A systematic review of risk-reducing cancer surgery outcomes for hereditary cancer syndromes

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ARTICLE INFO

ABSTRACT

Cancer predisposition genes are rare mutations that confer a high risk of cancer. For many hereditary cancer syndromes, risk reducing surgery is the single most effective strategy for preventing cancer, but it is irreversible. It has recently attracted significant media attention, following celebrity endorsement, which has led to a perceived lack of ill-effect and guaranteed successful outcome by the general public. Given these high expectations for risk-reducing surgery, a systematic review was performed to evaluate the reported complications for patients undergoing risk-reducing surgery. A systematic review of MEDLINE, EMBASE, CINAHL, AMED and PubMed work was conducted using PRISMA for risk-reducing surgery in adults for cancer predisposition genes in breast, ovary, stomach, thyroid and colorectal. The main outcomes were 30-day morbidity and mortality associated with these procedures. Twenty-five studies (2366 patients) reporting on outcomes following risk-reducing surgery were analysed, 5 related to breast and/or ovary, 3 for stomach, 2 for thyroid and the remaining 15 were colorectal. Risk-reducing surgery was uniformly associated with 30-day morbidity, particularly for breast (variable rates), colorectal (311/1400 patients (22%)) and stomach (35/75 patients (47%)) surgery. The 30-day morbidity for ovarian risk-reducing surgery was relatively low (11/244 patients (5%)). There was also a small mortality risk associated with colorectal (1/1400 patients) and stomach (1/75 patients). This study provides an important and necessary summary of the current data, enabling clinicians to better inform patients of the associated short and long-term outcomes in risk-reducing surgery for cancer predisposition genes.

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Introduction

Risk-reducing surgery has recently received significant media attention and gained public interest. In 2013, the New York Times published an editorial by Angelina Jolie outlining her own personal experience of risk-reducing surgery for BRCA 1 mutation [1]. Many experts and advocates widely applauded this disclosure, with the aim to benefit other women with strong family histories of breast cancer to get genetic tests [2]. However, others expressed concerns that this could be misinterpreted, fuelling a trend towards preventative surgery that is not medically necessary [2].

Next generation sequencing techniques allow for analysis of many different genes simultaneously, resulting in increased speed, access and lower costs of testing for hereditary cancer syndromes. As a result, and the increased public profile, an increasing number of patients are seeking genetic counselling and undergoing germline mutational testing. Patients with hereditary cancer syndromes

may choose several strategies for cancer risk reduction including surgery.

Cancer predisposition genes are rare mutations that confer a high risk of cancer [3] and for many hereditary cancer syndromes, risk-reducing surgery is the single most effective strategy for preventing cancer. This strategy exists for breast (BRCA1&2) [4,5], colon (APC) [6–8], ovary (BRCA1&2) [9], stomach (CDH-1) [10] and thyroid (RET) [6], which all have key cancer predisposition genes [3] and provide an opportunity for risk-reducing surgery. However, risk-reducing surgery is neither feasible nor practical for some hereditary cancer syndromes. For example, patients with PTEN hamartoma tumour syndrome have an estimated 34% lifetime risk of renal malignancy, but a bilateral nephrectomy is an impractical option [11]. This review therefore focuses on hereditary cancer syndromes with feasible risk-reducing surgery options.

An editorial by Professor Brennan emphasises some key issues surrounding risk-reducing surgery for hereditary cancer syndromes such as Familial Adenomatous Polyposis [12]. This highlights the sad reality that many societies have been seduced into believing that living is risk free and demands compensation when accidents, complications and errors occur, even in the absence of malfeasance, summarised as a minatory experience [12]. Professor Brennan further concludes that in an age where technical aspects of operations are sometimes denigrated, a scenario now exists in which technical perfection is to be the norm and society will expect an operative mortality of zero [12]. However, this is a figure that is never uniformly achievable. Given these high expectations for risk-reducing surgery, we sought to systematically review the reported complications for patients undergoing this type of surgery.

Methods

Search strategy

A systematic review of published work was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of a review study [13]. The study team developed a concept table and built a search strategy with a medical librarian to identify articles reporting outcomes from risk-reducing cancer surgery. Two concepts were developed: cancer genes and types of surgery. Exploded medical subject heading (MeSH) terms were combined with text word searching using the Boolean operator 'OR' for each concept. Each concept was combined with 'AND'. Variation in spelling were accounted for using '*' in the search to represent wildcard characters. No search limits were applied and all languages were included. Five databases were searched; MEDLINE, EMBASE, CINAHL, AMED, and PubMed (all inception to 29th June 2017). Reference lists of included articles were also searched and further articles included if appropriate. The full search strategy used is summarised in Appendix 1 (Table A1).

Inclusion and exclusion criteria

To minimise selection, reporting and publication bias, any case reports or small series from single centres (≤10 patients) were excluded. The criteria were also refined to studies reporting 30-day morbidity for risk reducing cancer surgery (breast, colon, ovary, stomach and thyroid) in humans with a median age ≥18 years. Studies reporting surgical outcomes that included patients with known cancer prior to surgery were excluded. Studies including surgery for other conditions other than risk-reducing cancer surgery were excluded if reported surgical outcomes were not specified between the groups. Any overlapping of data reporting

outcomes in studies from a single institution/database, then the largest study from that dataset was included.

Selection of articles

Using pre-defined data fields, two authors independently assessed the study titles and abstracts for inclusion. They discussed and resolved any differences in title selection between them, with a third assessor independently reconciling any differences in abstract selection. Full-text versions of potentially eligible studies were retrieved, which were further assessed by two independent study authors against the inclusion/exclusion criteria and a consensus was reached.

Data extraction & outcomes

One author extracted information from the studies using a standardised spreadsheet. Data extracted included study year, study design and purpose, patient demographics, cancer predisposition gene/condition, morbidity and mortality, type of surgical resection, incidental cancer diagnosis after surgery and length of follow-up.

Assessment of risk of bias in included studies

Two study authors assessed risk of bias independently and a third author resolved any discrepancies, using the Newcastle Ottawa Quality Assessment scale for cohort studies [14]. Data recorded included incomplete outcome data, clearly defined outcome measures and other sources of bias. Studies were assigned a score based on selection, comparability and outcome using the published criteria and is outlined in Appendix 2 (Table A2).

Data synthesis

The heterogeneous nature of the methodology and data collected from this systematic review did not allow meta-analysis to be conducted.

Results

Search results

Thirty-four thousand and eighty-nine studies were identified from the literature search of the electronic databases, which, following screening (inclusion/exclusion criteria and removal of duplicates), resulted in 25 full articles for inclusion in this qualitative synthesis (Fig. 1). Among the excluded studies, three were excluded because of duplication of reported outcomes of interest in other publications from the same institution [15–17]. All studies were assessed using the Newcastle Ottawa Scale for non-randomised studies [14] (Table A2).

Demographics of included studies

Of the 25 included studies reporting on outcomes following risk reducing surgery, 5 related to breast and/or ovary 3 for stomach, 2 for thyroid and the remaining 15 were colorectal (Table 1). The 25 studies span over four decades of risk-reducing surgery for cancer predisposition genes in breast, colorectal, ovary, stomach and thyroid, with the earliest studies reporting data from 1970 and the most recent up to 2017. The number of patients varied across the studies, but encompassed 2366 patients. Table 1 outlines the characteristics of the 25 studies included, published between 1987 and 2017, which the majority were conducted as retrospective data

Table 1
Study demographics.

Study	Aim of study	Patient demographics	Type of surgery	Incidental Cancer
Breast/Ovary				
Bogani et al., 2017 June 2014 to January 2017 Single centre (Milan, Italy) Prospective study	Investigate the incidence and predictive factors of 30-day surgery related morbidity and occult precancerous and cancerous conditions in BRCA patients undergoing risk reducing surgery	85 patients Mean age 47 (SD ± 8) Female 85 ASA 1 46 ASA 2 37 ASA3 2	Laparoscopic BSO 55 Laparoscopic TAH & BSO 30 Conversion to open 1	6 patients 3 early stage ovarian cancer 1 stage 3a ovarian 1 stage 3b ovarian 1 serous endometrial carcinoma 3 serous tubal intra-epithelial carcinoma (STIC)
Nurudeen et al., 2017 1997 to 2013 Single healthcare system (Boston, USA) Retrospective	Identify factors associated with unexpected procedures following risk reduction mastectomy or therapeutic mastectomy in BRCA patients	104 patients risk reducing mastectomy Median age 41 (range 21–65) Female 104	SSM 86 NSM 15 TM 3 Immediate 100 Delayed 4 Tissue expander 51 Single stage implant 28 Autologous 18 Autologous & implant 7 NSM with native nipple 15 Nipple & areola recon 35 Areola recon 3 Nipple recon 14 No nipple/areola recon 37	Not recorded
Peled et al., 2014 2001 to 2011 Single centre (San Francisco, USA) Retrospective review of prospective database	Evaluate oncologic outcomes after total skin sparing mastectomy (TSSM) & nipple/areolar preservation for therapeutic and prophylactic indications in BRCA patients	26 BRCA patients underwent bilateral TSSM for prophylactic indication, 26 aged-matched patients non-BRCA prophylactic TSSM Median age 41	2 stage expander/implant reconstructions 34 patients Pedicled transverse myocutaneous flaps 6 patients Microvascular flaps 6 patients Permanent implant recons 5 patients Latissimus dorsi flap 1 patient	In situ cancer at the nipple in 3 patients
Del Corral et al., 2014 2005 to 2012 Single centre (Philadelphia,USA) Retrospective review of prospective database	Evaluate outcomes and associated costs of simultaneous risk reducing surgery in BRCA patients	464 patients Mean age 46-49 All female	422 bilateral RRM & reconstruction 42 bilateral RRM & reconstruction & simultaneous TAH/BSO All free flaps	Not recorded
Kenkhuis et al., 2010 September 1995 to March 2006 Single centre (Groningen, Netherlands) Retrospective review of prospective database	Evaluate short term surgical outcomes and safety of risk reducing salpingo-oopherectomy in BRCA patients	159 patients BRCA 1 97 Median age 43 (range 30–61) BRCA 2 32 Median age 48 (range 34–67) Hereditary Breast-Ovarian Cancer 30 Median age 46 (range 33–69) All female	Laparoscopic 150 Conversion to open 4 Laparotomy 5	Not recorded
Stomach				
Strong et al., 2017 January 2005 to November 2015 Single centre (New York, USA) Retrospective review of prospective database	Evaluate postoperative outcomes of total gastrectomy for germline mutations in CDH1 patients	41 patients Median age 47 (range 20–71) Female 27	Open 25 Minimally invasive 16	35 (Stage 1A)
Haverkamp et al., 2015 April 2006 to May 2015 Single centre (Utrecht, Netherlands) Retrospective review of prospective database	Evaluate initial experience with prophylactic laparoscopic total gastrectomy with jejunal pouch in germline mutation of CDH1 patients	11 patients Median age 40 (range 22–61) Female 8 ASA 1 6 ASA 2 4 ASA 3 1	Laparoscopic 10 Conversion 1	9 (Stage 1A)
Hebbard et al., 2009 February 2006 to November 2008 Single centre (Newfoundland, Canada) Retrospective	Report experience with prophylactic total gastrectomy for germline mutations in CDH1 patients	23 patients Median age 45 (range 26–63) Female 14	Open 23	22 (Stage 1A)
Thyroid				
Pelizzo et al., 2015 1970 to 2012 Single centre (Rovigo, Italy) Retrospective	Evaluate the optimal timing of surgery for RET gene mutation carriers with no clinical evidence of disease	31 patients Mean age 23 (range 5–63) Female 18	Total thyroidectomy 31 Minimally invasive 4	21 patients Medullary thyroid cancer
Lau et al., 2009 2005 to 2009 Single centre (Hong Kong) Retrospective	Review experience of prophylactic thyroidectomy in RET gene mutation patients with no clinical evidence of disease	22 patients Median age 25 (range 6–72) Females 13	Total thyroidectomy 22	17 patients medullary thyroid cancer

Table 1 (continued)

Study	Aim of study	Patient demographics	Type of surgery	Incidental Cancer
Colorectal				
Yamadera et al., 2016 January 2000 to December 2012 Multi-centre cohort study (Tokyo, Japan) Retrospective	Trends in surgical treatment of FAP	147 patients Median Age 28 (range 12—66) Male 78 (%) ASA 1132 ASA 2 14 ASA 3 1	Ileoanal Anastomosis 105 Ileorectal anastomosis 42 Open 74 Laparoscopic 73 Diverting stoma Yes 51 No 96	No 123 Tis 22 Cancer 2
Quinn et al., 2016 1992 to 2015 Single centre (Rochester, USA) Retrospective	Investigate frequency of pouchitis & other pouch-related complications in patients with FAP after IPAA	113 patients Age 25 (range 4—66) Female 61	Ileoanal pouch anastomosis 113 Single stage 25 Two or more stages 88 Mean duration of diverting stoma 3 months	Not recorded
Al-Sanea et al., 2013 2001 to 2009 Single centre (Riyadh, Saudi Arabia) Retrospective	Single centre experience reported Comparing IPAA in UC vs FAP patients	21 patients with FAP Median Age 31 (range 16—45)	IPAA Majority open & stapled but not specified Median duration of diverting stoma 4.5 months	Not recorded
Fazio et al., 2013 January 1984 to March 2010 Single centre (Cleveland, USA) Retrospective review of prospective database	Report outcomes, complications and quality of life treated at a single institution	223 patients with FAP Mean age 32 (IQR ± 12) Female 106 (48%)	Primary IPAA Total proctocolectomy 156 (70%) Completion proctectomy 67 (30%) Pouch type: J 188 (84%), S 35 (16%) Diverting ileostomy 157 (70%) Laparoscopic 30 (14%) Double stapled anastomosis 168 (75%) Handsewn 55 (25%)	None
McNicol et al., 2011 April 2006 to March 2008 Single centre (London, UK) Case-control study Prospective	Compare the outcome of prophylactic laparoscopic colectomy & ileorectal anastomosis with conventional open surgery	25 patients laparoscopic 25 patients open controls Sex ratio (M:F) 1.3 Mean age 18 (range 12—68) ASA 1 22 ASA 2 3	Stapled end to end anastomosis in all patients	Not recorded
Bulow et al., 2011 Not recorded Single centre (Copenhagen, Denmark) Retrospective	Report the outcomes of a new technique of mucosectomy & stapled IPAA in FAP patients	14 patients Males 11 Median age 36 (range 12—50)	Mucosectomy & double stapled anastomosis 14 Loop ileostomy 14 Median duration of stoma 3 months	Not recorded
Cotte et al., 2011 June 1998 to June 2007 Two centres (Lyon, France) Retrospective	Assess and compare outcomes of laparoscopic total colectomy for a variety of indications	40 patients with FAP Female 17 (43%) Mean age 46 (SD ± 19)	37 ileo-rectal stapled anastomosis 3 ileo-sigmoid hand-sewn anastomosis	Not recorded
Vitellaro et al., 2010 September 2003 to September 2009 Single centre (Milan, Italy) Retrospective	Evaluate the feasibility, short and long-term outcomes after laparoscopic prophylactic surgery for FAP	55 patients Male 32 Median age 28 (range 15—68)	Laparoscopic total colectomy and ileo-rectal anastomosis 44 Laparoscopic proctocolectomy & IPAA 11, 9 with covering loop ileostomy Stapled anastomosis 50 Handsewn 5	9 incidental adenocarcinomas
Von Roon et al., 2008 Not recorded Single centre (London, UK) Retrospective	Evaluate postoperative complications and functional outcomes of secondary proctectomy and IPAA in patients with FAP after previous colectomy & IRA	185 patients Primary IPAA (107 patients) Male 58 Mean age 29 (SD ± 10) Secondary IPAA (78 patients) Male 46 Mean age 36 (SD ± 11)	Handsewn IPAA 104 Stapled 47 Not documented 26 Reservoir type: J 96 W 49 S 4 Not documented 28 Covering ileostomy 126	1 cancer
Elton et al., 2003 November 1990 to December 1999 Single centre (London, UK) Retrospective	Review postoperative mortality, morbidity and functional results after total colectomy and IRA	112 patients Not specified for FAP patients	Not specified	Not recorded
Heuschen et al., 2002 January 1988 to June 1999 Single centre (Heidelberg, Germany) Retrospective	Analyse the association between pre and perioperative factors in pouch related septic complications in ulcerative colitis and FAP after IPAA	212 patients with FAP 119 Females Median age 31 (IQR 22—38)	All handsewn anastomosis & J pouch IPAA with ileostomy 139 IPAA 44 2-stage IPAA 29	Not recorded
Barton et al., 2001 1983 to 2000 Single centre (Oklahoma, USA) Retrospective	Evaluate differences in postoperative outcomes between UC and FAP patients	24 patients with FAP Mean age 31	All handsewn anastomosis with J pouch IPAA with covering ileostomy	Not recorded

Table 1 (continued)

Study	Aim of study	Patient demographics	Type of surgery	Incidental Cancer
Soravia et al., 1999 January 1980 to December 1997 Single centre (Toronto, Canada) Retrospective	Evaluate surgical complications and long term outcomes for IRA & IPAA in FAP patients	110 patients with FAP Females 61 Mean age 34 (range 15–77)	IRA 60 Handsewn in 55 & stapled in 5 IPAA 50 26 J-pouch & 24 S-pouch, 48 had covering ileostomy	6 patients
Dozois et al., 1989 January 1981 to September 1988 Single centre (Rochester, USA) Retrospective	Compare immediate postoperative complications and long-term results of IPAA in FAP and colitis patients	94 patients with FAP Mean age 28 (SD ± 10) Male 52	J-pouch IPAA 91 S-pouch 2 W-pouch 1 Diverting ileostomy 76	Not reported
Heimann et al., 1987 1975 to 1985 Single centre (New York, USA) Retrospective	Report the outcomes of FAP patients surgically treated at a single centre	25 patients Mean age 23 (range 11–44) Female 10	Mucosal protectomy & ileo-anal anastomosis	Not reported

SD: Standard deviation, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oopherectomy, SSM: Skin-sparing mastectomy, NSM: Nipple-sparing mastectomy, TM: Total mastectomy, RRM: Risk-reducing mastectomy, IPAA: Ileal pouch anal anastomosis, UC: Ulcerative colitis, FAP; Familial adenomatous polyposis, IRA: Ileo-rectal anastomosis.

Table 2
Breast & ovary risk-reducing surgery outcomes.

Study	Early Complications	Length of hospital stay Length of Follow-up	Late Complications	30-day mortality
Bogani et al	Fever 3 Ileus 1	Mean length of hospital stay 1–2 days (SD ± 1) Mean follow up 18 months (SD ± 5)	Not recorded	0
Nurudeen et al	Skin necrosis 11 Infection 5 Seroma 1 Haematoma 3 Implant removal 7	Not reported Median follow up 43 months	59 patients underwent unexpected revisions Implant exchange/capsulotomy 24 Fat grafting 13 Revision nipple/areola 11 Revision of scar 27 Revision of donor scar 13 Liposuction 9 Conversion to flap 1	0
Peled et al	N = 104 Significant infections 9 Seromas 4 Expander/implant loss 4 Skin flap necrosis 4 Nipple/areolar complex necrosis 2	Not recorded Median follow up 44 months	Not specified	0
Del Corral et al	N = 928 Minor surgical (delayed wound healing, seroma, fat necrosis 7 infection) 236 Major surgical immediate 19 Delayed 34 Hernia 16 Flap loss 11 Fat necrosis 28 Skin necrosis 60 Haematoma 48 Seroma 17	Not recorded	Not specified Medical complications VTE 5 Arrythmia 9 Cardiac complication 12 GI bleed 1 Heart failure 3	0
Kenkhuis et al	Intraoperative complications: Broken needle 1 (removed) Haemorrhage 1 Postoperative: Wound infection 2 Haematoma 2 Pain 1	Median length of hospital stay 1 day (range 0–13)	Not recorded	0

VTE: Venous thrombotic event, GI: Gastrointestinal.

analyses. Table 1 also summarises the aim of each study, the type of surgery performed, the basic reported demographic data and the incidental cancer diagnoses if reported.

Breast & ovary

A total of 5 studies met the inclusion criteria for this systematic review (286 ovary & 594 breast patients), 2 studies reporting outcomes after risk-reducing surgery for ovary [18,19] and 2 studies for breast [20,21]. The other study reported outcomes for both breast and ovary risk-reducing surgery [22] in patients with germline mutations of BRCA 1 or 2. The types of surgery performed and the reported incidental finding of cancer on postoperative histology are outlined in Table 1.

Eleven patients (5%) suffered an early complication within 30-days of surgery in the two studies (244 patients) outlining outcomes for prophylactic ovarian surgery (Table 2). One patient required a laparoscopic converted to laparotomy to control the haemorrhage caused by injury to the inferior epigastric artery from a trochar insertion. Del Corral et al. described outcomes in 42
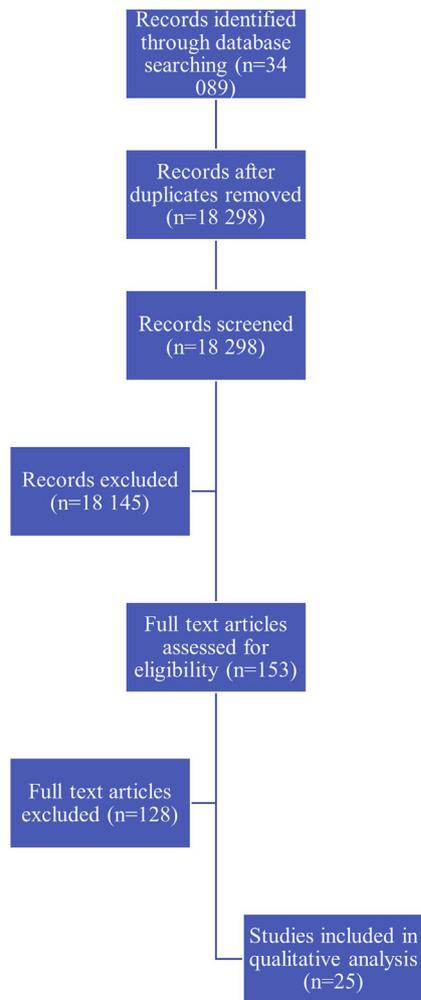
Fig. 1. PRISMA flow diagram.

patients who underwent both ovary and breast risk-reducing surgery [22]. The majority of postoperative complications related to breast surgery, however there were 7 (17%) patients who suffered a medical complication (Table 2).

The most common complications following prophylactic breast surgery from the three studies [20—22] were skin necrosis in 75 cases and haematoma in 51 cases. The reported loss of the implant occurred in 11 cases and there were also 11 separate cases of flap loss. Nurudeen et al. reported a serious complication rate (requiring surgery) of 26% (27 patients) and that 59 patients (57%) required a subsequent unexpected reconstruction revision [20].

Stomach

There were 3 studies reporting outcomes for prophylactic total gastrectomy in a total of 75 patients with germline mutations of CDH1 [23—25]. The basic patient demographics for each study are outlined in Table 1. Forty-eight patients underwent an open procedure, 26 had a minimally-invasive approach and 1 patient received a laparoscopic converted to open operation. A total of 66 (88%) patients had an incidental finding of invasive cancer (Stage 1A) on postoperative histology.

Thirty-five patients (47%) suffered one or more complications within 30-days of surgery, with a total of 44 reported complications (Table 3). There were 7 clinical anastomotic leaks (9%) and 4 subclinical leaks (detected on routine postoperative water-soluble swallows). The overall serious complication rate (Clavien-Dindo Type $\geq$3) [26,27] was 23% (17 patients). The 30-day mortality rate was 1%, which occurred in a patient with a history of kidney transplant and hepatitis, who developed pneumonia and sepsis and died secondary to multi-organ failure, however, the water-soluble swallow study was negative for an anastomotic leak [23].

The length of follow-up ranged from 1 to 96 months. One study reported delayed (>30-day) complications, with 6 gastrointestinal complications, which were 2 anastomotic strictures (1 patient requiring endoscopic dilatation), 2 patients developed Roux Limb syndrome requiring further surgery and finally 2 patients had internal hernias that required laparoscopic reduction and repair [23].

Table 3
Stomach risk reducing surgery outcomes.

Study	Early Complications	Length of hospital stay / Length of Follow-up	Late Complications	30-day mortality
Strong et al	Pulmonary complications 6 / Anastomotic leak 3 / Wound infection 3 / Duodenal stump leak 2 / Gastrointestinal bleed 2 / UTI 1 / Supraventricular arrythmia 1 / PE 1 / Multi organ failure 1 / Type $\geq$3 9	Median length of hospital stay 7 days (range 4—50) / Median follow-up 16 months (range 1—96)	>30 days / Internal hernias 2 / Roux limb syndrome 2 / Stricture 2 / PE 1 / Pleural effusion 1	1 patient
Haverkamp et al	Anastomotic leak 2 / Wound infection 1 / Pneumonia 1 / Type 3 2	Median length of hospital stay 10 days (range 7—23) / Not recorded	Not recorded	0
Hebbard et al	Anastomotic leak with abscess 2 / Intra-abdominal abscess 1 / VTE 3 / Subclinical leak 4 / Wound infection 4 / UTI 2 / Pneumonia 2 / SBO 1 / Ileus 1 / Type 3 5	Median length of hospital stay 11 days (range 9—107) / Follow up range 3—36 months	Not recorded	0

UTI: Urinary tract infection, PE: Pulmonary embolus, VTE: Venous thrombotic event, SBO: Small bowel obstruction.

Table 4
Thyroid risk reducing surgery outcomes.

Study	Early Complications	Length of hospital stay Length of Follow-up	Late Complications	30-day mortality
Pelizzo et al.	Permanent hypocalcaemia 1	Not recorded Median follow-up 72 months (range 12—288)	Not specified	0
Lau et al.	Postoperative hypocalcaemia 8	Not recorded Median follow up 49 months (range 13—128)	Permanent hypocalcaemia 3	0

There were also 2 non-gastrointestinal complications, one patient developed a pleural effusion which required drainage (negative swallow test) and the other developed small bilateral pulmonary emboli [23].

Thyroid

Two studies reported outcomes after prophylactic total thyroidectomy in 53 patients with the RET gene mutation [28,29]. Thirty-eight patients (72%) had an incidental medullary thyroid cancer at postoperative histology, but there was no lymph node involvement.

There were 8 patients who developed postoperative hypocalcaemia (Table 4) and 4 patients (8%) subsequently developed permanent hypocalcaemia. There were no recurrent laryngeal nerve palsies. The length of follow-up ranged from 12 to 288 months.

Colorectal

Fifteen studies reported outcomes from a combination of ileo-anal pouch and ileo-rectal anastomosis formation for colorectal risk-reducing surgery in 1400 patients with familial adenomatous polyposis (germline mutations in the APC gene) [30—44]. The types of surgery performed are outlined in Table 1. There were 18 (1%) reported cases of an incidental invasive cancer on postoperative histology.

Three hundred and eleven patients (22%) suffered an early complication following risk-reducing surgery (Table 5). The reported anastomotic leak rate was 4% (49 patients) and a further 48 patients (3%) had pelvic sepsis. It was not possible to classify the overall serious complication rate because many of the studies were published before the adoption of the Clavien-Dindo classification [26,27] for complications. There was one death within 30 days, due to unexplained disseminated intravascular coagulation [32].

The length of follow-up ranged from 4 to 156 months. Ten studies reported late complications for 1062 patients (Table 5). Small bowel obstruction was the most common reported late complication in 116 patients (11%) and 62 patients suffered an anastomotic stricture (6%). Nine hundred and fifty-eight patients had an ileoanal pouch anastomosis and 34 patients (4%) experienced pouch failure and/or pouch excision.

Discussion

This review highlights the importance of an individualised discussion for patients with cancer predisposition genes considering risk-reducing surgery. Despite the reported outcomes being from many high-volume centres, the morbidity and mortality associated with certain risk-reducing surgery for cancer predisposition genes remains significant. Whilst previously published studies have demonstrated patients are satisfied with the cancer risk reduction, their satisfaction with the surgical outcome is more variable [45].

Bilateral prophylactic salpingo-oopherectomy can reduce the risk of ovarian cancer by approximately 90% and the risk of breast cancer by approximately 50% in women at very high risk [7]. Moreover, bilateral prophylactic mastectomy has been shown to reduce the risk of breast cancer by 95% in women with cancer predisposition genes (BRCA 1 & 2) and by 90% in women with a strong family history of breast cancer [4,5,46,47]. Although prophylactic surgery substantially reduces the risk for patients with cancer predisposition genes, it is a major irreversible surgical intervention [48]. Breast risk-reducing surgery offers multiple techniques and reconstruction options. It is associated with complications such as haematoma, infection, skin necrosis, capsular contraction, seroma and loss of the implant and/or flap [20—22]. Reoperation or revision surgery was also required in 59% of women undergoing reconstruction [20], similar to a Cochrane review of risk-reducing surgery with a rate of adverse events requiring reoperation for reconstructions being up to 49% [45]. The rate of complications was far less in ovarian risk-reducing surgery, being only 5%, however, the description and characterisation of complications were different to other surgical specialities [18,19]. A recent review of health-related quality of life (HRQOL) after risk-reducing surgery showed that the majority of patients reported satisfaction with their decision and outcomes, with no significant impact on HRQOL following breast and/or ovarian surgery [48]. However, some patients experienced negative aesthetic changes, changes in body perception, pain and sexual dysfunction [48].

Risk-reducing surgery for colorectal cancer predisposition genes includes a total colectomy with ileo-rectal anastomosis, pan-proctocolectomy with ileal pouch-anal anastomosis or an end ileostomy. Regardless of the type of surgery, it is also associated with a significant early complication rate of 22%, including anastomotic leak and pelvic sepsis (Table 5). Furthermore, these procedures are associated with long-term complications such as pouch failure, poor functional outcomes, small bowel obstruction and sexual dysfunction [49]. Risk-reducing surgery for the stomach, which requires a total gastrectomy, is also associated with high morbidity of 47% within 30-day and 1% 30-day mortality rate (Table 3). Despite these risks, the majority of patients are able to tolerate this life-altering procedure with some preservation of HRQOL [48]. Thyroid risk-reducing surgery is associated with very few complications, with only a small proportion of patients (8%) suffering from permanent hypocalcaemia [28,29].

Although recent reports of well-known celebrities undergoing prophylactic surgery [2] and the perceived lack of ill-effect and successful outcome by the general public, compounded further by the high expectations of society for zero complications [12], this in fact is not the case. It is imperative that patients are fully informed of the potential outcomes from this type of surgery, particularly in light of changes in the law. The recent UK Supreme court's decision in the Montgomery case is a landmark judgment, which establishes beyond doubt the court's commitment to protecting patients' right to self-determination [50]. This was framed as a clash of values; patient autonomy versus medical paternalism [51]. However, in reality, medical decision making involves a nuanced negotiation of information and patients can expect a more active and informed

Table 5
Colorectal risk-reducing surgery outcomes.

Study	Early Complications	Length of hospital stay / Length of Follow-up	Late Complications	30-day mortality
Yamadera et al	38 patients Anastomotic Leak 1 Anastomotic stricture 6 Intra-abdominal Abscess 4 Small bowel obstruction 25 Others 12 Clavien Dindo I 7 II 12 IIIa 15 IIIb 4 IV 0	Not reported Not reported	Not recorded	0
Quinn et al	≤90 days 36 patients Wound infection 2 Anastomotic or pouch stricture 10 Anastomotic leak 8 Fistula or sinus tract 3 Intra-abdominal abscess 3 SBO/ileus 16 DVT/PE 3 Early pouch failure 1	Not reported Mean follow-up 8 years	Late complications >90 days 46 patients Anastomotic or pouch stricture 26 Anastomotic leak 3 Fistula or sinus tract 7 Intra-abdominal abscess 4 SBO/ileus 19 Pouch evacuation disorder 6 Pouch dysplasia 24 Pouch failure 3 Pouchitis 25	0
Al-Sanea et al.	≤30 days 4 patients Pelvic sepsis 2 Wound infection 2	Median length of stay 10 days (range 6–42) Median follow 36 months	Late complications >30 days Intestinal obstruction 3 Pouch excision 1	1 patient
Fazio et al	<90 days Pelvic sepsis 8 Anastomotic leak 10 Haemorrhage 6 Small bowel obstruction 10 Pouch fistula 5 Stricture 4	Mean length of stay 8 days (IQR ± 4) Median follow 84 months (range 24–138)	≥90 days Small bowel obstruction 40 Pelvic sepsis 7 Pouch fistula 4 Anastomotic leak 4 Stricture 17 Pouchitis 43 Chronic pouchitis 11 Pouch failure 8 Pouch excision 4	Not reported
McNicol et al	Laparoscopic cases: UTI 1 (4%) Wound haematoma 1 (4%) Anastomotic bleeding 1 (4%) Anastomotic leak 2 (8%) 2 reoperations Open cases: Anaemia requiring transfusion 1 (4%) UTI 3 (12%) Wound infection 3 (12%) SBO 1 (4%) Anastomotic leak 2 (8%) 3 reoperations	Mean length of stay 6 (range 4–33) & 9 (range 6–23)	Not reported	0
Bulow et al.	Pelvic abscess 2 (drained) Stricture 3	Not reported Median follow up 29 months (range 7–144)	Not specified	0
Cotte et al	≤30-days Wound abscess 2 Surgery for bowel obstruction 1 Aspiration pneumonia 1 Prolonged ileus 1 Segmental portal vein thrombosis 1 Intra-abdominal abscess 4 (2 required surgery, 1 required radiological drainage & antibiotics for the other)	Length of hospital stay 11 days (SD ± 4) Not recorded	Not reported	0
Vitellaro et al	≤30-days Anastomotic leak 3 Anastomotic bleed 1 Pelvic bleeding 1 Pancreatitis 1	Length of hospital stay median 7 (range 4–24) Median follow up 38 months (range 16–64)	>30-days Small bowel obstruction 2 Desmoid tumours 3	0
Von Roon et al	Failed IPAA attempt 8 Haemorrhage 4 Anastomotic leak 7 Pelvic sepsis 18 Wound infection 8 Wound dehiscence 2	Not recorded Median follow up 7 years (IQR 3–11)	Small bowel obstruction 38 Stricture 15 Pouch fistula 16 Pouchitis 5 Pouch failure 16 Desmoid disease 10	0

Table 5 (*continued*)

Study	Early Complications	Length of hospital stay / Length of Follow-up	Late Complications	30-day mortality
Elton et al	Anastomotic leak 6 Small bowel obstruction 17 Wound infection 12	Not specified	Not specified	Not specified
Heuschen et al	Not specified	Not recorded Median follow up 53 months (IQR 38—79)	At 1 year Pelvic abscess 2 Proximal pouch fistula 6 Anastomotic leak 2 Pouch-anal anastomotic fistula 9	0
Barton et al	≤30 days Non-operative complications Small bowel obstruction 1 Dehydration 1 Operative complication Haemorrhage 1	Median length of hospital stay 8 days Median follow up 19 months	>30 days Non-operative complications Small bowel obstruction 3 Dehydration 1 Operative complications Small bowel obstruction 3 Pouch excision 1	0
Soravia et al	IRA group Anastomotic leak 2 (1 reoperation) Pelvic sepsis 2 (1 reoperation) Partial SBO 10 (2 reoperation) Wound infection 1 IPAA group Anastomotic leak 6 (3 reoperation) SBO 12 (4 reoperations)	Not recorded Mean follow-up 6—8 years	IRA group SBO 4 Small bowel ischaemia 1 Stricture 2 Desmoid tumour 10 IPAA group Pouch excision 2 Stricture 2 Desmoid tumour 3	0
Dozois et al	24 patients (not fully specified) Partial SBO 13 Surgically managed SBO 5	Not reported Mean follow up 36 months (range 6—96)	Pouchitis 6 Excision of pouch 1	0
Heimann et al	Phlebitis 3 PE 1 Pelvic sepsis 3 SBO 1	Mean length of hospital stay 16 days (range 11—36) Mean follow up 47 months (range4—125)	Ileal retraction 1 SBO 4	0

UTI: Urinary tract infection, PE: Pulmonary embolus, DVT: Deep vein thrombosis, SBO: Small bowel obstruction, IPAA: Ileal pouch anal anastomosis, IRA: Ileo-rectal anastomosis.

role in treatment decisions, with a corresponding shift in emphasis on various values, including autonomy, in medical ethics [51]. The Montgomery ruling has not radically changed the process of consent; it has simply given appropriate recognition to patients as decision makers [51]. Therefore, patients considering risk-reducing surgery should be fully apprised of the short- and long-term ramifications of their decision, particularly as this is irreversible and associated with marked complications [48].

To our knowledge, this systematic review is the first attempt to pool the data to assess surgical outcomes for risk-reducing surgery. The majority of previous studies are single-centre or small collaborative data, which have their own inherent biases. This study provides an important and necessary summary of the current data, enabling clinicians to better inform patients of the potential short and long-term outcomes in risk-reducing surgery for cancer predisposition genes.

There are several limitations to this study, which need to be considered. Firstly, the study is retrospective, albeit based on data collected from multiple single centre series. Interpretation of these results are limited by heterogeneity, both within and between the included studies, which prevented a meta-analysis being conducted. The majority of studies reflect the large heterogeneity of the potential types of surgery and the various cancer predisposition genes. There were also variations in treatment strategies, reporting and grading of complications across the studies, partly reflected by the paucity of therapeutic guidelines and the differing treatment centres performing these cases. Other centres and certain specialities failed to report complications or amalgamated all outcomes with other pathologies, preventing inclusion within this study. There are also variations in the data collected between studies, because they had different objectives, so not all variables are available from each study. However, in the absence of randomised controlled studies, this systematic review provides large qualitative estimates of the clinical outcomes following risk-reducing surgery.

Conflict of interest and source of funding

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.034.

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