The Long-Term Risk of Knee Arthroplasty in Patients with Arthroscopically Verified Focal Cartilage Lesions

A Linkage Study with the Norwegian Arthroplasty Register, 1999 to 2020

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Background: Focal cartilage lesions are common in the knee. The risk of later ipsilateral knee arthroplasty remains unknown. The purposes of the present study were to evaluate the long-term cumulative risk of knee arthroplasty after arthroscopic identification of focal cartilage lesions in the knee, to investigate the risk factors for subsequent knee arthroplasty, and to estimate the subsequent cumulative risk of knee arthroplasty compared with that in the general population.

Methods: Patients who had undergone surgical treatment of focal cartilage lesions at 6 major Norwegian hospitals between 1999 and 2012 were identified. The inclusion criteria were an arthroscopically classified focal cartilage lesion in the knee, an age of ≥18 years at the time of surgery, and available preoperative patient-reported outcomes (PROMs). The exclusion criteria were osteoarthritis or "kissing lesions" at the time of surgery. Demographic data, later knee surgery, and PROMs were collected with use of a questionnaire. A Cox regression model was used to adjust for and investigate the impact of risk factors, and Kaplan-Meier analysis was performed to estimate cumulative risk. The risk of knee arthroplasty in the present cohort was compared with that in the age-matched general Norwegian population.

Results: Of the 516 patients who were eligible, 322 patients (328 knees) consented to participate. The mean age at the time of the index procedure was 36.8 years, and the mean duration of follow-up was 19.8 years. The 20-year cumulative risk of knee arthroplasty in the cartilage cohort was 19.1% (95% CI, 14.6% to 23.6%). Variables that had an impact on the risk of knee arthroplasty included an ICRS grade of 3 to 4 (hazard ratio [HR], 3.1; 95% CI, 1.1 to 8.7), an age of ≥40 years at time of cartilage surgery (HR, 3.7; 95% CI, 1.8 to 7.7), a BMI of 25 to 29 kg/m^2 (HR, 3.9; 95% CI, 1.7 to 9.0), a BMI of ≥30 kg/m^2 (HR, 5.9; 95% CI, 2.4 to 14.3) at the time of follow-up, autologous chondrocyte implantation (ACI) at the time of the index procedure (HR, 3.4; 95% CI, 1.0 to 11.4), >1 focal cartilage lesion (HR, 2.1; 95% CI, 1.1 to 3.7), and a high preoperative visual analog scale (VAS) score for pain at the time of the index procedure (HR, 1.1; 95% CI, 1.0 to 1.1). The risk ratio of later knee arthroplasty in the cartilage cohort as compared with the age-matched general Norwegian population was 415.7 (95% CI, 168.8 to 1,023.5) in the 30 to 39-year age group.

Conclusions: In the present study, we found that the 20-year cumulative risk of knee arthroplasty after a focal cartilage lesion in the knee was 19%. Deep lesions, higher age at the time of cartilage surgery, high BMI at the time of follow-up, ACI, and >1 cartilage lesion were associated with a higher risk of knee arthroplasty.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Focal cartilage lesions are common in the knee and represent a clinical challenge[1-3]. In the study by Heir et al., patients who were scheduled for cartilage surgery reported Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS QoL) subscores similar to those of patients scheduled for knee arthroplasty[4]. The intra-articular hyaline cartilage is unable to heal naturally[5]. Several treatment options (including microfracture, autologous chondrocyte implantation [ACI], and mosaicplasty) are available, but the optimum treatment has yet to be determined[6,7]. Furthermore, no treatment has been proven to restore hyaline cartilage or decrease the risk of osteoarthritis[5].

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H503).

Patients who have had previous knee surgery undergo knee arthroplasty at a significantly younger age than those who have not[8]. Several factors have been reported to increase the lifetime risk of knee arthroplasty, including age, body mass index (BMI), body height, sex, manual labor, knee injury, and family history[9,10].

Long-term articular cartilage studies have shown that the rate of knee arthroplasty has ranged from 0% to 17% following regenerative cartilage surgical procedures such as microfracture, ACI, chondroplasty, or mosaicplasty[11-14]. The relative risk of knee arthroplasty in patients with a previous focal cartilage lesion versus the general population remains unknown. Thus, the purposes of the present study were to (1) evaluate the long-term cumulative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions in the knee, (2) to investigate the risk factors for knee arthroplasty in patients with cartilage lesions, and (3) to estimate the relative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions as compared with the risk in the general population.

Materials and Methods

Patients and Methods

We identified patients with arthroscopically verified focal cartilage lesions that had been treated at 6 major Norwegian hospitals between 1999 and 2012 (Fig. 1). These hospitals were chosen because they had participated in several prospective clinical cartilage trials in the contemporary period[15-18].

The inclusion criteria in this study were (1) an arthroscopically verified and classified focal cartilage lesion in the knee and (2) an age of ≥18 years at the time of surgery. At least 1 preoperative patient-reported outcome measure (PROM) score had to be available. Exclusion criteria were cartilage lesions that were assessed as being osteoarthritis or "kissing lesions" intraoperatively by the surgeon (Fig. 1).

Patients who were found to be eligible for inclusion were contacted by mail. Patients who were listed in the Norwegian Population Register as emigrated or deceased were excluded. Informed consent was obtained. Each patient received a questionnaire regarding their current height, weight, level of education, knee function, additional knee surgery, and level of activity. The

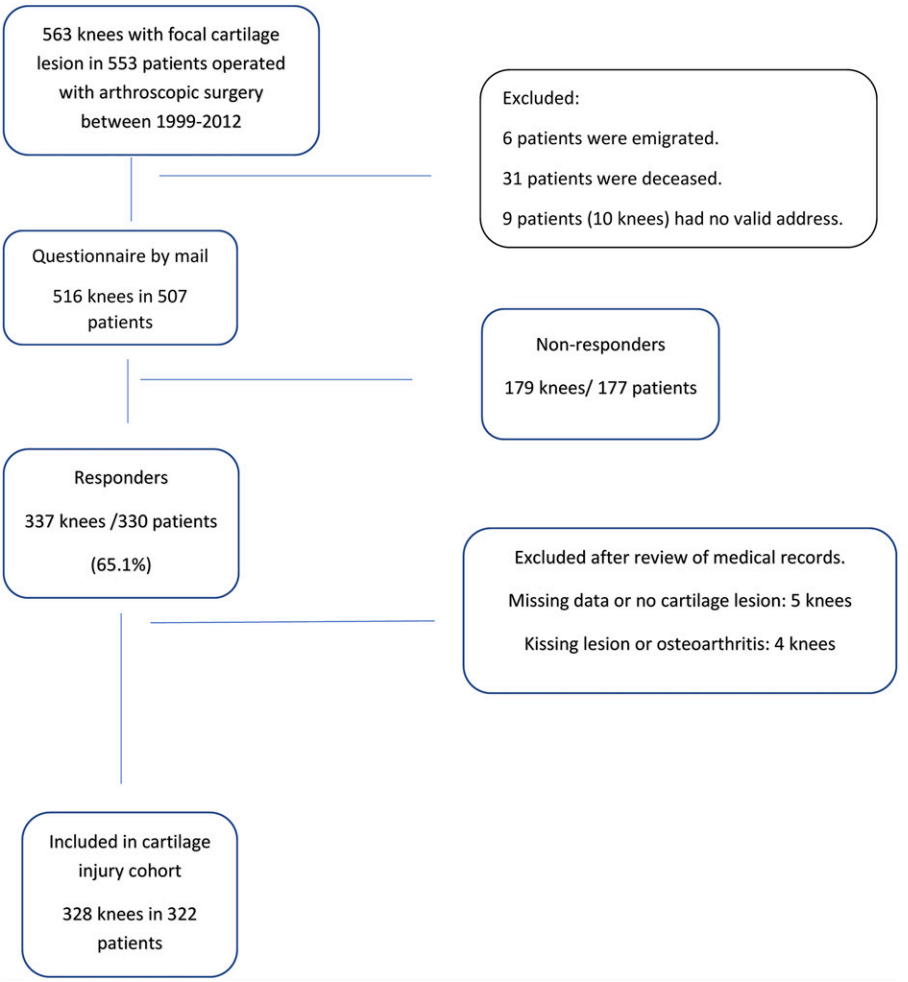

Fig. 1

Flowchart illustrating the inclusion of patients in the cartilage cohort.

PROMs that had been previously used were the KOOS score[19], Lysholm score[20], and International Cartilage Regeneration & Joint Preservation Society (ICRS) visual analog scale (VAS) for knee pain[21].

After informed consent had been obtained, the surgical report and/or trial data for each participant were made available to the main investigator (T.B.). The variables of interest included any previous cartilage surgery; the location, size, and ICRS classification of the cartilage lesions; the type of operative treatment; any additional procedures; and preoperative PROMs. Nine knees in 8 patients who met the exclusion criteria at the time of surgery were then identified and excluded (Fig. 1).

The Norwegian Arthroplasty Register (NAR) has captured data on knee arthroplasty interventions and outcomes in Norway since 1994 and has >95% completeness of reporting[22,23]. The patients in the current study and in the NAR are identified by their Norwegian unique identification number. Data from the NAR included the date of knee arthroplasty, surgeon-reported cause of knee arthroplasty (i.e., osteoarthritis, posttraumatic arthritis, inflammatory arthritis), type of prothesis, and laterality.

A patient was registered as having a knee arthroplasty when (1) the patient reported an ipsilateral knee arthroplasty in the questionnaire and/or (2) the ipsilateral knee was registered in the NAR.

The study was approved by the Regional Ethics Committee (2017/1387).

Statistical Analysis

The data were analyzed with use of SPSS Statistics (version 26; IBM). The level of significance was set at $p < 0.05$.

The cumulative risk of knee arthroplasty was estimated with use of the Kaplan-Meier method[24]. Cox regression models were used to investigate risk factors for knee arthroplasty in the study population. A graphical causal model (www.dagitty.net/dags.html) was used to identify variables to adjust for, as suggested by Westreich and Greenland[25]. Preoperative Lysholm and ICRS VAS pain scores were registered for 185 and 114 patients, respectively, and no patient had recorded >1 preoperative PROM. The linear assumption of the Cox model was confirmed for the preoperative VAS pain score with use of the Box-Tidwell procedure. Survival times were calculated as the time between cartilage surgery and knee arthroplasty or the end of the study on December 31, 2020. The proportional hazards assumption was fulfilled for all variables that were investigated except for BMI group and anterior cruciate ligament (ACL) surgery (yes or no). On the basis of a visual inspection of the Kaplan-Meier plot, both variables were analyzed separately according to the duration of follow up (<12 or ≥12 years).

A subgroup of patients without any concomitant procedures at the time of the index procedure were analyzed with use of the same Cox model as described above.

The relative risk of knee arthroplasty after a cartilage injury as compared with the risk in the age-matched general population was estimated. The absolute risk of knee arthroplasty in the cartilage injury cohort was estimated by dividing the number of knee arthroplasties by the total number of knees with cartilage injury in each age-matched group. For the general population, the numerator was the number of all other patients undergoing knee arthroplasty without inflammatory arthritis or previous cartilage surgery as reported to the NAR between January 1, 1999, and December 31, 2020. The denominator was the average number of Norwegian citizens in the same period, retrieved from Statistics Norway. The results were stratified in 10-year groups based on the age at the time of knee arthroplasty.

To further aid the clinical interpretation of the relative risk of knee arthroplasty in the cartilage injury cohort as compared with the general population, we also stratified each 10-year age group at the time of knee arthroplasty according to when the patient underwent the index cartilage procedure. For the general population, the absolute risk was estimated as described in the previous paragraph. In the cartilage injury cohort, the numerator was the number of knee arthroplasties in each 10-year age group (at the time of cartilage surgery) and the denominator was the total number of patients with cartilage injury in the same age group.

A power analysis was performed prior to inclusion. In order to achieve an 80% chance of detecting a 4-times higher rate of knee arthroplasty in the focal cartilage lesion cohort as compared with the general population, we needed to include at least 181 participants.

Source of Funding

The present study was funded by the Norwegian Research Council through the Norwegian Cartilage Project.

Results

Of the 553 patients (563 knees) who were identified, 507 patients (516 knees) were eligible, and, of those, 322 patients (328 knees) consented to participate (Fig. 1). One hundred and sixty-four patients (169 knees) had participated in studies with previously published intermediate to long-term results[26-28]. Most patients had a pre-enrollment radiograph that did not show any joint-space narrowing. The demographic characteristics of the patients are summarized in Table I. At baseline, there were no significant differences between the responders and nonresponders apart from the responders being a mean of 3.0 years older ($p = 0.002$).

The 20-year cumulative risk of knee arthroplasty after arthroscopic verification of a focal cartilage lesion was 19.1% (95% confidence interval [CI], 14.6% to 23.6%). The mean age at the index procedure for the treatment of the focal cartilage lesion was 36.8 years, and the mean duration of follow-up was 19.8 years. The results of the Cox regression model are summarized in Table II. The BMI classifications of overweight and obese at the time of follow-up were the 2 most important risk factors for knee arthroplasty, with an adjusted hazard ratio (aHR) of 3.9 (95% CI, 1.7 to 9.0) and 5.9 (95% CI, 2.4 to 14.3), respectively. The size of the cartilage lesion did not significantly influence the risk of later knee arthroplasty, but ICRS grade-3 and 4 lesions did increase the risk of knee arthroplasty (aHR, 3.1; 95% CI, 1.1 to 8.7). ACI treatment increased the risk of knee arthroplasty (aHR, 3.4; 95% CI, 1.0 to 11.4) compared

TABLE I Demographic and Descriptive Characteristics of 328 Knees with Focal Cartilage Lesions Treated with Arthroscopic Surgery in 6 Norwegian Hospitals Between 1999 and 2012*

No. of knees	328
Sex (male/female) *(no. of knees)*	188 (57%)/140 (43%)
Side (right/left) *(no. of knees)*	174 (53%)/154 (47%)
Age at time of surgery† *(yr)*	36.8 (35.6-38.0)
Time from index procedure to end of study† *(yr)*	19.8 (19.4-20.2)
ICRS grade *(no. of knees)*	
1-2	52 (15.9%)
3-4	276 (84.1%)
Size of cartilage lesion† *(mm^2)*	201.3 (178.9-223.7)
Preop. Lysholm score (n = 184)†	49.4 (46.9-51.8)
Preop. VAS pain score (n = 105)†	44.3 (39.6-49.0)
Location of cartilage lesion *(no. of knees)*	
Patellofemoral	73 (22.3%)
Medial	204 (62.2%)
Lateral	51 (15.5%)
Type of cartilage lesion *(no. of knees)*	
Traumatic	125 (38.1%)
OCD	17 (5.2%)
Degenerative	4 (1.2%)
Not reported	182 (55.5%)
Type of treatment *(no. of knees)*	
No cartilage treatment	93 (28.4%)
Microfracture	124 (37.8%)
Debridement	12 (3.0%)
ACI/MACI	30 (9.1%)
Mosaicplasty	53 (16.2%)
Other	16 (4.9%)
Level of education *(no. of knees)*	
High school	155 (47.3%)
Bachelor's/Master's degree	164 (50.0%)
Missing information	9 (2.7%)
BMI at end of study† *(kg/m^2)*	27.4 (26.9-27.9)
BMI category at end of study *(no. of knees)*	
<25 kg/m^2	100 (30.5%)
25-29 kg/m^2	137 (41.8%)
≥30 kg/m^2	75 (22.9%)
Missing information	16 (4.9%)
Ipsilateral ACL reconstruction *(no. of knees)*	50 (15.2%)
At index surgery	15 (4.6%)
Before or after index surgery	35 (10.7%)
None	278 (84.8%)
Ipsilateral meniscal resection *(no. of knees)*	100 (30.5%)
At index surgery	46 (14.0%)
Before or after index surgery	54 (16.5%)
None	228 (69.5%)
Knee arthroplasty *(no. of knees)*	59 (18.0%)
Male patients (n=188)	30 (16.0%)
Female patients (n=140)	29 (20.7%)
Knee arthroplasty procedures *(no. of knees)*	59 (18.0%)
Total knee arthroplasty (n = 59)	48 (81.4%)
Unicompartmental knee arthroplasty (n = 59)	8 (13.6%)
Patellofemoral knee arthroplasty	3 (5.1%)
Age at the time of knee arthroplasty† *(yr)*	
Male patients	56.4 (53.1-59.7)
Female patients	51.9 (47.6-56.1)
Time from index cartilage surgery to knee arthroplasty† *(yr)*	
Male patients	13.9 (11.9-16.0)
Female patients	11.4 (9.0-13.8)

*N = 328 unless indicated otherwise. ICRS = International Cartilage Repair & Joint Preservation Society, VAS = visual analog scale, OCD = osteochondritis dissecans, ACI = autologous chondrocyte implantation, MACI = matrix-induced ACI, ACL = anterior cruciate ligament. †The values are given as the mean, with the 95% CI in parenthesis.

with no cartilage treatment at index surgery. The preoperative Lysholm and VAS pain scores were analyzed as continuous variables. A low preoperative Lysholm score did not significantly increase the risk of knee arthroplasty, whereas a high preoperative VAS pain score did and was found to be linearly correlated with the risk. ACL reconstruction was not a risk factor for total knee arthroplasty (TKA) at the time of the latest follow-up, but there was an increased risk in the <12-year follow-up group (aHR, 3.2; 95% CI, 1.4 to 7.3) (subanalysis not presented). Increased BMI was a significant risk factor only in the ≥12-year follow-up group.

The subanalysis of patients without any concomitant procedures at the time of the index procedure demonstrated no significant difference in the risk of knee arthroplasty between the treatment groups (see Appendix). Furthermore, an additional Cox analysis including the time period of the index operation (1999 to 2004 or 2005 to 2012) did not alter our findings.

The Cox adjusted survival curves of the knees with a cartilage lesion, with knee arthroplasty as the end point, are presented in Figures 2-A through 2-D. The survival curves

TABLE II Twenty-Year Cumulative Risk (1 − Kaplan-Meier Survival) and Risk Factors Associated with Knee Arthroplasty After Cartilage Injury, 1999 to 2020, in a Focal Cartilage Lesion Cohort Linked to the Norwegian Arthroplasty Register§§§

	No. of Knees	No. of Knee Arthroplasties	No of Knee Arthroplasties (TKAs/ UKAs/PFs)	20-Year Cumulative Risk (95% CI)	Crude HR* (95% CI)	Adjusted HR† (95% CI)
Total	328	59 (18.0%) of 328		19.1 (14.6-23.6)		
Age at time of surgery† *(no. of knees)*						
18-29 yr	83 (25.3%)	9 (10.8%) of 83	9 (7/0/2)	13.8 (9.7-17.9)	1	
30-39 yr	128 (39.0%)	14 (10.9%) of 128	14 (12/2/0)	12.0 (5.7-18.3)	1.08 (0.47-2.50)	
≥40 yr	117 (35.7%)	36 (30.8%) of 117	36 (29/6/1)	32.2 (23.2-41.2)	3.69 (1.78-7.67)	
Sex† *(no. of knees)*						
Male	188 (57.3%)	30 (16.0%) of 188	30 (25/5/0)	14.1 (8.8-19.4)	1	
Female	140 (42.7%)	29 (20.7%) of 140	29 (23/3/3)	22.8 (15.4-30.3)	1.38 (0.83-2.30)	
BMI at end of study§ *(no. of knees)*						
<25 kg/m^2	100 (30.5%)	7 (7.0%) of 100	7 (5/1/1)	7.2 (2.1-12.3)	1	1
25-29 kg/m^2	137 (41.8%)	27 (19.7%) of 137	27 (20/6/1)	22.2 (14.6-29.8)	3.07 (1.34-7.06)	3.86 (1.65-9.00)
≥30 kg/m^2	75 (22.9%)	19 (25.3%) of 75	19 (17/1/1)	27.1 (16.3-37.9)	4.1 (1.74-9.88)	5.90 (2.43-14.32)
Size of lesion# *(no. of knees)*						
<200 mm^2	214 (65.2%)	40 (18.7%) of 214	40 (32/5/3)	20.3 (14.6-26.0)	1	1
≥200 mm^2	114 (34.8%)	19 (16.7%) of 114	19 (16/3/0)	16.1 (8.8-23.4)	0.92 (0.53-1.59)	0.99 (0.55-1.78)
ICRS grade# *(no. of knees)*						
1-2	52 (15.9%)	4 (7.7%) of 52	4 (4/0/0)	7.7 (0.4-15.0)	1	1
3-4	276 (84.1%)	55 (19.9%) of 276	55 (44/8/3)	21.5 (16.2-26.8)	3.35 (1.21-9.27)	3.09 (1.10-8.70)
Level of education** *(no. of knees)*						
High school	155 (47.3%)	33 (21.3%) of 155	33 (24/6/3)	20.8 (14.1-27.5)	1	1
Bachelor's/ Master's degree	164 (50.0%)	22 (13.4%) of 164	22 (20/2/0)	15.8 (9.7-21.9)	0.62 (0.36-1.06)	0.60 (0.35-1.02)
ACL reconstructed at any time†† *(no. of knees)*						
No	278 (84.8%)	50 (18.0%) of 278	50 (39/8/3)	19.1 (14.2-24.0)	1	1
Yes	50 (15.2%)	9 (18.0%) of 50	9 (9/0/0)	19.1 (7.1-31.1)	0.94 (0.46-1.91)	1.62 (0.76-3.47)
Meniscal resection at any time†† *(no. of knees)*						
Yes	100 (30.5%)	18 (18.0%) of 100	18 (18/0/0)	21.3 (12.5-30.1)	1	1
No	228 (69.5%)	41 (18%) of 228	41 (30/8/3)	18.1 (12.8-23.4)	1.0 (0.58-1.75)	0.96 (0.53-1.73)
Location of cartilage lesion§§ *(no. of knees)*						
Patellofemoral	73 (22.3%)	9 (12.3%) of 73	9 (7/0/2)	13.5 (5.3-21.7)	1	1
Medial	204 (62.2%)	38 (18.6%) of 204	38 (29/8/1)	19.7 (13.8-25.6)	1.53 (0.74-3.17)	1.27 (0.58-2.78)
Lateral	51 (15.5%)	12 (23.5%) of 51	12 (12/0/0)	23.3 (11.1-35.5)	1.8 (0.74-4.30)	1.40 (0.55-3.57)

continued

TABLE II (*continued*)

	No. of Knees	No. of Knee Arthroplasties	No of Knee Arthroplasties (TKAs/ UKAs/PFs)	20-Year Cumulative Risk (95% CI)	Crude HR* (95% CI)	Adjusted HR† (95% CI)
Cartilage lesions## *(no. of knees)*						
1 lesion	244 (74.4%)	33 (13.5%) of 244	33 (24/6/3)	14.2 (9.5-18.9)	1	1
>1 lesion	84 (25.6%)	26 (31.0%) of 84	26 (24/2/0)	31.2 (21.2-41.2)	2.25 (1.34-3.76)	2.05 (1.13-3.71)
Treatment at index operation*** *(no. of knees)*						
No cartilage treatment	93 (28.4%)	13 (14.0%) of 93	13 (11/1/1)	14.2 (7.1-21.3)	1	1
Debridement/ microfracture	136 (41.5%)	28 (20.6%) of 136	28 (23/3/2)	22.1 (14.5-29.7)	1.8 (0.95-3.56)	1.61 (0.70-3.70)
ACI	30 (9.1%)	7 (23.3%) of 30	7 (5/2/0)	21.0 (5.9-36.1)	2.0 (0.78-5.01)	3.43 (1.03-11.39)
OATS	53 (16.2%)	11 (20.8%) of 53	11 (9/2/0)	21.1 (9.9-32.3)	1.65 (0.74-3.69)	1.95 (0.67-5.69)
Other	16 (4.9%)	0	0	0	0.0 (0-3.89 × 10^{295})	0.0 (0.0)
Preop. VAS pain score†††,‡‡‡	105 (32.0%)	14 (13.3%) of 105			1.03 (1.01-1.06)	1.08 (1.03-1.14)
Preop. Lysholm score†††,‡‡‡	18 (56.1%)	42 (22.8%) of 184			0.99 (0.97-1.00)	1.0 (0.98-1.02)

§§§TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty, PF = patellofemoral knee arthroplasty, CR = cumulative risk, CI = confidence interval, BMI = body mass index, ICRS = International Cartilage Repair & Joint Preservation Society, ACL = anterior cruciate ligament, ACI = autologous chondrocyte implantation, OATS = osteochondral autograft transplantation system (mosaicplasty), VAS = visual analog scale. *HR = hazard rate ratio from Cox analysis. †Cox-adjusted for variables according to a graphical causal model ‡Not adjusted. §Adjusted for age at time of surgery, sex, level of education. #Adjusted for age at time of surgery, BMI, meniscal resection. **Adjusted for sex. ††Adjusted for age at time of surgery, BMI, sex, level of education. ‡‡Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, level of education. §§Adjusted for ACL reconstruction, age at time of surgery, sex, meniscal resection. ##Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, level of education, meniscal resection, size of lesion. ***Adjusted for age at time of surgery, ICRS grade, level of education, location of lesion, number of lesions, size of lesion. †††Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, ICRS grade, level of education, location of lesion, meniscal resection, number of lesions, size of lesion. ‡‡‡Adjusted for VAS pain and Lysholm scores analyzed as continuous variables.

are adjusted for the same covariates as in the Cox regression model.

Table III summarizes the risk of knee arthroplasty in the cartilage cohort as compared with that in the age-matched general population. Table IV summarizes the subsequent risk of knee arthroplasty according to age at the time of cartilage surgery. The risk ratio of subsequent knee arthroplasty in the cartilage cohort versus the age-matched general Norwegian population ranged from 3.6 in the 60 to 69-year age group to 415.7 in the 30 to 39-year age group.

The rate of knee arthroplasty was significantly increased in all age groups except the 70 to 79-year age group, ranging from 819 to 952 of 100,000 in the cartilage cohort as compared with 2.3 to 229 of 100,000 in the general population (Table III).

Table V summarizes the number of concomitant surgical procedures at the time of the index procedure.

Discussion

Principal Findings

Patients with an arthroscopically verified focal cartilage lesion in the knee had a 19.1% 20-year cumulative risk of knee arthroplasty and a significantly increased risk of knee arthroplasty compared with the general population. The relative risk was particularly elevated in the younger population. The factors that were associated with an increased risk of subsequent knee arthroplasty included an older age at the time of arthroscopy, ACI treatment of the cartilage lesion, the depth of the cartilage lesion, a higher VAS pain score at the time of the index procedure, and a higher BMI at the time of follow-up.

Strengths and Limitations

The main strength of the present study is that all focal cartilage lesions in the knee were evaluated arthroscopically. Furthermore, any concurrent meniscal or ligamentous lesions were registered. The patients in the present study had no malalignment (>5°) because of the inclusion criteria in the previous clinical trials[15,17,18]. The mean duration of follow-up of 20 years increases the ability to identify the long-term cumulative risk of knee arthroplasty. To our knowledge, this is the first long-term study outside of an ACL cohort that has included patients with arthroscopically verified focal cartilage lesions who have undergone no cartilage treatment[29,30]. As such, the findings of

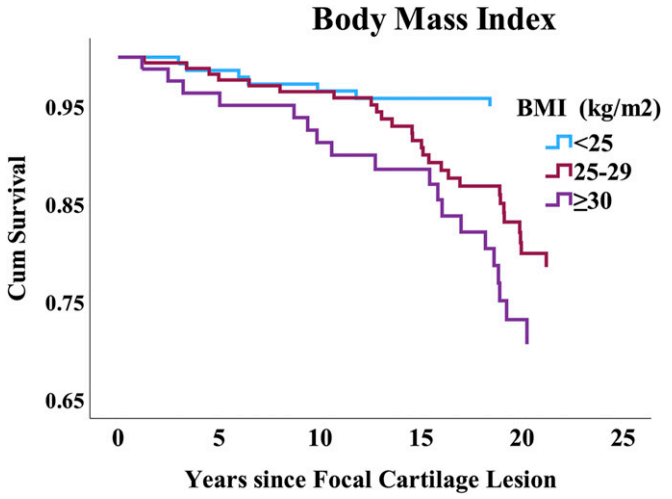

Fig. 2-A

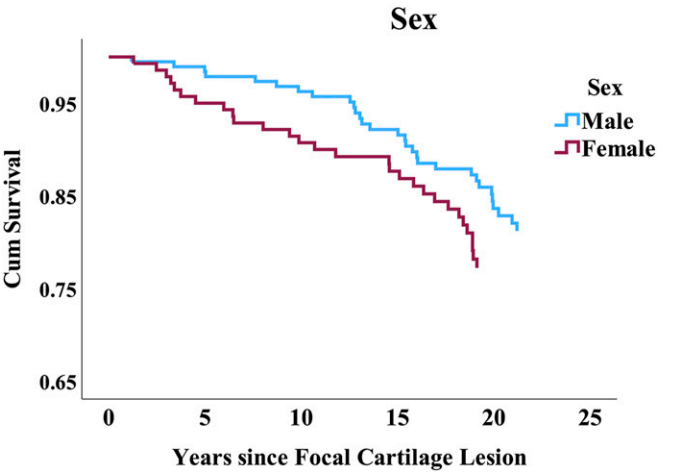

Fig. 2-B

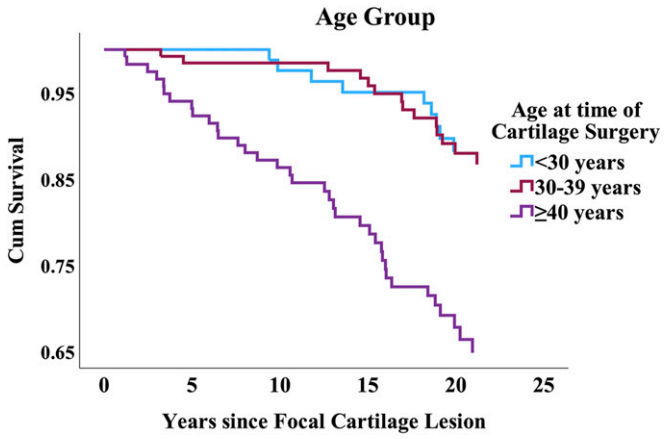

Fig. 2-C

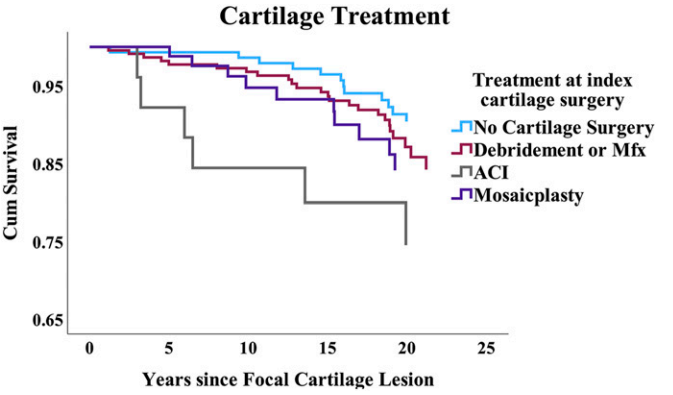

Fig. 2-D

Fig. 2-A through 2-D Cox adjusted survival curves of knees with focal cartilage lesions by World Health Organization BMI classes (adjusted for age at time of surgery, sex, and level of education) (**Fig. 2-A**), sex (unadjusted) (**Fig. 2-B**), age group at index surgery (unadjusted) (**Fig. 2-C**), and cartilage treatment (adjusted for age at time of surgery, ICRS grade, level of education, location of lesion, number of lesions, and size of lesion) (**Fig. 2-D**), with knee arthroplasty as the end point. Adjustment based on graphical causal model. Mfx = microfracture.

TABLE III Risk Ratio of Knee Arthroplasty in Cartilage Cohort Versus General Norwegian Population*

Cartilage Cohort			Age-Matched General Population†		
Age at Knee Arthroplasty	No. of Knee Arthroplasties	No. of Patients in Age Group	No. of Knee Arthroplasties, 1999-2020 *(per 10^5)*	No. of Knee Arthroplasties, 1999-2019 *(per 10^5)*	Risk Ratio (95% CI)
30-39 yr	4	20	952.4	2.3	415.69 (168.83-1,023.49)
40-49 yr	15	80	892.9	18.1	49.42 (31.01-78.76)
50-59 yr	25	126	944.8	83.3	11.35 (7.93-16.24)
60-69 yr	11	64	818.5	229.0	3.57 (2.07-6.17)
70-79 yr	3	31	460.8	363.4	1.27 (0.43-3.76)

*The relative risk of knee arthroplasty after a cartilage injury as compared with the general population. The absolute risk of knee arthroplasty in the cartilage cohort was estimated by dividing the number of knee arthroplasties by the total number of knees with cartilage injury in each group. For the general population, the numerator was all other patients with knee arthroplasty without inflammatory arthritis or previous cartilage surgery on the ipsilateral side as reported to the NAR between January 1, 1999, and December 31, 2020. The denominator was the average number of Norwegian citizens in the same period, retrieved from population data from Statistics Norway. One patient was 81 years old at the time of knee arthroplasty and was excluded. †General population excluded patients with previous cartilage surgery.

TABLE IV Risk Ratio of Knee Arthroplasty After Cartilage Surgery in Specific Age Ranges Versus Age-Matched General Norwegian Population*

Cartilage Cohort					Age-Matched General Population†	
Age at Cartilage Surgery	Age at Knee Arthroplasty	No. of Knee Arthroplasties	No. of Patients in Age Group	No. of Knee Arthroplasties, 1999-2020 *(per 10^5)*	No. of Knee Arthroplasties, 1999-2019 *(per 10^5)*	Risk Ratio (95% 3CI)
20-29 yr						
	30-39 yr	2	68	140.1	2.3	61.1 (15.5-240.6)
	40-49 yr	7	66	505.1	18.1	28.0 (13.8-56.6)
30-39 yr						
	30-39 yr	2	128	74.4	2.3	32.5 (8.2-129.0)
	40-49 yr	2	126	75.6	18.1	4.2 (1.1-16.6)
	50-59 yr	7	124	268.8	83.3	3.2 (1.6-6.6)
40-49 yr						
	40-49 yr	6	78	366.3	18.1	20.3 (9.4-43.9)
	50-59 yr	13	72	859.8	83.3	10.3 (6.3-17.0)
	60-69 yr	8	59	645.7	229.0	2.8 (1.5-5.4)
50-59 yr						
	50-59 yr	2	34	280.1	83.3	3.4 (0.9-12.9)
	60-69 yr	3	32	446.4	229.0	1.9 (0.7-5.8)
	70-79 yr	1	29	164.2	363.4	0.5 (0.1-3.1)

*The relative risk of knee arthroplasty in the cartilage cohort as compared with the general population, stratified in 10-year age groups at the time index cartilage procedure. For the general population, the absolute risk was estimated as described in Table III. In the cartilage cohort, the numerator was the number of knee arthroplasties in each 10-year age group (at the time of cartilage surgery) and the denominator was the total number of patients with a cartilage injury in the same age group. †General population excluded patients with previous cartilage surgery.

the present study enhance our knowledge of the natural history of focal cartilage lesions.

The present study had several limitations. The included patients were predominantly participants in previous clinical trials and may not be representative of the average patient with a focal cartilage lesion[31]. The follow-up rate of 65.1% may have introduced bias to the interpretation of the results, although the nonresponders had the same demographic characteristics as the responders, with the exception that they were a mean of 3 years younger. Patients with poor knee function or knee arthroplasty might have been more prone to participate in the study, thus leading to an overestimated risk of knee arthroplasty. Although the participants were asked if they had undergone additional surgery, we did not have complete

TABLE V Number of Additional Surgical Procedures at Time of Index Cartilage Procedure*

Index Cartilage Treatment	ACL Reconstruction	Meniscal Resection	Meniscal Suture	Lateral Release	Diagnostic Arthroscopy	Loose Body Removal	Total
No surgical treatment of cartilage (n = 93)	12	39	2	2	36	2	93
Microfracture/debridement (n = 136)	2	6	0	0	0	0	8
ACI/MACI (n = 30)	1	0	0	0	0	0	1
Mosaicplasty (n = 53)	0	0	0	0	0	0	0
Other (n = 16)	0	1	0	0	0	0	1

*ACL = anterior cruciate ligament, ACI = autologous chondrocyte implantation, MACI = matrix-induced ACI, Other = MaioRegen (Finceramica, Italy), Cartipatch (Xizia, Hong Kong), or TruFit (Smith & Nephew, USA).

medical records regarding later knee surgery. There were few knee arthroplasties in the younger age groups, which could have introduced bias.

The NAR does not include any details on BMI, and thus patients undergoing knee arthroplasty in the general population could have a significantly different BMI than those in our cohort. However, in 2020, the mean BMI values for Norwegian men and women were 26.5 and 25.6 kg/m^2, respectively, with a BMI value of >30 kg/m^2 reported for 59% and 47% of men and women, respectively[32]. These findings suggest that the BMI for our cartilage cohort was comparable with that the general Norwegian population. Three different PROMs were used preoperatively, and no patient had >1 preoperative PROM, limiting the ability to adjust on the basis of PROM data in the Cox model.

The present study was not a randomized trial, and the indications for the different cartilage treatments might have varied substantially. However, the patients who underwent ACI and several of those who underwent microfracture were participants in previous randomized trials, reducing the risk of selection bias. Patients who underwent cartilage surgery might have had more symptomatic lesions than those who did not. There also may have been unknown confounding factors (e.g., genetic disposition) that influenced the risk of knee arthroplasty[10].

Risk of Arthroplasty

Apold et al. identified increased BMI and heavy labor as risk factors for knee arthroplasty in the Norwegian general population[9]. In the present study, being overweight at the time of follow-up was associated with an increased risk of knee arthroplasty.

Several long-term clinical trials have investigated knee arthroplasty after cartilage surgery[12,33,34]. Ogura et al. reported a 20% rate of knee arthroplasty in a 20-year follow-up of first-generation ACI, which is in line with our results[12]. Gobbi et al. presented the 15-year results for focal cartilage lesions that had been treated with microfracture in an athletic patient cohort[13]. Those authors reported progression of osteoarthritis in 40% of the knees, with an 11% rate of failure (defined as subsequent surgery by the time of the latest follow-up); however, they did not report whether any of the subsequent procedures were knee arthroplasties. Older age at the time of cartilage surgery and large or multiple lesions were found to be the main risk factors for osteoarthritis. Possible explanations for the high rate of knee arthroplasty in our study may have been our somewhat older patient cohort (mean, 36.8 versus 31.4 years) as well as the 5-year-longer follow-up as compared with the study by Gobbi et al. Differences in the frequency of knee arthroplasty at a population level between regions, as demonstrated by Ackerman et al.[35], also might have contributed to the difference in the rate of knee arthroplasty.

Abram et al., in a study of almost 158,000 patients who had undergone previous chondroplasty in U.K. National Health Service (NHS) hospitals, found an increased risk of knee arthroplasty compared with that in the general British population[14]. The overall risk of knee arthroplasty within 8 years was 17.6%. Both sex and age were identified as risk factors for later knee arthroplasty. Abram et al. provided no information on BMI but found that an increased Charlson Comorbidity Index increased the risk of knee arthroplasty. The cohort in that study (mean age, 51.7 years) was older than our cohort. This is most likely the explanation why the 8-year risk of knee arthroplasty in the U.K. chondroplasty cohort approximated the 20-year risk in our study.

Both ACL injury and meniscal lesions are known to increase the risk of osteoarthritis and subsequent TKA[8,36-40]. In the present cartilage cohort, neither meniscal resection nor ACL surgery was associated with an increased risk of knee arthroplasty. A possible explanation could be that the cartilage lesion increases the risk of knee arthroplasty substantially more than ACL and meniscal injury do, thereby limiting the functional impact of the latter. Visnes et al. found a 3-times increased risk of knee arthroplasty in 30 to 39-year-old patients and a doubled risk in 40 to 49-year-old patients after ACL surgery compared with the general population[41]. In our cartilage cohort, the corresponding values were a 416-times increased risk and a 49-times increased risk, respectively. However, we do not have any information regarding nonoperative ACL treatment. Another possibility is that the surgeons might have misclassified arthritic lesions as focal cartilage lesions. We found that the oldest patients in our cartilage cohort had a tendency toward a decreased risk of subsequent knee arthroplasty (although this finding was not significant). This finding might be indicative that patients with arthritic lesions were excluded even in the older patient group.

In the present study, we found that treatment of the cartilage lesion with ACI increased the risk of subsequent knee arthroplasty by 3.4 times as compared with no treatment. To reduce the risk of including asymptomatic lesions in the nonoperatively treated group, we performed a subanalysis of the patients without any concomitant procedures at the time of the index procedure. The subanalysis revealed no significant difference between the treatment groups, suggesting that our finding of increased risk following ACI could have been due to confounding factors. Vasiliadis and Wasiak, in a Cochrane review, found that there is insufficient evidence of the superiority of ACI compared with other cartilage treatments[42]. In recent years, high-volume orthopaedic procedures such as meniscal surgery in middle-aged patients have been shown not to be superior to sham surgery or nonoperative treatment[43,44]. Consequently, we suggest that future clinical trials on the treatment of focal cartilage lesions in the knee should include a control group that is treated nonoperatively or with sham surgery[45].

Conclusions

In this study, the 20-year cumulative risk of knee arthroplasty after focal cartilage lesion in the knee was 19%. We found an up to 416-times increased risk of knee arthroplasty in patients with a focal cartilage lesion as compared with the general population.

Deep lesions, older age at the time of cartilage surgery, high BMI at the time of follow-up, ACI, and >1 cartilage lesion were associated with a higher risk of knee arthroplasty. Surgical treatment of cartilage lesions does not seem to decrease the risk of subsequent knee arthroplasty compared with no surgical cartilage treatment. Our findings should be viewed as hypothesis-generating and support the need for prospective randomized clinical trials including a sham surgery arm.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H504). ■

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References

1. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy. 2002 Sep;18(7):730-4.
2. Engen CN, Årøen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. BMJ Open. 2015 Nov 30;5(11):e008423.
3. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. Knee. 2007 Jun;14(3):177-82.
4. Heir S, Nerhus TK, Røtterud JH, Løken S, Ekeland A, Engebretsen L, Arøen A. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. Am J Sports Med. 2010 Feb;38(2):231-7.
5. Hunziker EB, Lippuner K, Keel MJ, Shintani N. An educational review of cartilage repair: precepts & practice—myths & misconceptions—progress & prospects. Osteoarthritis Cartilage. 2015;23(3):334-50.
6. Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. Knee. 2017 Jun;24(3):508-17.
7. Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. Am J Sports Med. 2009 Nov;37(Suppl 1):148S-55S.
8. Brophy RH, Gray BL, Nunley RM, Barrack RL, Clohisy JC. Total knee arthroplasty after previous knee surgery: expected interval and the effect on patient age. J Bone Joint Surg Am. 2014 May 21;96(10):801-5.
9. Apold H, Meyer HE, Nordsletten L, Furnes O, Baste V, Flugsrud GB. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. BMC Musculoskelet Disord. 2014 Jun 23;15:217.
10. Magnusson K, Scurrah K, Ystrom E, Ørstavik RE, Nilsen T, Steingrímsdóttir ÓA, et al. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. Osteoarthritis Cartilage. 2017;25(6):878-84.
11. Pareek A, Reardon PJ, Maak TG, Levy BA, Stuart MJ, Krych AJ. Long-term Outcomes After Osteochondral Autograft Transfer: A Systematic Review at Mean Follow-up of 10.2 Years. Arthroscopy. 2016 Jun;32(6):1174-84.
12. Ogura T, Mosier BA, Bryant T, Minas T. A 20-Year Follow-up After First-Generation Autologous Chondrocyte Implantation. Am J Sports Med. 2017 Oct;45(12):2751-61.
13. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. Knee Surg Sports Traumatol Arthrosc. 2014 Sep;22(9):1986-96.
14. Abram SGF, Palmer AJR, Judge A, Beard DJ, Price AJ. Rates of knee arthroplasty in patients with a history of arthroscopic chondroplasty: results from a retrospective cohort study utilising the National Hospital Episode Statistics for England. BMJ Open. 2020 Apr 16;10(4):e030609.
15. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grøntvedt T, Solheim E, Strand T, Roberts S, Isaksen V, Johansen O. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004 Mar;86(3):455-64.
16. Arøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG, Engebretsen L. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med. 2004 Jan-Feb;32(1):211-5.
17. Solheim E, Øyen J, Hegna J, Austgulen OK, Harlem T, Strand T. Microfracture treatment of single or multiple articular cartilage defects of the knee: a 5-year median follow-up of 110 patients. Knee Surg Sports Traumatol Arthrosc. 2010 Apr;18(4):504-8.
18. Solheim E, Hegna J, Oyen J, Austgulen OK, Harlem T, Strand T. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. Knee. 2010 Jan;17(1):84-7.
19. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003 Nov 3;1:64.
20. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982 May-Jun;10(3):150-4.
21. International Cartilage Repair Society. The cartilage standard evaluation form/knee. ICRS Newsletter, spring 1998.
22. The Norwegian National Advisory Unit. Norwegian National Advisory Unit on Arthroplasty and Hip Fractures. 2020. Accessed 2023 Mar 27. http://nrlweb.ihelse.net/eng/Rapporter/Report2020_english.pdf

23. Furnes O, Espehaug B, Lie SA, Vollset SE, Engesaeter LB, Havelin LI. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994-2000. Acta Orthop Scand. 2002 Apr;73(2):117-29.

24. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958;53(282):457-81.

25. Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol. 2013 Feb 15;177(4):292-8.

26. Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Ludvigsen TC, Løken S, Solheim E, Strand T, Johansen O. A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Long-Term Follow-up at 14 to 15 Years. J Bone Joint Surg Am. 2016 Aug 17;98(16):1332-9.

27. Solheim E, Hegna J, Inderhaug E, Øyen J, Harlem T, Strand T. Results at 10-14 years after microfracture treatment of articular cartilage defects in the knee. Knee Surg Sports Traumatol Arthrosc. 2016 May;24(5):1587-93.

28. Solheim E, Hegna J, Øyen J, Harlem T, Strand T. Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. Knee. 2013 Aug;20(4):287-90.

29. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. J Bone Joint Surg Am. 2003;85-A(Suppl 2):8-16.

30. Widuchowski W, Widuchowski J, Koczy B, Szyluk K. Untreated asymptomatic deep cartilage lesions associated with anterior cruciate ligament injury: results at 10- and 15-year follow-up. Am J Sports Med. 2009 Apr;37(4):688-92.

31. Engen CN, Engebretsen L, Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. Cartilage. 2010 Oct;1(4):312-9.

32. Abel MH. Diet and self-reported weight and weight-change based on data from the National Public Health Survey 2020. Norwegian Institute of Public Health.; 2021. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2021/rapport-nhus-2020.pdf

33. Minas T, Von Keudell A, Bryant T, Gomoll AH. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. Clin Orthop Relat Res. 2014 Jan;472(1):41-51.

34. Sanders TL, Pareek A, Obey MR, Johnson NR, Carey JL, Stuart MJ, Krych AJ. High Rate of Osteoarthritis After Osteochondritis Dissecans Fragment Excision Compared With Surgical Restoration at a Mean 16-Year Follow-up. Am J Sports Med. 2017 Jul;45(8):1799-805.

35. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, Furnes O, Garellick G, Graves SE, Haapakoski J, Havelin LI, Mäkelä K, Mehnert F, Pedersen AB, Robertsson O. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. Osteoarthritis Cartilage. 2017 Apr;25(4):455-61.

36. Lindanger L, Strand T, Mølster AO, Solheim E, Fischer-Bredenbeck C, Ousdal OT, Inderhaug E. Predictors of Osteoarthritis Development at a Median 25 Years After Anterior Cruciate Ligament Reconstruction Using a Patellar Tendon Autograft. Am J Sports Med. 2022 Apr;50(5):1195-204.

37. Poulsen E, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4-6 fold after knee injury - a systematic review and meta-analysis. Br J Sports Med. 2019 Dec;53(23):1454-63.

38. Enweze LC, Varshneya K, Sherman SL, Safran MR, Abrams GD. Risk of Subsequent Knee Arthroplasty After Sports Medicine Procedures. J Am Acad Orthop Surg Glob Res Rev. 2020 Aug;4(8):00125.

39. Everhart JS, Magnussen RA, Abouljoud MM, Regalado LE, Kaeding CC, Flanigan DC. Meniscus tears accelerate joint space loss and lateral meniscal extrusion increases risk of knee arthroplasty in middle-aged adults. J Orthop Res. 2020 Nov;38(11):2495-504.

40. Abram SGF, Judge A, Khan T, Beard DJ, Price AJ. Rates of knee arthroplasty in anterior cruciate ligament reconstructed patients: a longitudinal cohort study of 111,212 procedures over 20 years. Acta Orthop. 2019 Dec;90(6):568-74.

41. Visnes H, Gifstad T, Persson A, Lygre SHL, Engebretsen L, Drogset JO, Furnes O. ACL Reconstruction Patients Have Increased Risk of Knee Arthroplasty at 15 Years of Follow-up: Data from the Norwegian Knee Ligament Register and the Norwegian Arthroplasty Register from 2004 to 2020. JB JS Open Access. 2022 Jun 21;7(2):e22.00023.

42. Vasiliadis HS, Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. Cochrane Database Syst Rev. 2010 Oct 6;2010(10):CD003323.

43. Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Kalske J, Nurmi H, Kumm J, Sillanpää N, Kiekara T, Turkiewicz A, Toivonen P, Englund M, Taimela S, Järvinen TLN; FIDELITY (Finnish Degenerative Meniscus Lesion Study) Investigators. Arthroscopic partial meniscectomy for a degenerative meniscus tear: a 5 year follow-up of the placebo-surgery controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) trial. Br J Sports Med. 2020 Nov;54(22):1332-9.

44. Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ. 2016 Jul 20;354:i3740.

45. Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, Buchbinder R, Pinkney T, Bishop FL, Pugh J, Cousins S, Harris I, Lohmander LS, Blencowe N, Gillies K, Probst P, Brennan C, Cook A, Farrar-Hockley D, Savulescu J, Huxtable R, Rangan A, Tracey I, Brocklehurst P, Ferreira ML, Nicholl J, Reeves BC, Hamdy F, Rowley SC, Lee N, Cook JA. Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop. Health Technol Assess. 2021 Sep;25(53):1-52.