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Research Paper

Chondrosarcoma transformation in hereditary multiple exostoses: A systematic review and clinical and cost-effectiveness of a proposed screening model

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ABSTRACT

Background: The most serious complication of hereditary multiple exostoses(HME) is chondrosarcoma transformation. Numerous authors have suggested that screening might allow early chondrosarcoma detection. However, literature-quoted incidences of malignant transformation are highly variable.

Methods: A systematic review of malignant transformation by sex, exostosin-1 mutation(EXT1), age and site was conducted searching Medline, Embase and CINHAL. Three HME screening strategies were then developed and compared using cost per life-year gained and incremental cost-effectiveness ratio (ICER).

Results: Systematic review: 18 papers with 852 chondrosarcomas were identified. The incidence of chondrosarcoma transformation averaged 4%, 75.2% occurring between ages 20-40 and 56.2% at the pelvis and proximal femur. Screening model: In the general HME population, plain radiographs provided cost per life-year gain of £19,013 compared to £53,392 in MRIs. ICER in MRIs compared to X-rays was £80,218. However, for every generation of HME patients screened over 20 years, X-ray radiation induced 0.65 cancers. Psychological effects of false-positives were marginal. Screening only higher-risk groups (males or EXT1) reduced cost but benefited fewer patients.

Conclusions: Our results suggest that annual MRI screening for all HME patients between age 20-40 may be of value. However, the extent of anatomical imaging is subject to debate; it is possible that focused imaging protocols which scan from cervical spine to proximal femur may improve cost-effectiveness.

1. Introduction

Hereditary multiple exostoses (HME) is one of the commonest inherited musculoskeletal conditions with an incidence of 1 in 50,000 [1]. In this condition, multiple cartilage-capped exostoses develop during childhood and ossify when skeletal growth is complete [1,2]. These occur primarily at long bone metaphyses. Loss of heterozygosity in exostosin-1(EXT1) and exostosin-2(EXT2) genes have been implicated to cause HME [2,3]. Males are more commonly and severely affected due to incomplete EXT1 penetrance in females [4]. The most serious complication of HME is chondrosarcoma transformation [5–7]. Numerous authors have proposed a screening programme using X-ray or magnetic resonance imaging (MRI) to identify chondrosarcoma transformation in HME early [7–9]. There are several reasons for this. Firstly, even though most chondrosarcomas transformations are low-grade, their size and location close to major neurovascular bundles at diagnosis makes wide excision difficult. This is especially so with pelvic tumours [5,10]. Early diagnosis reduces the need for debilitating surgery. Secondly, assuming the lowest reported lifetime risk of chondrosarcoma at 2%, most of which occurs in the 2nd-4th decade of life, the annual risk in this age group would be 0.1% [9]. The figure increases in EXT1 male patients and becomes comparable to the occurrence of breast cancer at 0.2% per annum, for which there are currently widespread screening programs [11]. The risk of malignant transformation increases in males and having an EXT1 mutation [1,5,12]. However, the literature-quoted incidences of malignant transformation by sex, genotype and anatomical distribution, which are needed to guide a screening model, are highly variable [1,12,13]. A screening model to detect chondrosarcoma transformation in HME has never been developed before. This study hence aims to: 1) systematically review the literature for incidence of chondrosarcoma transformation by age, sex, genotype and anatomical distribution. 2) Propose a preliminary screening model for HME patients based on literature findings. 3) Evaluate the clinical- and cost-effectiveness of this

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screening model. 4) Compare the cost-effectiveness of MRI and X-rays as screening modalities we hypothesise that a MRI screening program for all HME patients is feasible if targeted at select anatomical sites. Our study, while not intended to give definitive guidance over whether HME screening should be established, will provide important parameters for more detailed analyses to be performed. In addition, this analysis may contribute to the debate about whether screening programs should be established in similar familial neoplastic traits such as Familial Retinoblastoma (Rb) [14].

2. Material and methods

2.1. Search strategy

The following databases were searched in Feb 2018: MEDLINE via PubMed (1948-February2018), EMBASE via PubMed (1980-February 2018), CINHAL via Ebsco host (1926-February 2018). MeSh and keyword headings used were: multiple hereditary exostos* or multiple cartilaginous exostos* or diaphyseal aclasis* or multiple osteochondroma*; chondrosarcoma* or bone tumour*; adult* or child*or infant*; male*or female* or gender*; exostosin-1*or exostosin-2*(Appendix A.1). Hand-searches were performed on reference lists of retrieved reports, abstracts at the last 6 years of key conferences (*European Sarcoma Conference* and *MHE International Research Conference*), and key journals (*Journal of Bone and Joint surgery American volume,* its *British volume* and *Cancer)*. A further two journals, *Spine* and *Journal of Neurosurgery,* were hand-searched because reviewers recognised that orthopaedic journals were less likely to report spinal exostoses. In addition, a citation search was performed using Web of Science.

We contacted authoritative researchers in the field to locate unpublished data. Attempts were also made to contact authors of potentially eligible studies presented in the 1980s but this was unsuccessful.

2.2. Selection criteria

One reviewer screened the titles and abstracts of all identified reports. Potentially relevant studies were than retrieved and selection criteria applied: 1) the study was a longitudinal study of HME within a general population; 2) demographics of chondrosarcoma transformation were reported.

As there was an expectation that few reports would meet these criteria, an expanded criteria was planned to include disease-specific case-control studies, cross-sectional studies and case series. Selection criteria for case-control and cross-sectional studies were that results reported on demographics of chondrosarcoma transformation. The selection criteria for case series was 1) > 30 cases of HME reported per case series 2) demographics of chondrosarcoma transformation were reported.

2.3. Data extraction and data analysis

One reviewer extracted data onto standardised data extraction forms. Any uncertainty was discussed with a second reviewer and disagreements resolved by consensus. The reviewers were not blinded to the author names, institutions or results of the study. Due to significant heterogeneity in methods of reporting, no attempt was made to pool and statistically analyse the data. Because of resource constraints, authors were not contacted where data was incomplete. This has been indicated in Appendix A.2.

Methodological quality of all studies was evaluated using relevant Newcastle-Ottawa Scale(NOS) for nonrandomised studies [15]. A detailed description of NOS is found elsewhere.

2.4. Screening model structure and measured outcomes

The base-population of HME patients used in this model was calculated using incidence estimates of 1 in 50,000 and an England & Wales population of 57.5million. HME patients were assumed to live average UK life expectancies of 80 years [16]. The effects of screening different subgroups of HME patients were compared using these outcomes: (a) cost per life-year gained (b) incremental cost-effectiveness ratio (ICER) for the more costly strategy (c) radiation-induced cancers in X-ray screening (d) psychological impact of false-positives. In line with UK National Institute of Health and Clinical Excellence (NICE) recommendations, a 3.5% annual discount rate was applied to all outcomes [17].

2.5. Values of key model parameters

Postulating from studies of primary pelvic chondrosarcomas where lesions < 10 cm at diagnosis gave an 18% improved survival rate over lesions > 10 cm, we assume that our model confers an 18% relative survival advantage in all HME subgroups by detecting lesions before they reach 10 cm [18].

On plain radiographs, progressive exosteal growth after growth plate fusion or a change in surface delineation predicts chondrosarcoma transformation [19]. MRI validation studies have shown that a cartilage cap thickness > 2 cm predicts secondary chondrosarcomas with a sensitivity of 98% [20]. Model costs for the basic screen, diagnostic workup and surgeon examinations were obtained from NHS Reference Costs 2013/14 [21]. Personal time cost for the screening visit was estimated from the Annual Survey of Hours and Earnings 2014 [22]. All costs were measured in U.K pounds sterling (Appendix A.3).

2.6. Evaluating cost-effectiveness

NICE has identified a willingness-to-pay threshold value of £30,000 per life-year gained [17]. We also compared our cost-effectiveness analysis to the cost per life-year gained in the UK NHS breast cancer screening programme (NHSBSP) of £7357 [23].

3. Results

3.1. Characteristics of selected studies

The literature search identified only 1 relevant longitudinal general population study that satisfied our initial criteria [12]. Because of the paucity of data, the criteria was broadened and 9 disease-specific retrospective case controls (including 1 unpublished study) [4–7,19,24–26], 5 disease-specific cross-sectional studies [1,13,27–29] and 3 case series met this inclusion criteria [30–32]. A total of 18 studies with 2509 HME patients were included in this systematic review. There were 3 studies where no chondrosarcoma was identified [12,25,32]. Appendix A.2 shows all studies that met inclusion criteria. Using NOS, the studies varied widely in methodological quality, with no study gaining the maximum of 5 stars, 3(17%) gaining 4 stars [30,31], 6(33%) gaining 3 stars [5,7,19,24,26,32] and 9(50%) gaining only 2 stars [1,4,6,12,13,25,27–29]. The highest scoring studies were unexpectedly case series reports [30,31]. Full scoring is shown in Appendix A.4.

3.2. Results of literature review

Studies on the incidence of chondrosarcoma transformation produced widely disparate estimates ranging from 0.88% to 25.1% (Appendix B.1). The contributing outliers were both studies from the Mayo clinic [13,27]. Excluding these outliers, the incidence of chondrosarcomas in the remaining 15 studies averaged 3.9%. On average, 80.1% of chondrosarcoma transformation occurred before age 40, with 75.2% taking place between ages20-40. This is in contrast to primary chondrosarcomas, where 65% of cancers occur between ages30-60 [18] (Fig. 1A).

A total of 852 chondrosarcomas developed in the 18 studies. There was a striking propensity for flat bones to undergo chondrosarcoma transformation, with the pelvis accounting for 47.9% of cancers the proximal femur 8.3% and the scapula 12.3%. 87.2% of chondrosarcomas were concentrated in the appendicular skeleton. The ribs and spine accounted for 12.8% of chondrosarcomas. (Fig. 1B).

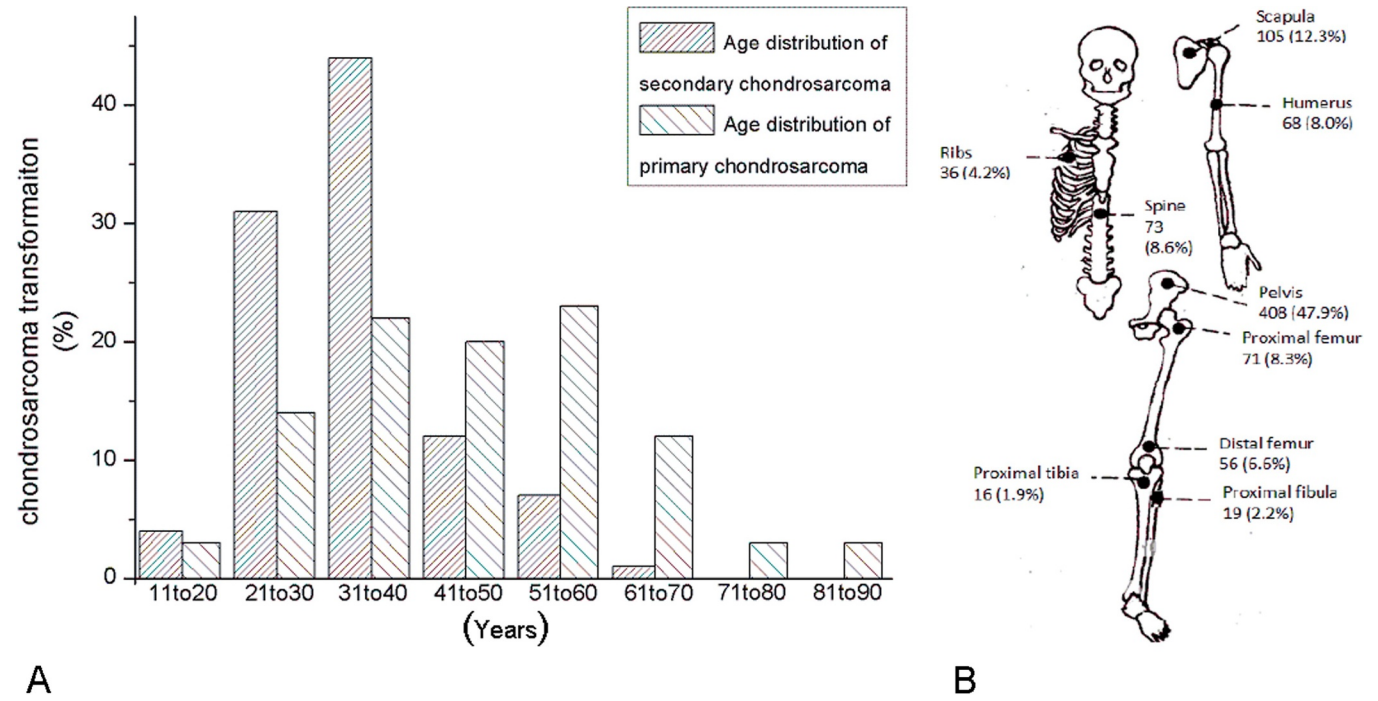

Fig. 1. A. Age distribution of chondrosarcoma transformation secondary to HME. This has been compared to the age distribution of primary chondrosarcomas. B. Anatomic distribution of the 852 chondrosarcomas. This is expressed as absolute numbers of exostoses, with percentage in brackets.

On average, 6.3% of males and 4.6% of females developed chondrosarcomas. When the 2 studies from the Mayo Clinic were excluded, percentages of males and females developing chondrosarcoma became 4.0% and 2.7% respectively. Several studies have suggested that the EXT1 cohort would be at 1.5–2 times greater risk of malignant change than in the unstratified HME cohort, we have adopted the lower figure of 1.5 times in our model for EXT1 individuals and 2.25 times for male EXT1 individuals.

In the Mayo Clinic studies, the survival rate for secondary chondrosarcomas at 20 years was 75% [13,27]. There was no specific literature on survival rates for chondrosarcomas in HME subgroups. We hence assumed the survival rates for secondary chondrosarcomas in EXT1 patients and EXT1 male patients to reflect that of the general HME population respectively.

3.3. Structure of the HME screening model

This simulates the experiences of a hypothetical cohort of 1150 HME patients attending screening between ages 20–40. Fig. 2 shows the screening model that was developed. Three annual screening strategies targeting different groups of HME patients were evaluated: (a) all HME patients, (b) HME patients with EXT1 genotype, and (c) HME male patients only with EXT1 genotype [1,4–7,12,13,19,24–32]. Screening was done with either plain radiographs or MRI. Our model assumed that only the pelvis and proximal femur would be imaged, (detecting he majority of chondrosarcomas). Lesions representing false-positives were not initially analysed in the base-model.

3.4. Model results

Our screening model indicated that it would take 3.9 years of screening to identify a single case of malignant change if all HME patients were screened (Table 1). The number of years of screening needed to detect a chondrosarcoma increased as the base population screened became smaller.

The chondrosarcoma mortality rates in the general HME cohort would become 20.5% with screening (compared to 25% without screening) and 46.1% in the EXT1 male patient cohort with screening (compared to 56.3% without screening). The cumulative radiation dose from 20 years of X-rays is 12mSv [33]. For every 100 chondrosarcomas picked up among the general HME population via plain radiography, a further 12 cancers would be induced by its radiation effects. The relative number of cancers induced by radiation decreased in the EXT1 subgroup and further decreased in the EXT1 male subgroup (Table 1).

3.5. Cost-effectiveness analysis

The number of life-years gained increased as the screening strategy targeted a more select group of patients, from 5.2 life-years in X-ray screening of all HME patients to 13.8 life-years in X-ray screening of the EXT1 male population and from 11.8 life-years in MRI screening of all HME patients to 17.3 life-years in the EXT1 male population. The cost per life-year reduced significantly as a more select group of patients was targeted, from £53,392 in MRI screening of all HME patients to £10,494 in MRI screening of the EXT1 male population.

Plain radiographs screening resulted in a low cost / life-year gained, ranging from £19,013 for all HME patients to £2084 for EXT1 males. When X-ray and MRI screening modalities were compared, MRI produced an ICER of £80,218 per life-year when applied to all HME patients (Table 2).

3.6. Psychological impact of false-positives

Our model predicts 0.11 false-positives in the general HME population which translated into a marginal extra cost of £25 per life-year gained. The impact of false-positives on cost effectiveness decreased as the base-population became smaller (Appendix B.2).

4. Discussion

Our systematic review showed that there was a scarcity of good quality studies on chondrosarcoma transformation in HME. In the studies that were identified, the incidence of chondrosarcoma transformation in the general HME population averaged 4%, with 75.2% occurring between ages 20–40 and 56.2% were located in the pelvis and proximal femur.

Based on the systematic review, a model was developed for screening to be done with either X-ray or MRI between ages 20–40 and

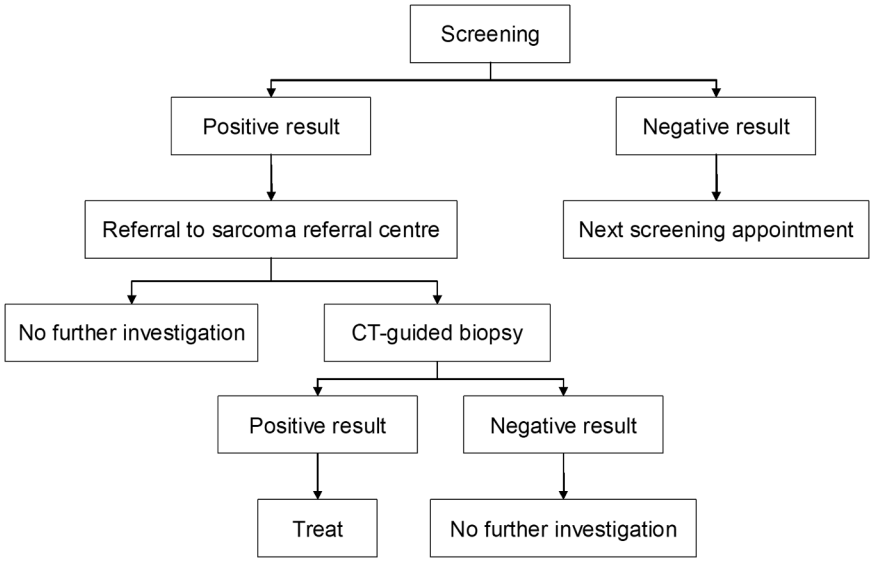

Fig. 2. Structure of the HME screening model. Reflecting current best-practice guidelines in the management of bone sarcomas, a positive screen result will require a diagnostic work-up comprising a clinical examination and a CT-guided biopsy [14].

Table 1
Screening results and cancers induced by radiation in an X-ray screening programme.

Scan strategy (age 20–40 years)	All HME patients[c]	EXT1 patients	EXT1 male patients
Population in this cohort (n)	288	144	83
Lifetime risk of CS (%)	4	6	9
Years needed to pick up 1 CS of pelvis/proximal femur (n)	3.86	5.09	5.90
CS mortality rate (%)[a]	20.5(25)[b]	30.8(37.5)[b]	46.1 (56.3)[b]
Radiation induced cancers (n) [33]	0.645	0.324	0.145
CS detected by screening program (n)	5.18	3.93	3.39
Ratio of cancer picked up: cancer induced	100:12	100:8	100:4

[a] screening confers an 18% survival advantage at all-time points and in all age-groups.
[b] (CS mortality rates without screening are bracketed)
[c] Given a hypothetical cohort of 1150 HME patients it is calculated that 25% (288 patients) will be between the ages 20–40 years.
Radiation induced cancers were calculated from a US report to assess health risks from radiation [33]
Abbreviations: CS, chondrosarcoma

concentrating on the pelvis and proximal femur. Our model suggests that screening the general HME population benefits the largest population of patients. However, when the NICE willingness-to-pay threshold of £30,000 per life-year gained was applied, a MRI screening strategy became cost-ineffective in the complete HME cohort. However x-ray screening was more cost-effective at £19,013 per life-year gained. When compared to the UK breast cancer screening program which yielded 1 life-year at £7357, screening became cost-effective only when using X-ray on patients with higher-risk profiles (EXT1 or EXT1 male patients) [22].

Nevertheless, we believe that MRI-screening becomes favourable if reasonable assumptions on increased effectiveness of MRI-screening are added to the model. We calculated that in the general HME cohort, MRI screening must produce an absolute improvement in chondrosarcoma mortality rates of 16.9% in order for cost per life-year gained to be < £7,357. Our base-model was developed with the concept that screening would enable a lesion to be picked up before it reached 10 cm in size [18]. This is a very conservative estimate as annual screening could allow growing lesions to be picked up at 1–2 cm, making a 16.9% improvement in chondrosarcoma mortality rate attainable.

Our model detects cancers close to the peak of the individual's economical productivity. Detecting a cancer early also reduces treatments and treatment-associated morbidity. However, quality-adjusted-life-years (QALY) gained are difficult to estimate accurately without a pilot study.

Table 2
Results of the different screening strategies.

Scan strategy	CS detected (n)	CS deaths (n)	Radiation induced cancer deaths[a]	Discounted (£)[b]			
				Life-years gained	Cost of program (£)	Cost/life year gained (£)	ICER[c] (£)
All HME pts							
Annual X-ray	5.18	1.06	0.132	5.15	97,916	19,013	–
Annual MRI	5.18	1.06	–	11.75	627,358	53,392	80,218
EXT1 pts							
Annual X-ray	3.93	1.21	0.099	8.24	49,384	5993	–
Annual MRI	3.93	1.21		13.19	313,969	23,803	53,451
EXT1 male pts							
Annual X-ray	3.40	1.57	0.066	13.83	28,829	2084	–
Annual MRI	3.40	1.57	–	17.28	181,351	10,494	44,209

[a] Assume that all radiation induced cancers were chondrosarcomas of the pelvis/proximal femur
[b] Discounted at the rate of 3.5% per annum
[c] ICER is derived by dividing the incremental cost of the more costly screening modality by the difference in life-years gained.
Abbreviations: CS, chondrosarcoma

MRI scans might hence be more cost-effective than this report implies.

We acknowledge that MRIs are more expensive than X-rays. However, the model highlighted an important trade-off in an X-ray screening program: for every generation of HME patients (n = 288) screened 20 times over a 20 year period, the associated exposure to X-rays induced 0.65 cancers. This compares to the breast cancer program, where in the same number of patients screened 6 times over 20 years, only 0.02 fatal breast cancers were induced [23]. One reason for this difference is that our model only picks up 5.2 cancers in the general HME population, making the relative number of radiation-induced cancers significant.

We also acknowledge that our base-screening model will fail to detect the appendicular chondrosarcomas and also ribs and spine chondrosarcomas. However, appendicular chondrosarcomas should be more easily palpable on clinical examination [1,7]. In order to detect rib and spine chondrosarcomas, a new 3-part coronal MRI protocol from the cervical spine to proximal femur could be developed. Because we are scanning for surveillance rather than diagnostic purposes, reducing the number of sequences and a widened field of view in the new protocol would reduce costs without sacrificing diagnostic sensitivity. The new MRI costing might hence not vary much from our existing model's costing [34].

There is an attractive alternative in the form of whole-body MRI techniques as these theoretically pick up 100% of chondrosarcomas [35]. However, conventional MRI systems are limited in performing whole-body scans and require patient repositioning [36]. The use of dedicated whole-body MRI scanners defeats the purposes of a screening programme where patients should be screened locally [35].

Another reason for proposing MRI over X-rays is that the orthopaedic literature might be under-reporting the incidence of spine exostoses because these come under the care of neurosurgeons [37–39]. Our handsearch of neurosurgical journals showed that on average, 60% of their HME cohorts had coincidental intra-spinal exostoses on MRI [37–39]. This is much higher than previously thought and indicates that the spine could be an important site for chondrosarcoma development [37–39]. We calculated that a 9.2% increase in spine chondrosarcomas would be sufficient to cause the cost per life-year gained with our current X-ray model in the general HME cohort go beyond the £30,000 NICE threshold.

Our model might has shown that screening EXT1 males only was the most cost effective at £10,494 per life-year gained and that it would cost 3–4 times more to gain one life-year in an EXT1 female. However, this evokes ethical issues: the prognosis for early chondrosarcomas is equally good in both genders, giving no reason beyond of financial costs to discriminate against screening females [10,18,40].

Our analysis has some limitations that must be acknowledged. Firstly, our systematic review revealed that there were only a limited number of small studies available. We acknowledge that this has made our model highly sensitive to parameters like incidence of malignant change and chondrosarcoma sites. We were unable to quantify biasness in each study and adjust for this in a statistical analysis because of the heterogeneity of data collected. However, Grimer's study had a large patient number (n = 719) which reduced our model's sensitivity to chondrosarcoma sites from smaller studies [41]. Secondly, all probabilities used to populate the model are estimates derived from the literature. Such estimates carry inherent uncertainty, as does using a hypothetical cohort. Thirdly, a low risk (0.03%) of gynaecological malignancies has been reported after exposure to high levels of pelvic radiation [42–44]. Our model may not have accurately identified incidence and survival rates from gynaecological malignancies which are themselves based on extrapolations from higher doses of irradiation. Last but not least, our model did not consider how a false-positive diagnosis might affect compliance in further screening rounds. We have shown however, that life-years lost due to anxiety are very marginal and believe the same to be true in terms of compliance rates. It is clear that more studies are needed to delineate the epidemiology of chondrosarcoma transformation in HME. A pilot study of an MRI scan of the pelvis and proximal femur could be commenced on a small number of HME patients. This identifies the minimum number of sequences and vision of field needed to detect chondrosarcomas. Radiology input is needed to develop the MRI protocol which scans from cervical spine to proximal femur and this also piloted.

5. Conclusion

While this model-based preliminary analysis is not intended to produce definitive conclusiveness, it does show that there is a case for annual screening of malignant transformation in HME patients. It also calculates the marginal gains and losses from screening different populations. Based on this report, we recommend that the screening programme should be an annual MRI scan encompassing all HME patients between ages 20–40. However, this report produced no definite conclusion on anatomical site to target. A specifically designed protocol which enables doctors to target more anatomical sites (from cervical spine to proximal femur) could prove more cost-effective.

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Conflict of interest

No competing interests were declared.

Authors' contributions

Clara Ngoh and Daniel Porter were involved in the conception and design of this study. Li Fei and Clara Ngoh were involved in the analysis. All authors contributed to the analysis and interpretation of the data, drafted and critically reviewed the manuscript and approved the final version.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.09.011.

Appendix A.1

MEDLINE VIA PUBMED (1948 – February 2015) / EMBASE VIA PUBMED (1980 –February 2015): 1. exp exostoses, multiple hereditary/2. HME.tw; 3. multiple cartilaginous exostos$.tw; 4. diaphyseal aclasis.tw; 5. osteochondroma$.tw; 6. 1 or 2 or 3 or 4 or 5; 7. exp chondrosarcoma/; 8. exp mesenchymal chondrosarcoma/; 9. exp bone neoplasm/; 10. 7 or 8 or 9; 11. Aged/; 12. Age distribution/; 13. Adult/; 14. Child/; 15. Child, preschool/; 16. Infant/; 17. 11 or 12 or 13 or 14 or 15 or 16; 18. Male/; 19. Female/; 20. Sex/; 21. 18 or 19 or 20; 22. Exostosin-1.tw; 23. EXT-1.tw; 24. Exostosin-2.tw; 25. EXT-2.tw; 26. 22 or 23 of 24 or 25; 27. 6 and 10; 28. 17 and 21 and 26 and 27

CINAHL VIA EBSCO HOST (1937 – February 2015): 1. multiple hereditary exostos*; 2. chondrosarcoma; 3. age OR adult OR child OR infant; 4. gender OR sex; 5. "exostosin-1" OR "exostosin-2"; 6. and/1–5.

Appendix A.2

Description of all studies that met the inclusion criteria.

Study	Type of study	No. of patients	Distribution of EXT1 (%)	Time period	Average follow-up (months)	Incidence of chondrosarcoma Transformati on[a]	Males (%)	Anatomic location of chondrosarcoma transformation (%)							Age of diagnosis[b]
								Humerus	*Scapula*	*Ribs and spine*	*Ilium and pubis*	*Prox femur*	*Dist femur*	*Tibia and fibula*	
Black et al. [12]	*Longitudinal general population*	35	–	1968–1988	240	0 (0%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Altay et al. [5]	*Case control*	92	–	1986–2004	93.6	10(9.2%)	20.0	8.3	16.7	8.3	25.0	16.7	16.7	8.3	35.9
Wuisman et al. [6]	*Case control*	288	–	1972–1994	83.8	17(5.9%)	76.5	6.8	17.2	13.8	37.9	17.2	3.4	3.4	34.0 (19–74)
Clement et al. [7]	*Case control*	172	61.7	1996–2000	96	7(4.1%)	85.7	14.1	28.1	28.1	14.3	14.3	0	0	–
Legeai-Mallet et al. [4]	*Case control*	175	41.0	1955–1995	102	1(0.6%)	100	0	0	0	100	0	0	0	35.0
Exner and Suter [24]	*Case control*	45	–	1971–2001	240	3(6.7%)	66.7	0	33.3	0	66.7	0	0	0	25.0 (20–30)
Pierz et al. [25]	*Case control*	*43*	36.5	1991–2001	101	0(0%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vanhoenacker et al. [19]	*Case control*	31	100	1968–1998	211	1(3.2%)	100	0	0	0	100	0	0	0	25.0
Suzaki et al. [26]	*Case control*	14	57.1	1963–1984	89	1(7.1%)	100	0	0	0	100	0	0	0	30.0
Grimer et al.[c] [41]	*Case control*	719	–	ongoing	ongoing	NA	56.0	8.0	16.0	8.0	48.0	8.0	8.0	4.0	37.4 (22–67)
Schmale et al. [1]	Cross-sectional	113	43	1994	NA	1(0.88%)	100	0	0	0	100	0	0	0	41.0
Ahmed et al. [13]	Cross-sectional	184	44	2001	NA	46(25.1%)	45.7	2.2	10.8	13.0	50.0	6.5	2.2	6.5	34.9 (15–77)
Garrison et al. [27].	Cross-sectional	183	–	1981	NA	35(19.1%)	65.7	8.6	11.4	14.3	45.7	5.7	0	5.7	30.7 (15–68)
Voutsinas and Wynne-Davies [28]	Cross-sectional	180	–	1995	NA	5(2.8%)	80.0	20.0	0	0	60.0	0	20.0	0	32.0 (30–40)
Wicklund et al. [29]	Cross-sectional	116	–	1983	NA	1(0.87%)	100	0	0	100	0	0	0	0	25.0
Gordon et al. [30]	Case repor	37	–	1981	92	1(2.7%)	100	100	0	0	0	0	0	0	23.0
Kivioja et al. [31]	Case repor	184	–	1999	145	4(8.3%)	50.0	50	0	0	50	0	0	0	37.7 (24–52)
Crandall et al. [32]	Case repor	180	–	1983	162	0(0%)	NA	NA	NA	NA	NA	NA	NA	NA	NA

- Data not available

[a] Result expressed as absolute number (percentage in brackets)

[b] Where it allows, the result is expressed as mean age (with range of ages in brackets)

NA: data not applicable because there were no chondrosarcomas in that study

[c] unpublished study from Mr Robert Grimer, Royal Orthopaedic Hospital in Birmingham. Data collection is still ongoing and some information unavailable.

Appendix A.3

Costs involved in basic HME screening and subsequent diagnostic workup.

Procedure	cost (£)
One part (pelvis) MRI	108.72
Plain film (pelvis)	16.71
CT guided biopsy	150
Clinical examination by surgeon	80
Administrative costs (notifying patient of results and recall)	3.50
Radiological visit (0.5 h): personal time 6.24*	6.24*

Estimated from median wage for a full-time 20–40 year old who worked 40 h a week [22].

Appendix A.4

Methodological quality of all studies included in this report as per NOS scale.

Methodological quality of longitudinal general population studies included in this systematic review

Study	Adequate definition of HME study group[b]	Follow up[c]	Blinding of researchers to outcome (i.e. chondrosarcoma transformation)	Method of chondrosarcoma diagnosis[d]
Bovee [8]	*	*		

Methodological quality of case-control studies included in this systematic review

Study	Representativeness of HME study group[a]	Adequate definition of HME study group[b]	Follow up [c]	Blinding of researchers to outcome (i.e. chondrosarcoma transformation)	Method of chondrosarcoma diagnosis[d]
Altay et al. [5]	*	*	*		
Wuisman et al. [6]	*		*		
Clement et al. [7]		*	*	*	
Legeai-Mallet et al. [4]	*	*			
Pierz et al. [25]	*	*			*
Suzaki et al. [26]	*	*		NA	NA
Health [21]		*	*		*
Garrison et al. [27]	*		**		
Grimer et al.[e] [41]	*	*	**		

Methodological quality of cross-sectional studies included in this systematic review

Study	Representativeness of HME study group[a]	Adequate definition of HME study group[b]	Blinding of researchers to outcome (i.e. chondrosarcoma transformation)	Method of chondrosarcoma diagnosis[d]
Grimer et al. [14]		*		*
Porter et al. [9]		*		*
Voutsinas et al. [28]		*		*
Wicklund et al. [29]	*	*		
Garrison et al. [27]	*	*		

Methodological quality of case series included in this systematic review

Study	Attempt to include > 5 generations of HME family[a]	Adequate definition of HME study group[b]	Follow up[c]	Method of chondrosarcoma diagnosis[d]
Kivioja et al. [31]	*	*	*	*
Crandall et al. [32]	*	*	*	*
Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation [33]	*	*	*	NA

[a] Studies received a * if HME patients were entered consecutively or at random into the study.

[b] Studies received a * if the HME study group was adequately defined with either > 1person extracting a single record at a time or if references were made to primary record sources like X-rays, MRIs or biopsies.

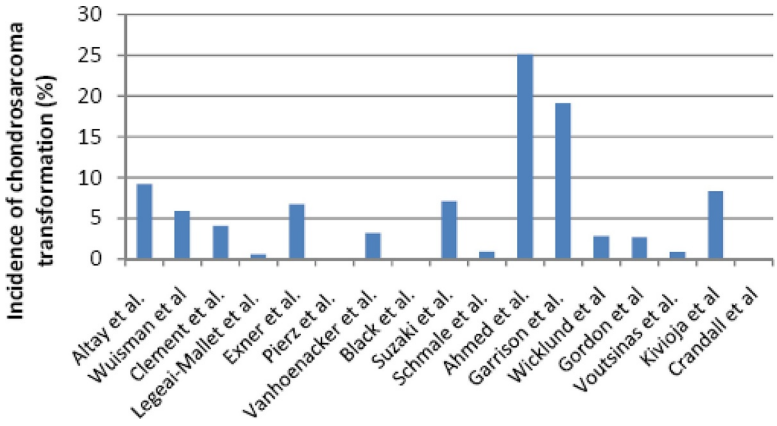
[c] Studies received a * if HME patients were followed up for at least 2 years and ** if patients were followed up for at least 5years.

[d] Studies received a * if the diagnosis of chondrosarcomas were confirmed using biopsy.

[e] Unpublished study from Mr Robert Grimer, Royal Orthopaedic Hospital in Birmingham. Data collection is still ongoing.

Columns were left blank if no * could be awarded

NA no chondrosarcomas developed in this study



Appendix B.1. Incidence of chondrosarcoma transformation by study author.

Appendix B.2

Impact of short-term anxiety on cost-effectiveness.

MRI scan strategy[a]	False-positive CS detected in a 20 year program	Anxiety per falsepositive result (life years)[b]	Revised cost/ life-year gained (£)
All HME	0.11	0.05	£ 53,417
Patients age 20–40 years		0.10	£ 53,442
EXT 1 patients	0.08	0.05	£ 23,810
		0.10	£ 23,820
EXT1 male patients	0.06	0.05	£ 10,497
		0.10	£ 10,500

[a] The false positive rate in MRIs was assumed to be 2% based on earlier mentioned MRI validation studies which showed that MRI scans had 98% sensitivity.

[b] The model had been re-run simulating the effect of different levels of anxiety on cost-effectiveness. This anxiety was defined in life-years lost (0.05 life-years and 0.10 life-years). The life-years lost from anxiety mimicked the anxiety levels in the breast cancer screening program.

Abbreviations: CS, chondrosarcoma

References

[1] G.A. Schmale, E.U. Conrad 3rd, W.H. Raskind, The natural history of hereditary multiple exostoses, J. Bone Joint Surg. 76 (7) (1994) 986–992.

[2] J. Ahn, H.J. Ludecke, S. Lindow, W.A. Horton, B. Lee, M.J. Wagner, B. Horsthemke, D.E. Wells, Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (EXT1), Nature Gen. 11 (2) (1995) 137–143.

[3] D. Stickens, G. Clines, D. Burbee, P. Ramos, S. Thomas, D. Hogue, J.T. Hecht, M. Lovett, G.A. Evans, The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes, Nature Gen. 14 (1) (1996) 25–32.

[4] L. Legeai-Mallet, A. Munnich, P. Maroteaux, M. Le Merrer, Incomplete penetrance and expressivity skewing in hereditary multiple exostoses, Clin. Genet. 52 (1) (1997) 12–16.

[5] M. Altay, K. Bayrakci, Y. Yildiz, S. Erekul, Y. Saglik, Secondary chondrosarcoma in cartilage bone tumors: report of 32 patients, J Orthop Sci 12 (5) (2007) 415–423.

[6] P.I. Wuisman, P.C. Jutte, T. Ozaki, Secondary chondrosarcoma in osteochondromas. Medullary extension in 15 of 45 cases, Acta orthopaedica Scandinavica 68 (4) (1997) 396–400.

[7] N.D. Clement, C.E. Ng, D.E. Porter, Shoulder exostoses in hereditary multiple exostoses: probability of surgery and malignant change, J. Shoulder Elbow Surg. 20 (2) (2011) 290–294 / American Shoulder and Elbow Surgeons ... [et al.

[8] J.V. Bovee, Multiple osteochondromas, Orphanet J. Rare Dis. 3 (2008) 3, https://doi.org/10.1186/1750-1172-3-3.

[9] D.E. Porter, L. Lonie, M. Fraser, C. Dobson-Stone, J.R. Porter, A.P. Monaco, A.H. Simpson, Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype study, J. Bone Joint Surg. 86 (7) (2004) 1041–1046.

[10] M.E. Pring, K.L. Weber, K.K. Unni, F.H. Sim, Chondrosarcoma of the pelvis. A review of sixty-four cases, J. Bone Joint Surg. 83-A (11) (2001) 1630–1642.

[11] L. Iselius, J. Slack, M. Littler, N.E. Morton, Genetic epidemiology of breast cancer in Britain, Ann. Hum. Genet. 55 (Pt 2) (1991) 151–159.

[12] B. Black, J. Dooley, A. Pyper, M. Reed, Multiple hereditary exostoses. An epidemiologic study of an isolated community in Manitoba, Clin. Orthop. Rel. Res. 287 (1993) 212–217.

[13] A.R. Ahmed, T.S. Tan, K.K. Unni, M.S. Collins, D.E. Wenger, F.H. Sim, Secondary chondrosarcoma in osteochondroma: report of 107 patients, Clin. Orthop. Rel. Res. (411) (2003) 193-206.

[14] R. Grimer, N. Athanasou, C. Gerrand, I. Judson, I. Lewis, B. Morland, D. Peake, B. Seddon, J. Whelan, UK guidelines for the management of bone sarcomas, Sarcoma 2010 (2010) 317462.

[15] G.A. Wells, B.J. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis, Appl. Eng. Agric. 18 (6) (2012) 727–734.

[16] Key population and vital statistics. 2001. Series VS no. 28, PP1 no. 24. The Stationary Office, London. ISBN 0 11 621649 2 (2003).

[17] M. Summerhayes, National Institute for Health and Clinical Excellence, Springer, Berlin Heidelberg, 2011.

[18] D.J. Pritchard, R.J. Lunke, W.F. Taylor, D.C. Dahlin, B.E. Medley, Chondrosarcoma: a clinicopathologic and statistical analysis, Cancer 45 (1) (1980) 149–157.

[19] F.M. Vanhoenacker, W. Van Hul, W. Wuyts, P.J. Willems, A.M. De Schepper, Hereditary multiple exostoses: from genetics to clinical syndrome and complications, Eur. J. Radiol. 40 (3) (2001) 208–217.

[20] S.A. Bernard, M.D. Murphey, D.J. Flemming, M.J. Kransdorf, Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging, Radiology 255 (3) (2010) 857–865.

[21] National schedule of reference costs: the main schedule. In: NHS Reference Costs 2013-2014. Department of Health and Social Care. London, (2015).

[22] Statistical bulletin: Annual Survey of Hours and Earnings (ASHE) 2014 Provisional Results. Office for National Statistics, London, (2014).

[23] Screening for Breast Cancer in England: Past and Future, Advisory Committee on Breast Cancer Screening, 2006 (NHSBSP Publication no 61) Department of Health Publications. ISBN 1 84463 026 9 (2006).

[24] V.H.A. Exner, GU Suter, A, Malignant transformation in hereditary multiple cartilaginous exostoses, Acta Orthop. Scand. Suppl. 62 (246) (1991) 62.

[25] K.A. Pierz, J.R. Stieber, K. Kusumi, J.P. Dormans, Hereditary multiple exostoses: one center's experience and review of etiology, Clin. Orthop. Relat. Res. 401 (2002) 49–59.

[26] A. Suzuki, S. Ito, H. Takechi, Follow-up study of cartilaginous bone tumors, Acta Medica Okayama 40 (3) (1986) 147–161.

[27] R.C. Garrison, K.K. Unni, R.A. McLeod, D.J. Pritchard, D.C. Dahlin,

Chondrosarcoma arising in osteochondroma, Cancer 49 (9) (1982) 1890–1897.
[28] S. Voutsinas, R. Wynne-Davies, The infrequency of malignant disease in diaphyseal aclasis and neurofibromatosis, J. Med. Gen. 20 (5) (1983) 345–349.
[29] C.L. Wicklund, R.M. Pauli, D. Johnston, J.T. Hecht, Natural history study of hereditary multiple exostoses, Am. J. Med. Gen. 55 (1) (1995) 43–46.
[30] S.L. Gordon, J.R. Buchanan, R.L. Ladda, Hereditary multiple exostoses: report of a kindred, J. Med. Gen. 18 (6) (1981) 428–430.
[31] A. Kivioja, H. Ervasti, J. Kinnunen, I. Kaitila, M. Wolf, T. Bohling, Chondrosarcoma in a family with multiple hereditary exostoses, J. Bone Joint Surg. 82 (2) (2000) 261–266.
[32] B.F. Crandall, L.L. Field, R.S. Sparkes, M.A. Spence, Hereditary multiple exostoses. Report of a family, Clin. Orthop. Relat. Res. 190 (1984) 217–219.
[33] Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII — Phase 2 Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, pg 156. National Research Council. The National Academies Press, Washington D.C. ISBN: 0-309-53040-7, 424 pages, 8 1/2 x 11, (2006).
[34] H. Kramer, Ch 4; Diagnostic Algorithms for Whole-Body Exams, in: M. Reiser, G.V. Kaick, C. Fink, S. Schoenberg (Eds.), Screening and Preventive Diagnosis with Radiological Imaging, Vol 13 Springer, Germany, 2008. 978-3-540-23553-8.
[35] G.P. Schmidt, M.F. Reiser, A. Baur-Melnyk, Whole-body imaging of bone marrow, Seminars Musculoskeletal Radiol. 13 (2) (2009) 120–133.
[36] O. Dietrich, S.O. Schoenberg, Ch 6; Diagnostic Algorithms for Whole-Body Exams, in: M. Reiser, G.V. Kaick, C. Fink, S. Schoenberg (Eds.), Screening and Preventive Diagnosis with Radiological Imaging, Vol 13 Springer, Germany, 2008978-3-540-23553-8.
[37] S. Albrecht, J.S. Crutchfield, G.K. SeGall, On spinal osteochondromas, J. Neurosurg. 77 (2) (1992) 247–252.
[38] R.S. Bess, M.R. Robbin, H.H. Bohlman, G.H. Thompson, Spinal exostoses: analysis of twelve cases and review of the literature, Spine 30 (7) (2005) 774–780.
[39] J.W. Roach, J.W. Klatt, N.D. Faulkner, Involvement of the spine in patients with multiple hereditary exostoses, J. Bone Joint Surg. 91 (8) (2009) 1942–1948.
[40] J. Bjornsson, R.A. McLeod, K.K. Unni, D.M. Ilstrup, D.J. Pritchard, Primary chondrosarcoma of long bones and limb girdles, Cancer 83 (10) (1998) 2105–2119.
[41] R. Grimer, Chondrosarcomas in HME Patients, Royal Orthopaedic Hospital, Birmingham, UK, 2011 Unpublished manuscript.
[42] B.E. Amendola, M.A. Amendola, K.D. McClatchey, C.H. Miller Jr., Radiation-associated sarcoma: a review of 23 patients with postradiation sarcoma over a 50-year period, Am. J. Clin. Oncol. 12 (5) (1989) 411–415.
[43] G. Gupta, A. Hafiz, J.S. Gandhi, Radiation-induced chondrosarcomas: a case report with review of literature, J. Cancer Res. Therapeutics 6 (3) (2010) 394–396.
[44] R.J. Mark, J. Poen, L.M. Tran, Y.S. Fu, J. Heaps, R.G. Parker, Postirradiation sarcoma of the gynecologic tract. A report of 13 cases and a discussion of the risk of radiation-induced gynecologic malignancies, Am. J. Clin. Oncol. 19 (1) (1996) 59–64.