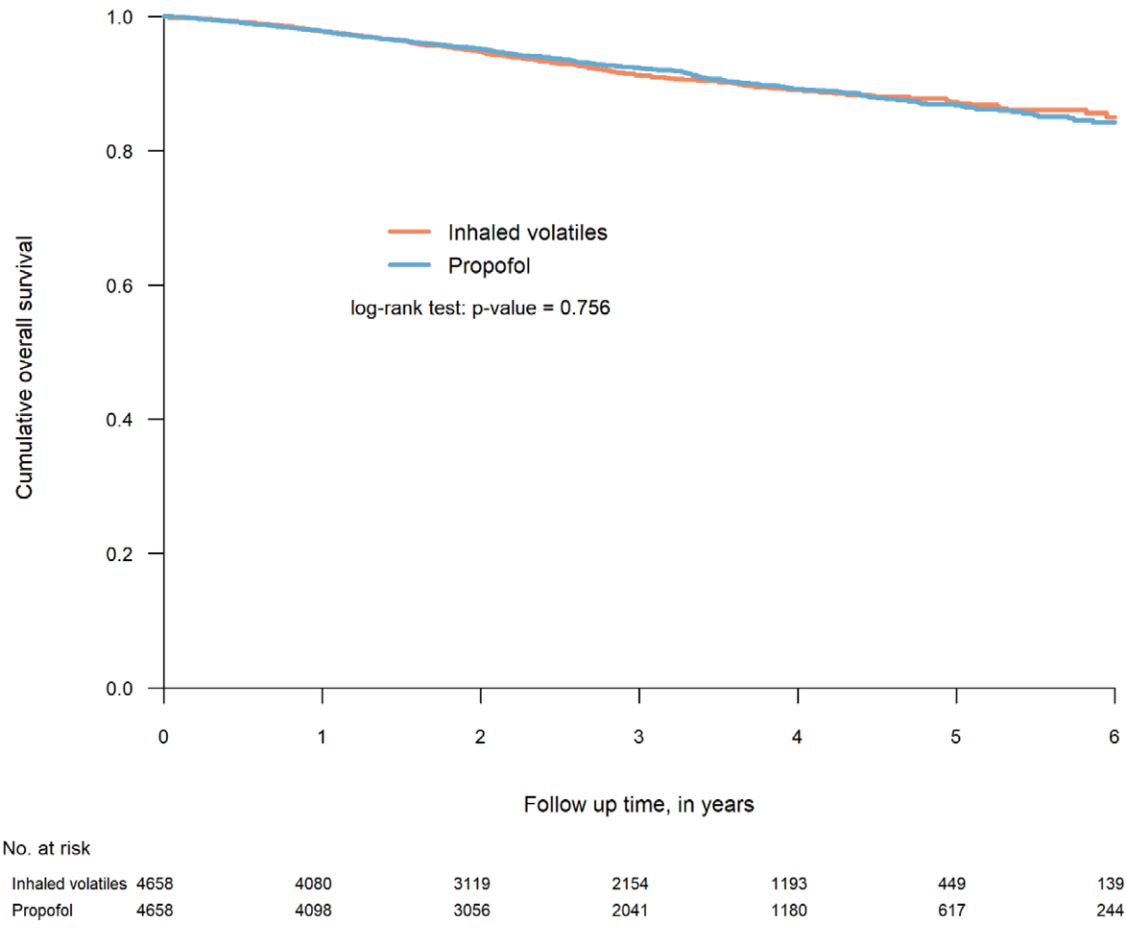

Fig. 3. Overall survival by type of anesthesia for 4,658 pairs from a full propensity score match of patients given an inhaled volatile anesthetic or propofol for anesthesia maintenance for breast cancer surgery.

studied in a randomized controlled trial with recurrence as the primary outcome in 2,132 patients with breast cancer.[37] The study was ended after a preplanned futility boundary was crossed, and the median follow-up time was 36 months. The recurrence rates were identical: 10% in both groups. While recurrence rate is distinct from a mortality outcome, the result indicates that anesthesia technique choice does not impact cancer recurrence. In addition, this study compared two different combinations of anesthesia: (1) general anesthesia with propofol combined with regional anesthesia and (2) general anesthesia with sevoflurane combined with an opioid. Despite these differences, the current results are consistent with this trial's observations.

Other Cancers and Perioperative Factors

Perioperative factors may also differ between different cancers depending on the complexity of the operation. Breast cancer, as a rather superficially localized cancer, is relatively easy to access, as opposed to intra- or retroabdominal organ tumors or lung and brain tumors. Not only may this affect the risk of seeding of cancer cells during manipulations of the cancer, but it may also affect the duration of anesthesia. If the hypothesis is valid for some other cancers, the time exposed to a volatile would be critical. Breast cancer operations are relatively short procedures, which may favor a null finding.

It is not only for breast cancer that the data do not support the hypothesis of different impact on long-term survival after cancer surgery depending on the choice of anesthetic. For example, in gastric cancer and lung cancer, there is one study for each of the two cancers indicating no difference in long-term survival between propofol and sevoflurane.[38,39] This contrasts with two other studies for gastric cancer and one other for lung cancer that support the hypothesis.[4,12,13] However, a large, recently published study, using a national registry, indicated no difference in long-term survival after gastrointestinal cancer,[40] whereas another national registry–based study on colorectal cancer found a benefit for propofol.[41]

Role of Propofol Used for Induction

Propofol was used for anesthesia induction in all patients, including those whose anesthesia was subsequently maintained with volatiles. It has been proposed in a large observational study that an increasing propofol dose was associated with reduced odds of 1-yr mortality in patients without a solid cancer but not in patients with solid cancer, a finding that was replicated for 5-yr mortality.[42] There were significant interactions between propofol dose and breast, colorectal, and hepatobiliary cancer with regard to 1-yr mortality, but the odds of 1-yr mortality increased with higher doses of propofol only in patients with colorectal or hepatobiliary cancer. Therefore, it is unlikely that an induction dose of propofol to the volatile group in our study would have a modifying effect on survival in the volatile group.

A strength of the current study was the availability of tumor characteristics, such as stage, receptors, and prognostic markers. The main limitation of the current study is that despite the use of prospectively collected data, it still is a retrospective observational study, and there is a risk of residual confounding by unmeasured or unknown covariates. For example, the absence of specific comorbidities, clinical provider information, postoperative management, or other intraoperative medication information in the registry is a significant limitation.

It should also be noted that the registry used for this study does not discriminate between volatiles. Sevoflurane dominates the Swedish market, but we cannot state the proportions between the three volatiles used (desflurane, isoflurane, and sevoflurane). This would be of interest if the three volatiles differ in the effects on the immune system, as suggested in a retrospective study of stage III ovarian cancer, in which patients exposed to sevoflurane had a higher rate of cancer recurrence compared with patients receiving desflurane.[43] Finally, cancer biology may modulate the response to the anesthetics, so these findings cannot be generalized to other cancers.

Conclusions

This observational study did not show any difference in survival between breast cancer patients receiving propofol general anesthesia compared with those receiving inhaled volatile general anesthesia.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Enlund: Uppsala University, Center for Clinical Research, Entrance 29, Västmanland Hospital, SE-721 89 Västerås, Sweden. mats.enlund@regionvastmanland.se. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Supplemental Digital Content

Information about Swedish Quality Registries, http://links.lww.com/ALN/C875
Supplemental Tables: Restricted Propensity Score Match, http://links.lww.com/ALN/C876
Overall Survival after a Full Propensity Score Match, http://links.lww.com/ALN/C877

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Romancing the Elements: Ether as Solidly Platonic?

Millennia before five regular convex polyhedra rolled into modern gaming, Plato (*left*) popularized these perfect solids as representing the four classical elements and *Aether* (or Ether) in his masterwork, *Timaeus*. Fascinated by connections between the sensed and unsensed world, Plato rationalized the physical properties of each solid as an idealized representation of a specific element in his theory of matter. The tetrahedron (*red, upper left*) rises to a stabbing point, like the unbearable heat of Fire; the spinnable octahedron (*yellow, lower right*), Air; and the flowing, nearly spherical icosahedron (*purple, lower left*), Water. All three elements are formed from the same elementary triangle. The squarely grounded cube, however, symbolized Earth (*green, upper right*) and is incompatible with Fire, Water, and Air. Encompassing all four classical elements in its vast godly space, Ether, represented by the dodecahedron (*blue, center*), approximated the quintessence of the universe. By the end of the Renaissance, Ether, the grandest Platonic solid, would lend its lofty name to a famously volatile gas that would revolutionize surgery centuries later. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

Melissa L. Coleman, M.D., Associate Professor, Department of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Hershey, Pennsylvania, and George S. Bause, M.D., M.P.H., Wood Library-Museum Curator Emeritus.