

Review Article

Occupational and genetic risk factors for osteoarthritis: A review

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Abstract.

BACKGROUND: Osteoarthritis (OA) is a multifactorial disease with strong genetic and occupational components. Although published studies have described several risk factors for OA, very few studies have investigated the occupational and genetic factors that contribute to this debilitating condition.

OBJECTIVE: To describe occupational and genetic factors that may contribute to the risk of developing (OA).

METHODS: A literature search was conducted in PubMed using the search terms osteoarthritis, occupation, work, and genetics.

RESULTS: Heavy physical work load was the most common occupational risk factor for OA in several anatomical locations. Other factors include kneeling and regular stair climbing, crawling, bending and whole body vibration, and repetitive movements. Numerous studies have also shown the influence of genetic variability in the pathogenesis of OA. Genetic variants of several groups of genes e.g., cartilage extracellular matrix structural genes and the genes related to bone density have been implicated in disease pathogenesis.

CONCLUSION: This review shows that occupational factors were extensively studied in knee OA unlike OA of other anatomical regions. Although genetic association studies performed to date identified a number of risk variants, some of these associations have not been consistently replicated across different studies and populations. Therefore, more research is needed.

Keywords: Joint disorders, joint pain, workers, occupation, genetics

1. Introduction

Several review studies have been published on general risk factors for osteoarthritis (OA). However, very few have been published on occupational risk factors for OA and each of these has focused on only one anatomical location [1]. No published studies have

been identified that have reviewed occupational exposures and genetic factors that contribute to OA in several anatomical locations. This paper does not provide a systematic review, but succinctly describes the occupational exposures and genetic factors that may contribute to or are associated with the risk of developing OA, and identifies the known research gaps in occupationally-related OA.

2. Definition of osteoarthritis

Osteoarthritis (OA) is a disorder characterized by chronic structural and functional degeneration of the

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whole joint [2]. The pathophysiology of OA presents as degeneration, destruction, and eventual loss of articular cartilage, which may be concomitant with changes in other soft tissues [3,4]. OA can be defined radiologically, clinically, or pathologically, with radiographic OA being considered the reference standard [5]. The symptoms that are consistently associated with OA are joint pain, stiffness, swelling, and limitation of joint function. Interestingly, some individuals who present with these symptoms may not demonstrate radiographic OA, while others who have been confirmed to have OA using radiographic techniques may not present with clinical manifestations of the disease [5]. These unique characteristics have made it difficult to identify the underlying mechanisms contributing to the disease and treatments for reducing the incidence and severity of the disease. In addition, the stimuli that may initiate the processes associated with OA are multifactorial and include occupational and non-occupational (e.g., genetics, obesity, age, etc.) factors.

3. Burden and economic costs of osteoarthritis

The burden of OA is substantial, and its prevalence varies by several characteristics (e.g., age, gender, race/ethnicity) for each affected anatomical location. Prevalence estimates also vary depending on whether the criterion used to define its presence is that provided by the American College of Rheumatology or some other source. Approximately 43 million persons in the United States are affected by OA [6].

OA of the knee appears to have the highest prevalence, with lower and varying results for OA of the hip, spine, neck, hand, and foot; it is relatively rare in other joints such as the ankle, wrist, elbow, and shoulder [6–8]. During 1991–1994, approximately 37% (13.3 million) of US adults aged ≥ 60 years, showed evidence of radiographic knee OA. Overall, 8% of the US adult population over 60 years had a history of symptomatic hand OA (~2.9 million persons) while 37.3% had asymptomatic radiographic hand OA [8]. According to results from the Women's Health Initiative study, the prevalence of self-reported OA overall is very high [44%] among nearly 146,500 postmenopausal women [9].

The economic burden associated with OA is extremely high. Leigh and colleagues [10] estimated the job related costs of OA, from medical (51%) and lost productivity at work (49%), to be \$3.41 to \$13.23 billion per year (in 1994 US dollars). Another source re-

ported that OA costs the United States economy more than \$60 billion per year [11]. According to one study, OA is a more costly disease than rheumatoid arthritis in economic terms because of its far higher prevalence [12]. Approximately one-third of direct OA expenditures are allocated for medication, much of which goes toward pain-related agents. Hospitalization costs comprise about 50% of direct costs, with most of these expenditures being consumed by a small proportion [5%] of OA patients who undergo knee or hip replacement surgery. Indirect costs for OA are also high, largely as a result of work-related losses and home-care costs [12]. It is estimated that 500 deaths due to OA occur annually and this number is most likely to be highly underestimated [13]. In 2009, OA was the fourth most common cause of hospitalization [14].

4. Occupational risk factors for osteoarthritis

4.1. Knee OA

One of the most common occupational risk factors for knee OA is heavy physical work load [15]. Other risk factors include frequent exposure to several biomechanical stressors such as bending of the knee, kneeling or squatting, standing for long hours (≥ 2 hour per day), walking ≥ 3 km/day, regular stair climbing, heavy lifting (≥ 10 kg), jumping, and vibration [15–23]. Results from a British study revealed a more than five-fold greater risk of knee OA among workers ≥ 55 years who were exposed to a combination of heavy lifting (> 25 kg) and kneeling/squatting or climbing stairs [18]. Those who reported regular knee flexion without lifting were only at 2.5 times greater risk. Results from the Clearwater Osteoarthritis Study showed that standing on a rigid surface was significantly associated with knee OA among women, and stair climbing and jolting of the legs were significantly associated with knee OA among men [24].

In a case-control study of Japanese men, physical work as the principal occupation remained independently and significantly associated with knee OA after controlling for other risk factors [25]. Occupations in which a considerable amount of time is spent in knee-straining positions (e.g., floorlayers, carpenters, and compositors) were shown to be a risk factor for the development of knee OA but only in workers above the age of 50 years [26].

Two cross-sectional studies reported results that were contrary to expectations. In a case-control study

of Japanese women, sedentary work during initial employment was associated with a decreased risk of knee OA and total working years was associated with a slight increased risk of knee OA [27]. Goekoop and colleagues investigated factors that were associated with the absence of OA in 82 senior citizens (age = 90 years) [28]. Among these individuals, absence of OA was associated with male gender, a normal body mass index, absence of familial predisposition for OA, and, most surprisingly, heavy occupational work. The authors speculated that this cohort may have had a genetic predisposition for excellent tissue repair which resulted in the preservation of healthy joints [28].

Workers in several occupations are at increased risk for knee OA. They include workers in construction, firefighting, agriculture, fisheries, forestry, and mining [15,17,21,29–31]. In a case-control study, men who worked for 11–30 years in building and construction work had a 3.7 fold greater risk of developing knee OA, after adjustment for confounding factors [29]. Several studies have reported that male workers in manual labor occupations had higher odds of knee OA [7,32,33].

Among Danish adults, male floor- and bricklayers had an increased risk of developing knee OA compared to office workers [33]. The risk increased by the number of years in the occupations. Among male healthcare assistants, an elevated risk of developing knee OA was only seen in those who had worked > 10 years [33]. Female healthcare assistants and female construction workers who had worked > 5 years had increased risk of developing knee OA.

Among male workers employed in the Swedish construction industry, there was a significantly increased risk of surgically treated OA in the knee among floor layers, asphalt workers, sheet-metal workers, rock workers, plumbers, brick layers, wood workers and concrete workers [34].

Women with 11–30 years in farm work had a tendency towards an increased risk, although it did not reach statistical significance [29]. Farm work was not shown to be associated with an increased risk of knee OA among men [29]. However, exposure to construction or farm work in combination with excess weight significantly increased the risk of developing knee OA. Andersen and colleagues [33] did not find strong evidence for a risk of knee OA among female farmers. Among 582 Japanese women, 195 women [33.5%] suffered from knee OA but the occupation of farming was not associated with knee OA [35].

4.2. Hip OA

Compared to knee OA, relatively few studies have focused on occupational OA in the hip. Heavy physical work load or manual labor involving heavy loads was identified as a common occupational risk factor for hip OA [36,37]. Yoshimura and colleagues [38] reported statistically significant associations for occupational lifting and regular lifting of 25 kg (first job) or 50 kg (main job) for hip OA. In contrast, those subjects who spent > 2 hours each day sitting during their first job were significantly less likely to have hip OA. Permanent damage as a consequence of any musculoskeletal injury was also an independent predictor of hip OA [37]. Other occupational risk factors include crawling, doing heavy work while standing, more occupational walking and standing, and less sitting [39, 40].

One of the earliest published studies of occupational OA was conducted by Kellgren and Lawrence [30] on 84 miners and 87 other workers (manual workers and office workers). Hip OA was found in three workers, all of whom were miners. Other occupational groups that are at increased risks for hip OA include farmers and other agricultural workers, construction workers, firefighters, food processing workers, female mail carriers, and female cleaners [41,42]. Compared to office workers in Denmark, male farmers had an increased risk of developing hip OA [33]. The risk increased by number of years in the occupations. Male farmers had an increased risk of hip OA following 1–5 years of work as farmers and threefold increased risk after 10 years [33]. Female farmers who had worked for 6–10 and > 10 years had an approximate two-fold increased risk of hip OA. The authors did not find strong evidence for risk of hip OA among female construction workers. Female healthcare assistants who had worked > 5 years had increased risk of developing hip OA [33].

In a case-control study, farmers with larger dairy and swine confinement operations (sows) had an increased risk of acquiring OA of the hip [43]. Those who milked more than 40 cows daily had an increase in risk in relation to those who did not work in dairy production. Those who had large farm areas had a significantly decreased risk in relation to those who had smaller farm areas.

Among male workers employed in the Swedish construction industry, the incidence rates for OA in hip and knee were positively correlated [34]. The authors reported a trend towards increased relative risks for OA

of the hip in floor layers, asphalt workers, wood workers and concrete workers, but they were not statistically significant. The risk factors seem to be of greater importance for OA in the knee compared with the hip.

4.3. Spine and neck OA

As has been reported with knee and hip OA, heavy physical work load was also an occupational risk factor that was found to be associated with spine and neck OA. Videman and colleagues [36] studied the pathology of the lumbar spine in relation to occupation and other factors in male cadavers. While heavy work appeared to be related to moderate and severe osteophytosis of the vertebrae, aging was the only significant variable in multivariate analysis. Bending, twisting, reaching, and stretching were the occupational activities associated with greater functional limitations and radiographic damage in patients with longstanding ankylosing spondylitis [44]. Exposure to whole body vibration was also associated with more radiographic damage [44].

Significantly elevated odds ratios were found for cervical spondylosis among meat carriers, dentists, and miners [45]. Among 658 Dutch patients with ankylosing spondylitis, the severity of the condition was greater among those with a manual job compared to those with a non-manual job and the observed effect was stronger in male than in female patients.

4.4. Hand and shoulder OA

Jobs that require workers to use repetitive movements, lift heavy weights, to work at a fast pace, or have what is perceived to be insufficient rest breaks have been shown to be associated with OA of the hand [41,46]. Workers who had been highly exposed to vibration also had an elevated odds ratio for hand OA but it was attenuated after simultaneous adjustment for manual work. Jolting of the hands was significantly associated with hand OA among women [24]. In contrast, no significant association was found between the physical workload history and thumb carpometacarpal OA among 8000 Finnish adults [47]. A cross-sectional study conducted in Sweden among construction workers found that those workers who lifted more than 709 tons had an increased risk of developing severe OA of the right acromioclavicular joint [48].

Construction workers were at increased risk of shoulder OA [47]. From the few articles that investigated hand OA, cotton workers, dentists, and construc-

tion workers were shown to be more at risk than other workers [47,49]. In a study comparing female dentists to female teachers, OA of the right-hand thumb, index and middle fingers was significantly more severe among the dentists compared with the teachers [49]. Solovieva and colleagues [50] studied whether the pattern of dental work tasks was associated with finger OA among 291 middle-aged female dentists. The dentists with a history of low task variation had a greater prevalence of OA in the thumb, index, and middle fingers compared with dentists with high variation. The pattern of dental work task history is associated with the localization of OA in the fingers.

4.5. Foot OA

One published epidemiologic study was found that investigated occupational risk factors for OA of the foot. Bernard and colleagues [24] reported that stair climbing was associated with foot OA. Descatha and Deschamps [51] reported the case of a 55-year old woman suffering from pains in the feet. Over 40 years as a professional dancer and dance teacher caused localized OA of the tarsometatarsal joint, or at least accelerated the degenerative process. Results from the Clearwater Osteoarthritis Study showed that among persons with foot OA (17.7% of women and 25.1% of men), there was a significant positive association with OA of several other joints [52].

5. Genetic determinants of osteoarthritis

The genetic contribution to OA has been extensively investigated in family based studies, linkage analysis and association studies. Twin and family aggregation studies have demonstrated skeletal site specific differences in OA heritability [53–55]. The estimate of heritability has been reported to be 40% for the knee, 60% for the hip, 65% for the hand, and about 70% for the spine [56]. Epidemiological studies revealed a non-Mendelian transmittance pattern for OA [57]. These studies suggested a multifactorial inheritance and emphasized the need for genetic linkage studies to identify chromosomal regions involved in the disease process. Genetic association studies helped identify the effects of specific gene variants on OA pathogenesis. Although family and epidemiological studies have consistently indicated an important genetic contribution to OA, the genetic variants identified to date had only small effects indicating the complex polygenic nature

of OA. In a recent study, the additive effect of a number of genetic variants in the risk of developing OA was found to be predictive of knee OA risk both in men and women [58]. Another recent study provided evidence for a gene-environment interaction in the etiology of knee OA. This study indicated a significant interaction between smoking and family history of OA. In subjects with at least one parent having severe primary knee OA, smoking was associated with knee cartilage loss and defect development [59]. The genetic factors also act in a gender-specific manner, likely modulated by environmental and local biomechanical factors, and distributed differently between men and women. Overall, females are more commonly affected than males [60].

5.1. Linkage studies

Numerous genome-wide linkage scans identified several regions (chromosomes 2, 3, 4, 6, 7, 11, 16, the X) likely to harbor OA susceptibility genes [57, 61–63]. The most consistent linkage was reported between chromosome 2q13–32 and specific OA phenotypes [62,64,65]. This particular region includes the IL-1 (interleukin-1) gene cluster, frizzled-related protein 3 (FRZB) and cartilage structural protein matrilin-3 (MATN3). Chromosomes 6 and 16 have also provided linked loci for hip and hand OA [66–68]. The denser linkage analysis showed that major susceptibility locus on chromosomes 6 and 16 were within the interval at 6p12.3–q13, and 16p12.3–p12.1, respectively. Some of the markers that showed an association with OA susceptibility was positioned close to the alpha 1 type IX collagen (COL9A1), bone morphogenetic protein 5 (BMP5) and IL-4R genes. Regions on chromosome 4 (4q35) and chromosome 7 (7q34–7q36.3, 7p15–7p21, 7q22) were also linked to hip, knee and hand OA [69–72]. Other regions identified through genome-wide association studies were on chromosomes 3 and 11 which include susceptibility genes, the double von Willebrand factor domain A (DVWA) (3p24.3) and low density lipoprotein receptor-related protein 5 (*LRP5*) (11q12–13) [73,74]. These linkages served as a starting point for narrowing the interval of linkage and identification of potential candidate genes.

5.2. Candidate gene studies

Candidate gene studies focused on several groups of genes such as cartilage extracellular matrix (ECM)

structural genes (e.g., COL2A1, COL9A3, COL11A1, cartilage matrix protein (CRTM)); the genes related to bone density (e.g., vitamin D receptor (VDR), estrogen receptor alpha (ESR1)); the genes related to chondrocyte cell signaling and signal transduction (e.g., BMP5, FRZB, IL-4R α); and inflammatory cytokine genes (e.g., IL-1, IL-10, TGF β 1, IL-6, TNF α). Involvement of many candidate genes has already been confirmed within a joint category by two or more independent studies such as; asporin (ASPN) hip and knee OA; FZRB, hip OA; growth differentiation factor 5 (GDF5), hip OA; and VDR, knee OA. Some of these associations (FRZB and GDF5) were also replicated in different populations. Table 1 lists selected published associations with OA. Only representative examples will be discussed here.

The initial candidate gene studies focused on several cartilage ECM structural genes such as COL2A1 (12q13.11). COL2A1 is a major component of articular cartilage and intervertebral discs and plays an important role in the structure and strength of connective tissues that support muscles and joints. The Arg519Cys variation in the COL2A1 gene was found to reduce the durability of the articular cartilage against mechanical stress and has been linked to hip and knee OA [75,76]. While the COL2A1 Gly976Ser variation was linked to early-onset OA [77] single nucleotide polymorphisms (SNP) rs3737548 and rs2276455 and their haplotypes [2-1] conferred an increased risk of hand OA in Finnish female dentists and teachers. When stratified by occupation, the increased risk was mainly attributed to the dentists [78]. Recently, association of two COL2A1 SNPs (T2088C and G4006A) with OA was investigated in Han Chinese women. The frequency of G4006A AA homozygous genotype was significantly increased in the OA patients, compared with the controls. In addition, the TG haplotype was found to be a protective factor for OA while TA was a risk factor [79].

The matrilins are noncollagenous extracellular matrix adaptor proteins which mediate interactions between collagen fibrils and other matrix components [80]. Increased expression levels of MATN3, an important component of human articular cartilage matrix, were found in osteoarthritic cartilage matrix. The Thr303Met variation of MATN3 gene was linked to hand OA in an Iceland population and this association was replicated in two German cohorts [81–83].

Estrogens affect articular cartilage metabolism directly via estrogen receptors (alpha and beta) in chondrocytes and play important roles in the pathophysi-

Table 1
Selected genetic associations with OA

Gene/Chromosome	Variation	Ethnicity/gender	Skeletal site	OR [95%CI] or <i>P</i> value	Reference
ASPN [Chr 9]	D repeat	Japanese	Knee	1.87 (1.3–2.6)	[114]
			Hip	1.70 (1.1–2.5)	
		Korean	Knee	1.65 (1.07–2.54)	[115]
COL2A1 [Chr 12]	rs1635560 rs2276455	UK/male	Knee	0.68 (0.51–0.89)	[60]
		Finnish/female dentists	Hand	2.18 (1.18–4.06)	[78]
COL9A3 [Chr 20]	1740 C<T	Japanese	Knee	1.48 (1.15–1.91)	[76]
CRTM [Chr 1]	CA repeat in the 3'-UTR, allele 2	Dutch/Men	Hip	0.50 (0.26–0.95)	[116]
DIO2 [Chr 14]	Haplotype (rs225014, rs12885300)	Caucasian/female	Hip	1.79 (1.37–2.34)	[103]
DVWA [Chr 3]	rs7639618	Japanese	Knee	1.54 (1.32–1.81)	[74]
ESR1 [Chr 6]	-1174 (TA) _n	Greek	Knee	1.9 (1.03–3.5)	[117]
	rs2228480	Korean	Knee	1.38 (1.01–1.88)	[118]
	Haplotype (rs2234693, rs827421, rs1801132, rs2228480)	Caucasian/Women	Knee	3.6 (1.18–10.98)	[87]
	rs2234693	Caucasian/Women	Knee	0.76 (0.59–0.97)	[88]
FRZB [Chr 2]	rs7775	UK/female	Hip	1.5 (1.1–2.1)	[93]
	rs7775	Dutch	Multiple sites	1.6 (1.1–2.3)	[94]
	rs288326	UK/female	Knee	1.43 (0.99–2.05)	[60]
	Haplotype, rs7775, rs288326	Caucasian/Women	Hip	1.90 (1.22–2.96)	[95]
GDF5 [Chr 20]	rs143383	Japanese/Chinese	Hip	1.79 (1.53–2.09)	[97]
		European	Knee, hip	1.28 (1.08–1.51)	[98]
		Thai	Knee	2.41 (1.02–5.67)	[101]
		Caucasian	Knee	1.17 (1.12–1.23)	[102]
IL-1 β [Chr 2]	rs1143633	Caucasian	Hand	2.58 (<i>p</i> = 0.02)	[106]
	rs1143627	Japanese	Knee	2.04 (1.05–3.98)	[107]
	rs16944	Croatian	Hip	0.72 (0.52–0.99)	[113]
IL-1RN [Chr 2]	VNTR, allele 2 rs9005	Dutch	Hip	3.3 (1.4–7.8)	[64]
		Caucasian	Knee	0.15 (0.065–0.349)	[110]
IL-1R1 [Chr 2]	rs2287047	Finnish	Hand	0.16 (0.06–0.45)	[112]
IL-4R [Chr 16]	rs1805016	UK/female	Hip	2.1 (1.3–3.5)	[67]
IL-6 [Chr 7]	rs1800795	Italian	Hip	0.4 (0.1–0.9)	[119]
MATN3 [Chr 2]	T303M	German	Hand	4.28 (1.18–14.8)	[120]
VDR [Chr 12]	<i>Apa</i> I	Finnish/female	Hand	1.93 (1.00–3.70)	[50]
	Haplotype (COL2A1 4B, VDR 1)	Dutch	Hand	2.68 (1.41–5.10)	[89]
HLA-DQB1 [Chr 6]	rs7775228	Caucasian	Knee	1.34 (1.21–1.49)	[121]
BTNL2 [Chr 6]	rs10947262	Caucasian	Knee	1.32 (1.19–1.46)	[121]

*OR = odds ratio; 95% CI = 95% confidence interval.

ology of bone and cartilage-related diseases [84]. The *Pvu* II and *Xba* I restriction fragment – length polymorphisms in the ESR1 gene (6q25.1) were found to be associated with generalized OA in Japanese women and knee OA in the Rotterdam study [85,86]. Another study investigating the association of four ESR1

SNPs with knee OA reported that the TAGA haplotype consisting of rs2234693, rs827421, rs1801132 and rs2228480 SNPs is associated with an increased risk of knee OA in women [87]. Recently, the CC genotype of the ESR1 rs2234693 SNP was associated with reduced knee and hip OA risk in women, but with in-

creased risk of hip OA in men [88].

The VDR gene (12q12eq14) is one of the most frequently studied genes in OA due to its importance in calcium homeostasis, bone development and mineralization. Three VDR polymorphisms in exon 9 (TaqI) and intron 8 (BsmI and ApaI) were found to be in strong linkage disequilibrium and associated with hand and knee OA [50,89].

OA susceptibility genes have also been identified in the Wnt, transforming growth factor- β and thyroid signaling pathways in different populations [90]. The genes located in these pathways are involved in skeletal morphogenesis [91]. FRZB is a glycoprotein that antagonizes Wnt signaling through the frizzled membrane-bound receptors and plays a role in chondrocyte maturation and bone development [92]. The R324G variant (rs288326) of the FRZB gene showed reduced ability to antagonize Wnt in vitro. This functional SNP and a haplotype of R200W and R324G SNPs were associated with an increased risk of hip OA in females [93]. The R324G SNP was also found to be associated with generalized OA in the Rotterdam and the Genetics, Osteoarthritis and Progression (GARP) studies [94]. The FRZB rs7775 and rs288326 SNPs have also been implicated in the risk of hip and knee OA [60,95].

The GDF-5 gene is a member of the TGF- β superfamily of signaling pathways and is involved in skeletal and joint development, maintenance and repair [96]. The T allele of functional SNP (+104T/C; rs143383) in the 5'-UTR of the GDF5 gene was found to be associated with hip and knee OA in both Asian and European populations [97,98]. The susceptibility +104T allele showed lower in vitro transcriptional activity and this was confirmed in vivo in articular cartilage of patients with severe OA [98,99]. The C allele of the rs143383 SNP had a 37% lower risk for hand OA and a 28% lower risk for knee OA in female homozygotes. A meta-analysis of data from Europe and Asia (more than 11 000 individuals) confirmed the association between rs143383 SNP and knee OA [100]. In recent studies, the TT genotype of the rs143383 SNP was found to be associated with an increased risk of knee OA in a Thai population [101] and the T allele of the same SNP was associated with a 17% increased risk of knee OA in Caucasians [102].

Recently recognized susceptibility gene iodothyronine-deiodinase enzyme type 2 (DIO2, 14q24) is a member of thyroid signaling pathway. It encodes an enzyme determining bioavailability of local active thyroid (T3) which stimulates chondrocyte differentia-

tion and initiates formation of bone in the growth plate. DIO2 haplotype containing the minor allele of the rs225014 SNP and common allele of rs12885300 was associated with advanced hip OA in female cases [103].

The DVWA gene (3p24.3) is another novel gene involved in cartilage production through its interaction with beta-tubulin. The rs7639618, rs11718863 and rs9864422 SNPs of the DVWA gene showed consistent associations with knee OA in Japanese and Chinese cohorts [74]. The strongest association was for rs7639618 and the meta-analyses of data from European, Chinese and Japanese studies provided a global association of this SNP with knee OA [104].

Synovial inflammation has been shown to trigger cartilage destruction and development of OA. Pro-inflammatory cytokines such as IL-1 and TNF α are known to be involved in the pathogenesis of OA as they induce articular cells to produce other cytokines such as IL-6, IL-8 and mediate up-regulation of matrix proteases [105]. The rs1143633 (5810 G>A) and rs1143627 (-31 T>C) SNPs in the IL1 β gene were found to be associated with hand and knee OA, respectively [106,107]. The IL-1RN*2 allele of the VNTR polymorphism in the IL-1 receptor antagonist gene (IL-1RN) was found to be associated with hip and knee OA [64,108]. In addition, the C-CTG-1TT of the IL1A-IL1B-IL1RN complex and the CCA-1TT haplotype of IL1B-IL1RN conferred a four-fold increased and decreased risk of knee OA, respectively [109]. The AA/GA genotypes of the IL-1RN rs9005 SNP was associated with lower odds of radiographic severity, greater joint space width and lower synovial fluid cytokine levels [110]. In another study investigating the association between IL-1 gene polymorphisms and bilateral distal interphalangeal (DIP) joint OA in dentists and teachers, two IL1 β SNPs (rs1143634 and rs1143633) and extended haplotypes of IL1 β -IL1RN (211-1 and 121-1) were found to be associated with DIP OA. In addition, there was an interaction between the rs1143634 and the IL1R1-IL1RL2 and IL1B-IL1RN extended haplotypes and occupation [111]. Recently, association of IL-1R1 SNPs with severe hand OA was investigated in Finnish subjects. The SNP rs2287047 located in intron 1 of the IL1R1 gene was found to be protective for severe hand OA [112]. In addition, the GA genotype of the IL1B rs16944 SNP was found to be protective for hip OA in a Croatian population [113].

6. Limitations and gaps in occupational osteoarthritis research

The lack of recent data on the incidence and prevalence of OA made it difficult to comprehensively describe the current burden of this health problem and place it in proper perspective. In addition, the majority of published studies were cross-sectional or case-control in design which prevented causal inferences from being made and some of the studies were limited by very small sample sizes. Considerably more research is needed on the epidemiology of occupational osteoarthritis for all anatomical locations, but especially those locations (i.e., everything except knee) on which little research has been conducted to date. Many epidemiological studies collect minimal information on occupational exposures. In cases where such information is available, it is usually subjective in nature. To facilitate such research, several actions could be implemented. Development of large observational studies which focus on occupational exposures and outcomes could be initiated by federal government agencies or private companies with adequate resources. Understandably, this may be difficult in many situations. A more feasible approach pertains to data systems for which the infrastructure already exists. Surveillance systems and medical databases could begin collecting such occupational data and/or expand the collection of such information. These recommendations also apply to the collection of genetic data.

Although genetic research in OA has progressed significantly over recent years, a consistent relationship has not been reported for some of the genes across different studies and specific genes have not been associated with OA phenotypes to date. This might be explained by the differences in study populations examined, skeletal-site, gender, disease characterization, sample size, assessment of intermediate phenotypes, statistical inconsistencies and other potentially modifiable risk factors such as physical activity and nutritional factors. In addition, there are only a limited number of studies that investigated joint effects of occupational and genetic risk factors in the development of OA. More research using new technological developments is needed to fully understand a complex disease like OA. Advances in genetics, genomics and epigenetics and the use of integrative approaches will provide the tools to dissect the complex etiology of this disease and help translate these findings to the clinical setting. It is hoped that future genetic association studies with large, well characterized populations will in-

crease understanding of the pathogenesis of this common disease and help identify novel targets for the development of new therapeutic approaches.

7. Conclusions

In summary, more research is needed to identify additional occupational factors that are associated with or contribute to increased risk of OA for all anatomical regions. While we were able to locate a relatively larger number of epidemiologic studies that investigated factors associated with knee OA, very few studies were found for OA of the hip, spine and neck, hand and shoulder, or foot. Biomechanical stressors such as heavy physical work load, long hours of kneeling, squatting, or standing, vibration, and repetitive movements were found to be factors that contribute to higher risk of several types of OA. Persons employed in occupations where these stressors are most prevalent were more likely to be affected with OA. Examples of these occupations are construction and other manual labor jobs, farming, mining, firefighting, food processing, building services or hotel room cleaning, dentistry, and professional dancing. Genetic research has progressed rapidly over recent years and a number of susceptibility markers have been reported. However, no definitive genes associated with all OA phenotypes were identified to date and no clinical translation has been made for risk prediction. In addition, the joint effect of occupational and genetic risk factors in the development of OA has not been extensively explored. Therefore, more research is warranted on both epidemiological and genetic aspects of OA. In addition, the use of large, prospective cohort and evaluation studies will be needed to allow causal inferences to be made. After adequate testing, interventions should be targeted at workers who are most likely to be exposed to factors which have been shown to contribute to increased OA risk.

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