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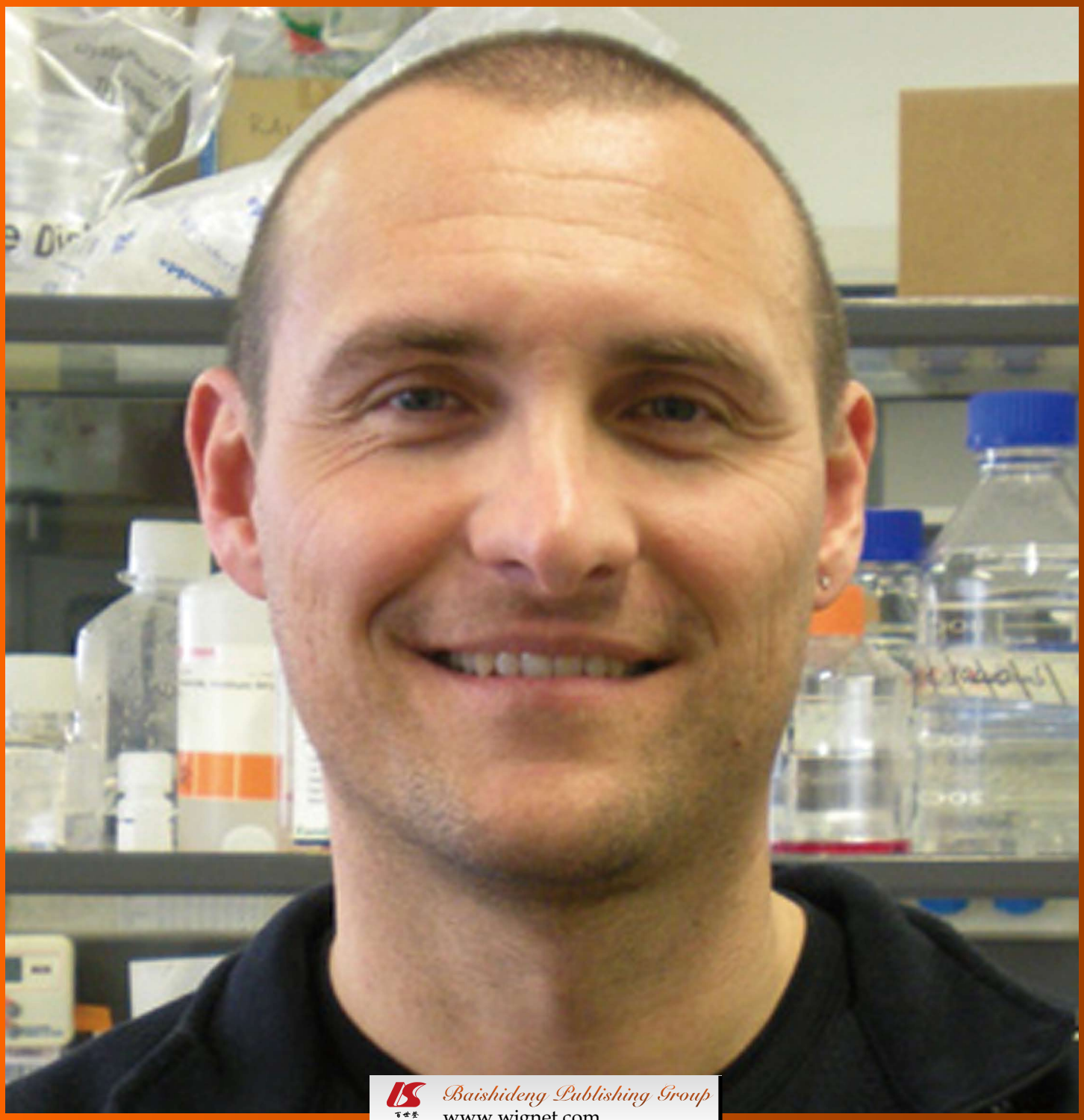

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TOPIC HIGHLIGHT

Ashim K Mitra, Professor, *Series Editor*

Retinoblastoma and treatment: A current evaluation of advanced therapy

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Abstract

Retinoblastoma is the most common primary childhood ocular tumor, affecting nearly 3.5 per million children worldwide. A mutation in the *RB1* gene, which presents as either germline or sporadic, along with additional mutational events, promote neoplastic growth in the retina. Fortunately, current treatment protocols result in success rates approaching 99% at specialized centers, with many children maintaining useful vision. Overall, treatment is guided by aggressiveness and size, and is classified by systems such as the Reese-Ellsworth System and the International Classification of Retinoblastoma. Due to advances in chemotherapy protocols combined with use of focal laser consolidation, treatment paradigms have shifted from enucleation to external beam radiation therapy to chemotherapy as globe-salvaging therapies. Smaller, less complex tumors may be controlled by plaque radiotherapy or focal laser ablative therapy. However, larger and more complex tumors, such as those that have vitreous or subretinal seeding, require methods of chemoreduction combined with focal consolidation to yield better outcomes. Standard chemotherapy protocols utilize vincristine, etoposide, and carboplatin with or without cyclophosphamide. Finally, there has been a recent push in local treatments for retinoblastoma to minimize systemic toxicities. These modalities include intravitreal or subconjunctival injections and more recently, direct chemotherapy administration into the ophthalmic artery. As a result, enucleation is used less often, but remains an important treatment for the most aggressive, refractory cases. The advancement of retinoblastoma treatment looks promising; however, worldwide access to these treatments and the lack of long-term follow-up of new local treatment modalities constitute current and future challenges.

Key words: Retinoblastoma; Treatment

Core tip: Retinoblastoma is the most common primary childhood ocular tumor, affecting nearly 3.5 per million children worldwide. Due to advances in chemotherapy protocols combined with use of focal laser consolidation, treatment paradigms have shifted from enucleation to external beam radiation therapy to chemotherapy as globe-salvaging therapies. The advancement of retinoblastoma treatment looks promising; however, worldwide access to these treatments and the lack of long-term follow-up of new local treatment modalities constitute current and future challenges.

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INTRODUCTION

With nearly 3.5 per million children affected worldwide[1],

retinoblastoma remains the most common primary childhood ocular cancer, accounting for nearly 3% of childhood tumors[2,3]. Heritable or familiar retinoblastoma occurs from a germline mutation in the *RB1* gene, and typically presents within the first year of life with bilateral disease, often with multifocal tumors. The more common sporadic (non-heritable) form typically presents later with unilateral disease with a single tumor focus. The *RB1* mutation, with additional proposed mutational events, promotes neoplastic growth in the retina, leading to clinical retinoblastoma tumors with risk of vision loss, extraocular extension, optic nerve invasion, metastasis, and death.

The worldwide incidence of retinoblastoma ranges between 7000-8000 cases a year. The worldwide mortality rate of 3000-3376 ranges among nations: from 3%-5% in North America and Europe to 20% in Latin America, 39% in Asia, and up to 70% in Africa. Fortunately, due to advances in treatment and early detection, the survival rate for retinoblastoma in the United States and other countries has approached 99% at specialized centers[3,4].

Treatment of retinoblastoma is complex and involves participation from various medical specialties including ocular oncology, pediatric oncology, pediatrics, interventional radiology, and ocular pathology. Factors affecting management include size and location of the tumor, metastatic risk, location, and laterality[5,6]. Due to advances in the past decade, systemic chemotherapy combined with focal laser treatment has gained popularity, particularly since it preserves the globe with hopes of maintaining some vision[5,6]. Treatment ranges from chemotherapy, to plaque radiation, to enucleation for the more severe and refractory cases. Recently, local treatments such as intra-arterial chemotherapy offer a novel alternative by demonstrating promise as a primary and salvage treatment, while minimizing systemic toxicities. The current review discusses the evolution of retinoblastoma treatment, highlighting recent advances with the aim of saving the life, eye, and vision of children with retinoblastoma.

Classification

Various classification guidelines have been created to classify the severity of retinoblastoma. The Reese-Ellsworth (R-E) classification (Table 1) was developed when the primary mode of treatment consisted of external beam radiotherapy (EBRT) and enucleation. This classification system is based on tumor size and location, with vitreous and subretinal seeding reserved for stage Vb tumors. The R-E classification system offered information regarding globe salvage with EBRT. More recently, in the era of chemoreduction with focal consolidation, a new system to predict response to this treatment was developed. In 2003, the International Classification of Retinoblastoma (ICRB) (Table 2) was introduced to stage retinoblastoma and accounted for the advances in chemotherapy. Previous methods such as the R-E classification system can be used to predict the success rates of chemoreduction, but does so in a non-incremental fashion[7]. Newer methods of classification, such as the "Practical Grouping system of RB" have also been effective tools. The Practical System also accounts for the distance of the seeds from the tumor, and the presence of glaucoma, hemorrhages, and optic nerve invasion[8]. Overall, the newer classification systems are based on clinical features involving the presence of subretinal fluid, subretinal seeds, and vitreous seeds, key factors that determine treatment success.

TREATMENTS

Children with unilateral, sporadic retinoblastoma have several management options, which include enucleation, plaque radiotherapy, laser therapy, systemic chemotherapy, and intra-arterial chemotherapy. If the tumor is small to medium size and there is little subretinal fluid, plaque radiotherapy can generally achieve tumor control. Small tumors may also be amenable to focal laser ablative therapy. Larger tumors or those with vitreous or subretinal seeding or subretinal fluid usually require methods of chemoreduction combined with focal consolidation utilizing laser ablation. The largest size retinoblastoma, with no potential for functional vision, often requires enucleation[5,9]. Most children with trilateral retinoblastoma, which is defined as bilateral retinoblastoma with pineal gland involvement, are treated with intravenous chemoreduction[10,11]. Novel therapies have been investigated for local delivery of chemotherapeutics, including focal, periocular injection of carboplatin, as well as superselective intra-arterial delivery of chemotherapeutics.

Radiation

EBRT previously served as primary globe-salvaging treatment, but is now rarely used due to risk of recurrence and to radiation-induced side effects. Such ocular side effects include cataract, radiation maculopathy, and radiation optic neuropathy, as well as effects on bony development leading to facial malformations. Additionally, EBRT toxicity may lead to secondary cancers in the radiation field involving the orbital soft tissue as well as osteosarcomas[11-13].

Radioactive plaques with various isotopes, but more commonly iodine-125 in the United States, are temporarily placed onto the scleral surface of the eye under ultrasound guidance, to deliver 40-45 Gy of radiation to the tumor apex[14]. They are most effective in small tumors < 15 mm in diameter or < 10 mm thickness. Other factors involve location of tumor in relation to optic nerve and fovea, plaque placement feasibility, and refractory nature of the tumor[14]. A study on 208 tumors undergoing plaque brachytherapy for RB showed that plaque therapy is most effective in tumors refractory to chemoreduction, laser, thermotherapy, and cryotherapy. These patients displayed tumor control of 83% at 1 year and 79% at 5 years. The study found the most common 5-year side effects were cataract, papillopathy, maculopathy, and glaucoma. Evidence suggests that prognostic factors for successful radiation treatment include tumors that lack subretinal or vitreous seeding[14,15]. Although radiation is a reliable

Table 1 Reese-Ellsworth classification

Group	Globe salvage likelihood	Features
I	Very favorable	< 4 disc diameters at or behind equator (1) solitary (2) multiple
II	Favorable	4-10 disc diameters, at or behind equator (1) solitary (2) multiple
III	Doubtful	(1) anterior to equator (2) solitary, > 10 disc diameter behind equator
IV	Unfavorable	(1) multiple tumors, some > 10 disc diameters (2) lesion extends anteriorly to ora serrata
V	Very unfavorable	(1) tumors occupying over 50% of retina (2) vitreous seeding

Source: Adapted from[56].

method, it may not outweigh the risk of radiation retinopathy[15], and with the development of novel delivery techniques such as periocular and intra-arterial chemotherapy, plaque brachytherapy is used less often in salvage or primary therapy.

Laser therapy

Laser therapy consists of using a diode laser *via* indirect ophthalmoscopy to apply precise burns to the entirety of the tumor. Laser therapy is performed during exam under anesthesia (EUA), and is used as monotherapy, combined with systemic or intraarterial chemotherapy, or for focal tumor recurrences. For small, unilateral tumors, local laser ablative therapy may spare a child systemic or local chemotherapy and can be used as monotherapy. However, children must continue to have frequent EUAs, as new tumors can occur at sites away from the solitary lesion. Studies have shown that systemic chemotherapy combined with focal laser consolidation is more efficacious than systemic chemotherapy alone, with in-depth discussion in the next section. Finally, laser therapy does not prove efficacious for vitreous or subretinal seeds, but is often used for focal, marginal recurrences following primary tumor treatment. Overall, laser ablative therapy plays an important role in the primary management of retinoblastoma.

Chemotherapy

To maintain globe-salvage while eliminating the risk of radiation complications, systemic chemotherapy has become a popular treatment modality in the management of retinoblastoma[16]. Due to carboplatin's success among treatment of other pediatric tumors, it remains a widely used choice to treat RB[16] and is combined with other agents such as etoposide, vincristine, and occasionally cyclophosphamide[17,18]. Evidence suggests that such multi-agent chemotherapy may have better outcomes when given in combination with focal laser ablation. For instance, of 36 eyes with R-E Group I -V that were given carboplatin and vincristine at 3-wk intervals over a 6 mo period, nearly half (52%) of eyes showed tumor growth and 42% had vitreous seeding, indicating that multi-agent chemotherapy alone may not be sufficient[19]. Shields *et al*[9] showed that of 83 eyes in R-E Groups I -IV, chemoreduction with 6 cycles of Fluorouracil (5FU), epirubicin and cyclophosphamide combined with cryotherapy, thermotherapy, or plaque radiotherapy showed treatment failure of 10% by 5 years, causing the need for additional EBRT; for eyes in R-E Group V, combination failure was 47% at 5 years. The study also showed that by 5 years, 35% of eyes required enucleation. The eyes requiring enucleation included 15% of R-E Group I -IV eyes and 53% of R-E Group V eyes. Although there was no long-term follow-up, no child developed metastasis or died in the series[9].

When treatment involves both 4-9 cycles of chemotherapy and a diode laser ablation to all tumor areas including macular and foveal components, tumor control rates for R-E Group I -IV have been reported to be 100% at 3 years[20]. Further evidence suggests that recurrence rates of more aggressive (R-E Group Vb and Group D) tumors may decrease when treated with systemic chemotherapy and local consolidation. Shields *et al*[21] demonstrated that ICRB Group D tumors (or RB with diffuse seeds) had a 47% success rate with chemoreduction combined with focal consolidation. Schefler *et al*[20] has also shown success rates as high as 83% in aggressive Group V tumors that were treated with the diode laser therapy to the macular and foveal components of the tumor in combination with 4-9 cycles of systemic chemotherapy. Of note, 57% of these patients retained a 20/80 or better vision outcome, despite direct ablation to the fovea[20].

Lastly, the most aggressive ICRB Group E tumors benefit most from enucleation and histological analysis. High-risk features on histopathologic analysis may be considered for adjuvant chemotherapy. These factors include deep choroidal invasion, or involvement of the anterior chamber, iris, ciliary body, or optic nerve. Successful prognostic factors for systemic chemoreduction include tumor margins at least 3 mm from fovea/optic disk and lack of subretinal fluid[22]. Poor prognostic features include anterior chamber seeding, iris infiltration, ciliary body infiltration, involvement of optic nerve, choroidal involvement, and infiltrates into the sclera[23].

Standard chemotherapy protocols utilize vincristine, etoposide, and carboplatin with or without cyclophosphamide. Other medications that have been the subject of more recent studies involving systemic treatment and local delivery include melphalan, paclitaxel, topotecan, and cisplatin.

Paclitaxel, an antineoplastic agent that stabilizes microtubules, and topotecan, a topoisomerase I inhibitor, have shown early promise. At the cellular level, paclitaxel used in combination with β-lapachone has been shown to induce apoptosis in human RBY79 cells[24]. In animal models, local delivery of paclitaxel *via* subconjunctival injections resulted in reduced tumor size in a dose-dependent manner. Toxicities observed were conjunctival and corneal toxicity and lens opacification[25]. Another antineoplastic agent that shows potential therapeutic effects for retinoblastoma treatment is topotecan, which

Table 2 International classification of retinoblastoma

Group	Subgroup	Quick reference	Features
A	A	Small tumor	size ≤ 3 mm
B	B	Larger tumor	Size > 3 mm
		Macula	≤ 3 mm to foveola
		Juxtapapillary	≤ 1.5 mm to disc
		Subretinal fluid	Clear subretinal fluid ≤ 3 mm from margin
C	C1	Focal seeds	Subretinal seeds ≤ 3 mm from tumor
	C2		Vitreous seeds ≤ 3 mm from tumor
	C3		Both subretinal and vitreous seeds ≤ 3 mm from tumor
D	D1	Diffuse seeds	Subretinal seeds > 3 mm from tumor
	D2		Vitreous seeds > 3 mm from tumor
	D3		Both subretinal and vitreous seeds > 3 mm from tumor
E	E	Extensive retinoblastoma	> 50% globe involvement or Neovascular glaucoma hemorrhage in anterior chamber, vitreous, or subretinal space Invasion to postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

Source: Adapted from[7].

traps the cell cycle in S-phase[26]. Studies showed similar topotecan vitreous drug levels in rabbit eyes that were administered *via* the periocular or systemic route[27] although murine retinoblastoma models suggest prolonged drug levels when delivered intravitreously[28]. Chantada *et al*[29] administered various periocular doses in a pilot study on 5 children with retinoblastoma, which showed dose-dependent systemic absorption with no toxicities. Another study on children showed tumor reduction with a median dose of 3.72 mg/m^2 when periocular topotecan was combined with fibrin, causing reduced tumor volume and lowering rates of enucleation or additional systemic chemotherapy[30].

Although chemotherapy has been shown to be efficacious in the treatment of RB, it is not without risks, especially when toxic chemotherapeutics are administered to children and infants. Systemic chemotherapy has been associated with systemic toxicities, including pancytopenias requiring hospitalizations and transfusions[31]. In addition, there is concern for nephrotoxicity, as well as ototoxicity in platinum-based chemotherapy agents. Carboplatin related ototoxicity has been reported in up to 5% of patients undergoing treatment for retinoblastoma, the risk increasing when carboplatin is administered with cisplatin[32]. However, there is controversy regarding the actual incidence of ototoxicity in children treated with chemotherapy for RB with recent reports by the Childrens' Oncology Group indicating a very low incidence and recommendation that these agents not be withheld for these concerns. Nonetheless, focus has shifted on adjuvant agents that avoid or decrease systemic doses of chemotherapy, as well as local delivery of chemotherapeutics to avoid systemic administration.

In the pre-clinical setting, vascular targeting agents, such as anecortave acetate, have proven efficacious in the LHBETATAG mouse model for retinoblastoma, demonstrating a decrease in the vascularity of tumors while enhancing tumor control when combined with chemotherapy or other agents[33]. Glycolytic inhibitors, such as 2-deoxy-D-glucose, have also been investigated in the LHBETATAG model and shown to target hypoxic regions of tumors. Retinoblastoma tumors have been shown to have up to 21% hypoxia, areas that consist of slow-growing tumor cells unlike other hyperproliferation areas[34]. These hypoxic cells are resistant to chemotherapy and radiation therapy which target hyperproliferation cells. Advanced retinoblastoma tumors universally fail due to persistent vitreous seeding, tumor foci without an established blood supply and proposed regions of hypoxia[35]. Further studies and human trials are needed to determine the utility of glycolytic inhibitors, anti-angiogenic agents, as well as other novel agents. Of note, the use of adjuvant agents must be optimally timed and used in combination to maximize the efficacy and synergistic effect[36].

Local treatments

Local treatment forms include subconjunctival (sub-Tenons') injections, intravitreal injections[37,38] and intra-arterial administration. The advantage of administering chemotherapeutic agents locally includes the ability to administer higher concentrations of medication that would otherwise cause considerable toxicity if administered systemically. Local chemotherapy in the form of intravitreal or subconjunctival/sub-Tenon's injections has been shown to have benefits in murine/animal models, where subconjunctival carboplatin injections had a dose dependent effect on tumor control[37,38]. The rational for this treatment is to provide a deeper chemotherapy administration that bathes the sclera. Leng *et al*[39] demonstrated that periocular carboplatin injection may especially be an effective adjunct in the treatment of resistant, advanced retinoblastoma. A case report of retinoblastoma refractory to diode laser ablation showed tumor regression with chorioretinal scarring after receiving periocular injections of carboplatin. In a phase I / II trial, Abramson *et al*[40] investigated the efficacy and toxicity of up to 2 mL and 20 mg/injection of peri-ocular carboplatin injection for treating intraocular retinoblastoma. Three of five eyes

with vitreous disease showed a response to treatment while the eye with subretinal seeding did not display a response. Although 54% of eyes had vitreous seeding, major tumor response was observed. Toxicities included transient periorbital edema, optic atrophy, muscle fibrosis, and vascular alteration. Such vascular sclerosis may lead to subsequent delay in transit through the vessels, a factor that must be considered when administering other future treatments, including systemic chemotherapy or local intra-arterial delivery. Thus, there seems to be promise of periocular carboplatin injections for treating resistant retinoblastoma with vitreous seeding, but vascular alterations need to be considered when planning intra-arterial delivery in patients that have received periocular carboplatin in the past.

To avoid systemic chemotherapy and to deliver concentrated doses to local tissue, local delivery of chemotherapeutics is currently being investigated *via* intra-arterial delivery. A group in Japan[41,42] pioneered the technique of selective ophthalmic arterial infusion (SOAI). A catheter is passed into the carotid artery and advanced past the ostium of the ophthalmic artery. A balloon is then used to occlude distal flow, followed by infusion of chemotherapeutics, thus minimizing exposure to the brain. In a study involving 187 patients (610 eyes) treated with intraocular retinoblastoma, technical success rates of the procedure were as high as 97.51%[41]. The study found no complication of brain infarction from catheterization. Side effects included bradycardia, facial redness, and mild eye-lid swelling. This study concluded that for patients with intraocular retinoblastoma, SOAI using balloon occlusion may provide a safe and effective form of drug delivery. Of note, this initial study failed to report on tumor control rates or visual outcomes, but provided proof of principle for this novel delivery technique.

Following these initial studies, other groups investigated techniques for intra-arterial delivery, including direct cannulation of the ophthalmic artery, termed superselective intra-arterial chemotherapy[43]. Initial phase I / II studies showed promise as salvage therapy as 6 of 8 eyes were spared from enucleation[43]. Abramson *et al*[43] showed that intra-arterial chemotherapy could also be used as a primary therapy. Effective drug combinations showing promise in R-E Group V classification patients include melphalan alone, melphalan with topotecan, and melphalan with topetecan and carboplatin. A 4-year prospective study on 95 eyes undergoing intra-arterial chemotherapy *via* selective catheterization of the ophthalmic artery further showed promising results. Chemotherapy injections included melphalan with or without topotecan. Two-year survival rates free of ocular events were as high as 81.75% for eyes that received this treatment as primary therapy. In addition, no eyes in R-E Group I -IV were enucleated. Enucleation was performed, however in 19 of 83 (23%) of Group V eyes due to vitreous seeding[44]. One of the largest studies on SOAI involved 1452 procedures on 408 eyes with Group A-E retinoblastoma that received melphalan[42]. The patients were followed from 1988-2007, and showed a technical success rate of 98.8%. In terms of therapeutic response, secondary neoplasms occurred in only 11 patients, the 15-year cumulative incident rate being 5.8%. Hundred percent of ICRB Group A eyes were salvaged, 88% of Group B, 65% of Group C, 45% of Group D, and 30% of Group E. For patients with non-macular tumors, over half (51%) of eyes had a visual acuity greater than 0.5 and 36% of eyes had a visual acuity > 1.0 at the last follow up visit. Side effects noted were severe orbital inflammation in 0.5% of cases, diffuse chorioretinal atrophy in another 0.5%, and transient periocular swelling in some cases. No patients showed systemic toxicities[42].

A study by Vajzovic *et al*[45] at Bascom Palmer Eye Institute studied the complication and safety profile of intra-arterial melphalan chemotherapy in 12 eyes of 10 children with advanced RB (R-E stage Vb or International Classification Group D). The study of 12 eyes receiving ophthalmic artery melphalan for 9 mo showed no tumor progression at the 6-mo follow up visit. The study suggested that melphalan holds promise as a globe-conserving treatment option in advanced RB cases[46]. Further study showed that in the most severe cases requiring enucleation, infusing melphalan directly in the ophthalmic artery has proven to significantly decrease the enucleation rate from 100% to 23.5%[37]. Additional patients from Bascom Palmer were included in a study by Peterson *et al*[46] showing that of 17 tumors of 15 patients, 76% of the tumors were spared enucleation due to its response to melphalan. Of note, the study demonstrated that doses below 5 mg had a higher rate of failure and vitreous hemorrhage compared to those eyes treated with 5 mg or higher. These findings suggest further studies are needed determine ideal dosing strategies. Finally, Shields *et al*[47] published a series of reports on children with Rb undergoing intra-arterial chemotherapy. They showed that Group C or D eyes showed 100% and 33% globe salvage, respectively. The treatment showed promise for patients with subretinal seeds where 9/11 (82%) demonstrated complete response, and 6/9 (67%) of eyes with vitreous seeds showed complete response.

For cases presenting with vitreous seeding, studies have shown promise in melphalan administered *via* intravitreal injections, showing long term success rates of eye preservation up to 60%[15,41]. However, penetrating an eye harboring retinoblastoma presents the risk of extraocular extension. Recent techniques have been described combining elimination of vitreous reflux and application of cryotherapy to the sight of injection to minimize the risk of extraocular extension. Nonetheless, in cultures where enucleation is not acceptable, risks *vs* benefits of these treatments must be weighed and discussed thoroughly with the family.

For cases with bilateral retinoblastoma, melphalan administration with focal ablative treatment may also avoid enucleation[12,45]. Evidence suggests that subsequent, bilateral administration of chemotherapy through the ophthalmic artery may be safe and effective, termed tandem therapy. A case series on 4 patients by Abramson *et al*[43] showed no metastasis, and a 100% salvage rate, although 1 patient did develop neutropenia.

Intra-arterial melphalan has been shown to cause several local side effects and warrants some discussion. The study by Vajzovic *et al*[45] on 12 children showed local side effects such as retinal and choroidal microemboli in 9% of cases, vitreous hemorrhage in 25% of cases, and myositis in 8% of cases. Other side effects reported with melphalan include lid edema, forehead hyperemia, eyelash loss[12], as well as neutropenia, intraretinal hemorrhages, peripapillary cotton wool spots, vitreous hemorrhages, and periocular edema from myositis[45]. Other vascular side effects include ophthalmic artery stenosis, and potentially blinding vascular obstruction from thrombotic events[47-49]. A report by Shields *et al*[47] showed that of 16 cases, eyelid edema, blepharoptosis, and orbital congestion with temporary loss of motility were seen, but resolved within 6 mo. Permanent and potentially blinding complications included 3 cases of ophthalmic artery stenosis, 2 cases with retinal artery occlusion[47], and other reports of ciliary thrombosis in enucleated eyes receiving IAC have been reported[47,49].

Failure rates of intra-arterial melphalan therapy are higher for tumors refractory to other treatment modalities. A histopathologic case series of the enucleated eyes of 3 patients showed the presence of viable tumor, even after super-selective intra-arterial melphalan treatment. Two of the three eyes were high grade tumors, based on TNM staging, with optic nerve invasion[50]. A recent study by Graeber *et al*[51] also showed presence of non-necrotic, non-calcified tumor cells in 5/9 enucleated eyes that underwent chemosurgery.

PROGNOSIS

Children who do not develop tumor recurrence for at least 5 years are considered cured[52]. Lifetime follow up is still required due to risks of metastatic spread and death from secondary malignancies, which can be as high as 40% within 50 years of diagnosis for bilateral/hereditary RB[53]. Trilateral retinoblastoma, which involves both eyes and the pineal gland, is highly fatal, with a median survival of 9 mo[54]. Long-term survivors should also be followed for the development of second malignancies with periodic physical examination, laboratory screening, and radiology testing, depending upon specific risk factors.

CONCLUSION

Overall, the characteristics of retinoblastoma in terms of classification, size, location, and presence of seeding, guide the ocular oncologist to determine potential treatment modalities. However, it is of utmost importance to include the family in the decision-making process. Treatment paradigms have shifted from enucleation and EBRT as primary therapy to chemoreduction with focal laser consolidation. Current treatment protocols result in success rates approaching 99% in specialized centers, with many children maintaining useful vision. The next era of retinoblastoma treatment is shifting to local delivery of agents to avoid systemic chemotherapy. However, much remains unknown regarding the long-term efficacy of these local treatments, as well as the side effect profile. Despite these advancements in developed countries, one of the challenges in treating retinoblastoma worldwide remains access to care: if every patient with RB could be referred to tertiary care centers, mortality would drop by 62% to reach 1200/year[55]. The advancement of retinoblastoma treatments look promising, but future studies looking at long-term outcomes of various treatment modalities, toxicities, and the effect on genetic manipulation is warranted.

REFERENCES

1 **MacCarthy A**, Birch JM, Draper GJ, Hungerford JL, Kingston JE, Kroll ME, Onadim Z, Stiller CA, Vincent TJ, Murphy MF. Retinoblastoma in Great Britain 1963-2002. *Br J Ophthalmol* 2009; **93**: 33-37 [PMID: 18838413]

2 Retinoblastoma-Childhood. Available from: URL: http://www.cancer.net. July 11, 2011

3 **Gombos DS**, Chevez-Barrios AP. Current treatment and management of retinoblastoma. *Curr Oncol Rep* 2007; **9**: 453-458 [PMID: 17991352 DOI: 10.1007/s11912-007-0063-7]

4 **Desjardins L**, Levy C, Lumbroso L, Doz F, Schlienger P, Validire P, Asselain B, Bours D, Zucker JM. [Current treatment of retinoblastoma. 153 children treated between 1995 and 1998]. *J Fr Ophtalmol* 2000; **23**: 475-481 [PMID: 10844307]

5 **Shields CL**, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. *Curr Opin Ophthalmol* 2010; **21**: 203-212 [PMID: 20224400 DOI: 10.1097/ICU.0b013e328338676a]

6 **Gombos DS**, Kelly A, Coen PG, Kingston JE, Hungerford JL. Retinoblastoma treated with primary chemotherapy alone: the significance of tumour size, location, and age. *Br J Ophthalmol* 2002; **86**: 80-83 [PMID: 11801509 DOI: 10.1136/bjo.86.1.80]

7 **Linn Murphree A**. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005; **18**: 41-53, viii [PMID: 15763190 DOI: 10.1016/j.ohc.2004.11.003]

8 **Shields CL**, Mashayekhi A, Demirci H, Meadows AT, Shields JA. Practical approach to management of retinoblastoma. *Arch Ophthalmol* 2004; **122**: 729-735 [PMID: 15136321 DOI: 10.1001/archopht.122.5.729]

9 **Shields CL**, Honavar SG, Meadows AT, Shields JA, Demirci H, Singh A, Friedman DL, Naduvilath TJ. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol* 2002; **133**: 657-664 [PMID: 11992863 DOI: 10.1016/S0002-9394(02)01348-X]

10 **Shields CL**, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). *Arch Ophthalmol* 2001; **119**: 1269-1272 [PMID: 11545631 DOI: 10.1001/archopht.119.9.1269]

11 **Abramson DH**, Ellsworth RM, Kitchin FD, Tung G. Second nonocular tumors in retinoblastoma survivors. Are they radiation-induced? *Ophthalmology* 1984; **91**: 1351-1355 [PMID: 6595610]

12 **Abramson DH**, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. *Ophthalmology* 1998; **105**: 573-579; discussion 579-580 [PMID: 9544627 DOI: 10.1016/S0161-6420(98)94006-4]

13 **Wong FL**, Boice JD, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF, Li FP. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA* 1997; **278**: 1262-1267 [PMID: 9333268 DOI: 10.1001/jama.1997.03550150066037]

14 **Shields CL**, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001; **108**: 2116-2121 [PMID: 11713089 DOI: 10.1016/S0161-6420(01)00797-7]

15 **Kaneko A**, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. *Jpn J Clin Oncol* 2003; **33**: 601-607 [PMID: 14769836 DOI: 10.1093/jjco/hyg113]

16 **Gallie BL**, Bunding AS, Chan H. New chemotherapy and focal therapy for intraocular retinoblastoma. *Ophthalmology* 1995; **102** Suppl: 109

17 **Shields CL**, Honavar SG, Meadows AT, Shields JA, Demirci H, Naduvilath TJ. Chemoreduction for unilateral retinoblastoma. *Arch Ophthalmol* 2002; **120**: 1653-1658 [PMID: 12470138 DOI: 10.1001/archopht.120.12.1653]

18 **Advani SH**, Rao SR, Iyer RS, Pai SK, Kurkure PA, Nair CN. Pilot study of sequential combination chemotherapy in advanced and recurrent retinoblastoma. *Med Pediatr Oncol* 1994; **22**: 125-128 [PMID: 8259098 DOI: 10.1002/mpo.2950220212]

19 **Wilson MW**, Rodriguez-Galindo C, Haik BG, Moshfeghi DM, Merchant TE, Pratt CB. Multiagent chemotherapy as neoadjuvant treatment for multifocal intraocular retinoblastoma. *Ophthalmology* 2001; **108**: 2106-2114; discussion 2114-2115 [PMID: 11713087 DOI: 10.1016/S0161-6420(01)00805-3]

20 **Schefler AC**, Cicciarelli N, Feuer W, Toledano S, Murray TG. Macular retinoblastoma: evaluation of tumor control, local complications, and visual outcomes for eyes treated with chemotherapy and repetitive foveal laser ablation. *Ophthalmology* 2007; **114**: 162-169 [PMID: 17070578 DOI: 10.1016/j.ophtha.2006.06.042]

21 **Shields CL**, Shields JA. Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol* 2006; **17**: 228-234 [PMID: 16794434 DOI: 10.1097/01.icu.0000193079.55240.18]

22 **Rodriguez-Galindo C**, Wilson MW, Haik BG, Merchant TE, Billups CA, Shah N, Cain A, Langston J, Lipson M, Kun LE, Pratt CB. Treatment of intraocular retinoblastoma with vincristine and carboplatin. *J Clin Oncol* 2003; **21**: 2019-2025 [PMID: 12743157 DOI: 10.1200/JCO.2003.09.103]

23 **Honavar SG**, Singh AD. Management of advanced retinoblastoma. *Ophthalmol Clin North Am* 2005; **18**: 65-73, viii [PMID: 15763192 DOI: 10.1016/j.ohc.2004.09.001]

24 **D'Anneo A**, Augello G, Santulli A, Giuliano M, di Fiore R, Messina C, Tesoriere G, Vento R. Paclitaxel and betalapachone synergistically induce apoptosis in human retinoblastoma Y79 cells by downregulating the levels of phospho-Akt. *J Cell Physiol* 2010; **222**: 433-443 [PMID: 19918798 DOI: 10.1002/jcp.21983]

25 **Suárez F**, Jockovich ME, Hernandez E, Feuer W, Parel JM, Murray TG. Paclitaxel in the treatment of retinal tumors of LH beta-Tag murine transgenic model of retinoblastoma. *Invest Ophthalmol Vis Sci* 2007; **48**: 3437-3440 [PMID: 17652710 DOI: 10.1167/iovs.06-0796]

26 **Dennis MJ**, Beijnen JH, Grochow LB, van Warmerdam LJ. An overview of the clinical pharmacology of topotecan. *Semin Oncol* 1997; **24**: S5-12-S5-S5-12-18 [PMID: 9122737]

27 **Carcaboso AM**, Bramuglia GF, Chantada GL, Fandiño AC, Chiappetta DA, de Davila MT, Rubio MC, Abramson DH. Topotecan vitreous levels after periocular or intravenous delivery in rabbits: an alternative for retinoblastoma chemotherapy. *Invest Ophthalmol Vis Sci* 2007; **48**: 3761-3767 [PMID: 17652749 DOI: 10.1167/iovs.06-1152]

28 **Tsui JY**, Dalgard C, Van Quill KR, Lee L, Grossniklaus HE, Edelhauser HF, O'Brien JM. Subconjunctival topotecan in fibrin sealant in the treatment of transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 2008; **49**: 490-496 [PMID: 18234990 DOI: 10.1167/iovs.07-0653]

29 **Chantada GL**, Fandino AC, Carcaboso AM, Lagomarsino E, de Davila MT, Guitter MR, Rose AB, Manzitti J, Bramuglia GF, Abramson DH. A phase I study of periocular topotecan in children with intraocular retinoblastoma. *Invest Ophthalmol Vis Sci* 2009; **50**: 1492-1496 [PMID: 18978345 DOI: 10.1167/iovs.08-2737]

30 **Mallipatna AC**, Dimaras H, Chan HS, Héon E, Gallie BL. Periocular topotecan for intraocular retinoblastoma. *Arch Ophthalmol* 2011; **129**: 738-745 [PMID: 21670340 DOI: 10.1001/archophthalmol.2011.130]

31 **Wood PA**, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. *J Clin Invest* 1995; **95**: 1650-1659 [PMID: 7706473 DOI: 10.1172/JCI117840]

32 **Jehanne M**, Lumbroso-Le Rouic L, Savignoni A, Aerts I, Mercier G, Bours D, Desjardins L, Doz F. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer* 2009; **52**: 637-643 [PMID: 19148943 DOI: 10.1002/pbc.21898]

33 **Boutrid H**, Piña Y, Cebulla CM, Feuer WJ, Lampidis TJ, Jockovich ME, Murray TG. Increased hypoxia following vessel targeting in a murine model of retinoblastoma. *Invest Ophthalmol Vis Sci* 2009; **50**: 5537-5543 [PMID: 19578014 DOI: 10.1167/iovs.09-3702]

34 **Boutrid H**, Jockovich ME, Murray TG, Piña Y, Feuer WJ, Lampidis TJ, Cebulla CM. Targeting hypoxia, a novel treatment for advanced retinoblastoma. *Invest Ophthalmol Vis Sci* 2008; **49**: 2799-2805 [PMID: 18326690 DOI: 10.1167/iovs.08-1751]

35 **Dewhirst MW**, Cao Y, Moeller B. Cycling hypoxia and free radicals regulate angiogenesis and radiotherapy response. *Nat Rev Cancer* 2008; **8**: 425-437 [PMID: 18500244 DOI: 10.1038/nrc2397]

36 **Piña Y**, Houston SK, Murray TG, Koru-Sengul T, Decatur C, Scott WK, Nathanson L, Clarke J, Lampidis TJ. Retinoblastoma treatment: impact of the glycolytic inhibitor 2-deoxy-d-glucose on molecular genomics expression in LH(BETA)T(AG) retinal tumors. *Clin Ophthalmol* 2012; **6**: 817-830 [PMID: 22701083]

37 **Harbour JW**, Murray TG, Hamasaki D, Cicciarelli N, Hernández E, Smith B, Windle J, O'Brien JM. Local carboplatin therapy in transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 1996; **37**: 1892-1898 [PMID: 8759359]

38 **Hayden BH**, Murray TG, Scott IU, Cicciarelli N, Hernandez E, Feuer W, Fulton L, O'Brien JM. Subconjunctival carboplatin in retinoblastoma: impact of tumor burden and dose schedule. *Arch Ophthalmol* 2000; **118**: 1549-1554 [PMID: 11074812 DOI: 10.1001/archopht.118.11.1549]

39 **Leng T**, Cebulla CM, Schefler AC, Murray TG. Focal periocular carboplatin chemotherapy avoids systemic chemotherapy for unilateral, progressive retinoblastoma. *Retina* 2010; **30**: S66-S68 [PMID: 20419851]

40 **Abramson DH**, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. *Ophthalmology* 1999; **106**: 1947-1950 [PMID: 10519590 DOI: 10.1016/S0161-6420(99)90406-2]

41 **Yamane T**, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol* 2004; **9**: 69-73 [PMID: 15108036 DOI: 10.1007/s10147-004-0392-6]

42 **Suzuki S**, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology* 2011; **118**: 2081-2087 [PMID: 21715012 DOI: 10.1016/j.ophtha.2011.03.013]

43 **Abramson DH**, Dunkel IJ, Brodie SE, Marr B, Gobin YP. Bilateral superselective ophthalmic artery chemotherapy for bilateral retinoblastoma: tandem therapy. *Arch Ophthalmol* 2010; **128**: 370-372 [PMID: 20212212 DOI: 10.1001/archophthalmol.2010.7]

44 **Gobin YP**, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol* 2011; **129**: 732-737 [PMID: 21320950 DOI: 10.1001/archophthalmol.2011.5]

45 **Vajzovic LM**, Murray TG, Aziz-Sultan MA, Schefler AC,

Wolfe SQ, Hess D, Fernandes CE, Dubovy SR. Supraselective intra-arterial chemotherapy: evaluation of treatment-related complications in advanced retinoblastoma. *Clin Ophthalmol* 2011; **5**: 171-176 [PMID: 21383945]

46 **Peterson EC**, Elhammady MS, Quintero-Wolfe S, Murray TG, Aziz-Sultan MA. Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: initial experience with 17 tumors. *J Neurosurg* 2011; **114**: 1603-1608 [PMID: 21294621 DOI: 10.3171/2011.1.JNS10466]

47 **Shields CL**, Bianciotto CG, Jabbour P, Ramasubramanian A, Lally SE, Griffin GC, Rosenwasser R, Shields JA. Intra-arterial chemotherapy for retinoblastoma: report No. 1, control of retinal tumors, subretinal seeds, and vitreous seeds. *Arch Ophthalmol* 2011; **129**: 1399-1406 [PMID: 21670328]

48 **Shields CL**, Shields JA. Intra-arterial chemotherapy for retinoblastoma: the beginning of a long journey. *Clin Experiment Ophthalmol* 2010; **38**: 638-643 [PMID: 20584015 DOI: 10.1111/j.1442-9071.2010.02297.x]

49 **Eagle RC**, Shields CL, Bianciotto C, Jabbour P, Shields JA. Histopathologic observations after intra-arterial chemotherapy for retinoblastoma. *Arch Ophthalmol* 2011; **129**: 1416-1421 [PMID: 21746972 DOI: 10.1001/archophthalmol.2011.223]

50 **Vajzovic LM**, Murray TG, Aziz-Sultan MA, Schefler AC, Fernandes CE, Wolfe SC, Hess DJ, Dubovy SR. Clinicopathologic review of enucleated eyes after intra-arterial chemotherapy with melphalan for advanced retinoblastoma. *Arch Ophthalmol* 2010; **128**: 1619-1623 [PMID: 21149791 DOI: 10.1001/archophthalmol.2010.296]

51 **Graeber CP**, Gobin YP, Marr BP, Dunkel IJ, Brodie SE, Bornfeld N, Char DH, Folberg R, Imhof SM, Lin AY, Berry JL, Al Mesfer S, Moll AC, Abramson DH. Histopathologic findings of eyes enucleated after treatment with chemosurgery for retinoblastoma. *Open Ophthalmol J* 2011; **5**: 1-5 [PMID: 21399766 DOI: 10.2174/1874364101105010001]

52 **Kopelman JE**, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology* 1987; **94**: 371-377 [PMID: 3587919]

53 **Marees T**, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst* 2008; **100**: 1771-1779 [PMID: 19066271 DOI: 10.1093/jnci/djn394]

54 **Kivelä T**. Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. *J Clin Oncol* 1999; **17**: 1829-1837 [PMID: 10561222]

55 **Kivelä T**. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009; **93**: 1129-1131 [PMID: 19704035 DOI: 10.1136/bjo.2008.150292]

56 **Reese AB**. Retinoblastoma. In: Reese AB, editor. Tumors of the eye. 1st ed. New York: Harper and Row, 1963: 155-156

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MINIREVIEWS

Preventive medicine and the traditional concept of living in balance

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Abstract

Chronic diseases such as arthritis, heart disease and type 2 diabetes are becoming much more common. The cost of maintaining patients inflicted with these diseases increases yearly. These diseases were less common prior to 1970. This paper will consider several questions. How do toxic lifestyles contribute to these chronic diseases? What is preventive medicine? How can traditional healing help educate people about disease prevention? What is the traditional concept of balance and how is it important in modern medicine? The dangers of obesity are discussed in terms of inflammatory adipokine and inflammatory fat production. Mechanisms of disease causation or promotion are reviewed for heart disease, type 2 diabetes, arthritis and cancer. A preventive medicine approach to preventing or perhaps curing these diseases is given which involves treating toxic lifestyles and encouraging people to live in balance. The traditional concept of balance is explained in traditional Chinese medicine terms and in scientific terms. Yin and yang are cold and hot but can also be seen as agonist and antagonist. In addition, yin and yang can be seen as rest and exercise. When yin and yang are in balance, chi flows in the body. Chi is the flow of extracellular and intracellular signaling compounds and processes in the body. When the body is in balance, it can heal itself. The traditional concept of balance should be taught as a central principle of preventive medicine.

Key words: Preventive medicine; Traditional healing; Balance; Arthritis; Heart disease; Type 2 diabetes; Cancer

Core tip: When the body is in balance, the body can heal itself. Balance involves balancing rest and exercise, body fat and body muscle. Nutrition is critical to balance and requires balancing meat and vegetable/fruit intake. Preventive medicine should teach patients to exercise regularly, eat properly, drink no more than one alcoholic drink daily and avoid smoking. Following this protocol, patients can keep themselves thin, strong and in balance. This will prevent or perhaps cure chronic diseases such as heart disease, type 2 diabetes, arthritis and cancer.

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INTRODUCTION

The Organisation for Economic Co-operation and Development reports that medical costs in the United States were almost 18% of the gross national product in 2010. This is more than a threefold increase from about 5% of the gross national product in 1960. Healthcare costs are increasing every year around the world. Healthcare costs increase because of increasing incidences of heart disease, arthritis, type 2 diabetes and cancer according to the Centers for Disease Control in the United States. As of 2010, about 8% of United States adults have type 2

diabetes. What causes the incidence of these diseases to increase yearly?

HOW DO TOXIC LIFESTYLES CONTRIBUTE TO CHRONIC DISEASES?

Several factors are involved in toxic lifestyles: stress, smoking, alcohol consumption, lack of exercise and obesity[1]. All of these factors increase the risk of suffering from chronic diseases and cancer[1]. Stress is a well-known risk factor for the development of heart disease[2,3]. It is less clear how much stress contributes to other diseases. Smoking is known to cause heart disease[4]. Nicotine interacts with nicotinic acetylcholine receptors in endothelial cells and stimulates oxygen radical formation that damages arteries[5]. This damage increases atherosclerosis. Smoking is also well known to increase the incidence of cancer in several organs as discussed at the Centers for Disease Control website.

Alcohol consumption upregulates the synthesis of sterol regulatory element binding protein[6]. This induces several lipogenic genes leading to triglyceride and ceramide accumulation and endocannabinoid synthesis. Ceramide and endocannabinoids, in excess, are toxic and damage endothelial cells and other cells[1]. Excessive alcohol consumption causes visceral fat to accumulate and release several inflammatory adipokines[1].

Obesity results in visceral fat accumulation. Visceral fat is the fat that surrounds the intestines and other visceral organs. This fat releases toxic lipids, such as ceramides and endocannabinoids, and inflammatory proteins, called inflammatory adipokines[1]. Subcutaneous fat does not perform these functions. However, perivascular fat may function like visceral fat in terms of the induction of inflammation by releasing toxic factors.

Lack of exercise is a risk factor for chronic diseases since sedentary people lose muscle mass and tend to accumulate fat, including visceral fat. How muscle mass is important in health is not entirely known. Muscles are certainly important for motion, balance and can prevent falls. Exercise stimulates stem cell growth in every organ[7-10]. Exercise also stimulates nerve growth in the adult human brain[11]. Stem cells are important for maintenance of normal organ functions.

Why is obesity so important? Visceral fat secretes inflammatory adipokines and toxic lipids[1]. There are many adipokines including: visfatin, leptin, C-reactive protein, tumor necrosis factor α, resistin, angiotensin II, heparin binding epidermal growth factor like growth factor, angiotensin II and interleukin 6. The mechanisms of action of some adipokines are still under investigation. However, the mechanisms of toxicity of many adipokines are well described. As visceral fat accumulates, it becomes hypoxic, resulting in down regulation of peroxisome proliferator activated receptor γ 1 and less production of vascular endothelial growth factor[12]. Hypoxia inducible factor 1 is produced and upregulates the production of inflammatory adipokines in fat cells and macrophages. Macrophages and T cells infiltrate into hypoxic visceral fat and are stimulated to secrete cytokines and adipokines.

It is clear that visceral fat causes heart disease by a multifactorial process described below[1,13-15]. Ceramide causes inducible nitric oxide synthase to dysfunction and produce oxygen radicals. This is toxic to the kidney and increases blood pressure. Endothelin synthesis increases resulting in hypertension. Visfatin and leptin cause defects in artery walls. Tumor necrosis factor α, resistin and C-reactive protein cause adhesion molecule synthesis that leads to adherence of neutrophils and macrophages. These inflammatory cells become activated by visfatin and leptin and start the process of plaque accumulation. Smooth muscle cell proliferation is stimulated by platelet derived growth factor, angiotensin II and heparin binding epidermal growth factor like growth factor. Eventually the plaque becomes unstable due to induction of matrix metalloproteinase activity by C-reactive protein and visfatin.

Visceral fat causes type 2 diabetes by a multifactorial process[16-20]. Increased ceramide inhibits tyrosine phosphorylation of the insulin receptor and causes insulin receptor dysfunction. Ceramide also causes inducible nitric oxide synthase dysfunction and oxygen radical formation that can damage the pancreas. Resistin and resistin like molecules antagonize the actions of insulin. Visfatin, tumor necrosis factor α and interleukin-6 are involved in long term dysfunction of the insulin receptor. They also increase fatty acid release from adipocytes. These fatty acids are taken up by muscle and cause muscle to become resistant to insulin.

Visceral fat causes osteoarthritis by a multifactorial process[21-25]. Endocannabinoids are made by visceral fat and synovial fibroblasts, and activate synovial macrophages that make inflammatory adipokines[26]. Macrophages invade into synovial spaces after stimulation by adipokines from visceral fat such as leptin, C-reactive protein and interleukin-6. Macrophages, neutrophils and T cells instigate an inflammatory process in the joint. Macrophages can be stimulated by fibroblast derived colony stimulating factor-1 to invade bone and become osteoclasts. Activated macrophages release resistin that stimulates fibroblasts. This is a vicious cycle where synovial fibroblasts stimulate macrophages that stimulate fibroblasts. This vicious cycle results in pain and joint destruction. Even when osteoarthritis is not present, obesity increases osteoporosis in women and men[27].

Unfortunately, current pain treatment in arthritis and other conditions all too often involves opioids that are addictive, cause seizures and respiratory depression. In the United States, as of 2013, there are about 14000 people dying yearly from prescription opioid overdose according to the Centers for Disease Control. This is more than 4 times the number of people who die yearly from heroin overdose in the United States.

Cancer is caused by damage to DNA. The growth of cancer is promoted by obesity. Obesity increases the risk of developing cancer and mortality from cancer[28]. Cancer can grow only when the body is not able to kill

tumor cells adequately. Visceral fat releases inflammatory adipokines, such as interleukin-6, tumor necrosis factor α and leptin, that promote the growth and malignancy of tumor initiating stem cells[29]. In the presence of inflammatory adipokines, the body is not able to mount an adequate defense against tumor cell growth and metastasis.

The chronic diseases and cancer discussed above are each caused by the activation of multiple genes resulting in multiple adipokines and toxic lipids being produced. Clearly the concept of one gene malfunctioning and producing any of these diseases is incorrect. Treatment of these chronic diseases has focused on single, highly selective drugs that block one specific pathway in the disease process. This is somewhat like placing a small rock in a large stream. The stream simply flows around the rock. The use of highly selective drugs may slow down, but does not stop the disease process. Drugs that control blood glucose, blood pressure and blood cholesterol are important and can keep patients alive. However, the disease processes continue. Patients must remain on these drugs for the rest of their lives and must contend with the toxicities of the drugs for the rest of their lives. Modern medicine has forgotten that drugs do not cure. Drugs help the body to heal itself[1,30]. Currently, there is far too much dependence on drugs to improve health and not enough use of preventive medicine.

WHAT IS PREVENTIVE MEDICINE?

Preventive medicine is the practice of helping patients live healthy lifestyles and stop living toxic lifestyles. This involves stress reduction techniques, mindfulness therapy, exercise therapy, nutritional guidance, smoking and alcohol cessation, weight loss therapy and other therapies. Stress and anxiety are constant companions of each person. That cannot be changed. What can be changed is how each person reacts to stress and anxiety. This is where stress reduction and mindfulness techniques are helpful[2]. In the United States, nutritional guidance comes from television, newspaper and magazine information. This information is frequently incorrect. Nutritional information from these sources usually over emphasizes the importance of eating meat in order to maintain adequate protein intake. However, meat eating frequently results in high fat intake. For instance, hamburger may provide 65% or more of its calories from fat, not protein. High fat diets are toxic[1]. Smoking and alcohol cessation therapies exist and can be successful in many patients. Weight loss therapies and surgeries exist, but are sometimes not successful at all[31]. Frequently the benefits of weight loss surgery and therapy do not last for more than a few years[32].

Obesity is an addiction to eating fat, such as triglycerides. Fat is abundant in fast foods and convenience foods. Fat consumption leads to endocannabinoid synthesis, opioid peptide synthesis and the upregulation of brain opioid receptors[33-35]. Endocannabinoids stimulate transient receptor potential cation channels in the brain leading to pain relief and more hunger. Opioid peptides, including enkephalin and dynorphin are pain relievers and are addictive. Eating fat also stimulates ghrelin release in the gut that stimulates appetite[36]. Obesity should be treated as an addiction.

Why is exercise so important in preventive medicine? Exercise can reverse heart disease and increase longevity[37]. Exercise decreases the progression of arthritis[38-47]. Exercise decreases the progression of type 2 diabetes[48-50]. Exercise may help patients survive cancer[51]. The combination of weight loss and exercise may help patients suffering from these diseases and should be examined in clinical trials. The questions that should be asked are as follows. Can a combined program of weight loss and exercise cure heart disease? Can a combined program of weight loss and exercise cure type 2 diabetes? Can a combined program of weight loss and exercise cure arthritis? Can a combined program of weight loss and exercise decrease the risk of developing cancer?

HOW CAN TRADITIONAL HEALING HELP?

Traditional Chinese medicine teaches people to live in balance, to learn how to balance yin and yang in the body[52]. Yin is cold and wet. Yang is hot and dry. Basically, each person must balance cold, sedentary times of the day with hot, physical times. In other words, daily exercise may be required to balance times of rest. Similarly, a balanced diet must be consumed. Yang foods such as meats and chilis, must be balanced with yin foods such as melons and vegetables. A person's body must be in balance with the correct amount of fat (yin) balanced by the correct amount of muscle (yang). Balance allows the flow of life forces in the body called chi[52]. Chi has recently been proposed to be composed of signaling processes in the body controlled by endogenous signaling compounds and receptors[52]. When chi flows, the body can maintain its health. In traditional China, obesity was a dishonor to the ancestors who give each of us our bodies. Each of us must keep our bodies in balance for ourselves and our families, in order to keep ourselves healthy. If a person lives in balance, the body can heal itself.

Traditional medicine in many areas of the world teaches people to live in balance[53]. Among American Indians, to live in balance means: love God, love your family, respect all people, work for your community, keep yourself thin and strong, take only what you need, and do not pollute[53,54]. American Indians recognize a balance between hot and cold as well as wet and dry. Maintaining this balance in the body is essential for health. American Indians approach hot and cold very directly. If a person needs to be treated with hot treatments, they are put in the sweat lodge, hot spring or similar hot treatment[54,55]. If a person needs a cold treatment, they are told to swim in the sea, a lake or similar cold treatment. Daily physical activity is required and must be balanced with times of rest. If a person lives in balance, the body can heal itself.

In Arab traditional medicine, there is a similar concept of balance[56]. The normal state of the body is balance, which is health. Illness results from being out of balance.

Balance is derived from worshipping Allah, loving your family, respecting all people, working productively, maintaining a fit body, and eating a balanced diet. A diet must be balanced in terms of quality and quantity of food.

Traditional medicine has kept human beings alive for the entire existence of the human species, about 200000 years. During the hunter gatherer period, daily running and walking were essential to survival. Our bodies have evolved for 200000 years with daily running and walking. This means that people who were good runners and walkers survived and passed on their genes. There has been a natural selection for running and walking. Prior to 1970, cancer and chronic diseases such as heart disease, type 2 diabetes, and arthritis were uncommon, as can be seen at the Centers for Disease Control website. This is because people used to keep themselves thin and strong, in other words in balance. Obesity was uncommon prior to the 1970's according to the Centers for Disease Control. People used to follow what traditional medicine taught. This teaching was frequently passed down from a person's grandparents.

Traditional medicine should be revitalized in modern society. We should teach again the principles of living in balance to allow the body to heal itself. Traditional medicine should be integrated into preventive medicine. Traditional medicine should be taught to healthcare professionals. Preventive medicine should become a major focus of modern medicine. It is very possible that when people learn to live in balance the incidences of heart disease, type 2 diabetes, arthritis and cancer will decrease.

REFERENCES

1 **Adams JD**, Parker K. Extracellular and intracellular signaling. London: Royal Society of Chemistry, 2011 [DOI: 10.1039/9781849733434]

2 **Kivimäki M**, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Ferrie JE, Geuskens GA, Goldberg M, Hamer M, Hooftman WE, Houtman IL, Joensuu M, Jokela M, Kittel F, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Kumari M, Madsen IE, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Rugulies R, Salo P, Siegrist J, Singh-Manoux A, Suominen SB, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M, Steptoe A, Theorell T. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012; **380**: 1491-1497 [PMID: 22981903 DOI: 10.1016/S0140-6736(12)60994-5]

3 **Steptoe A**, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol* 2012; **9**: 360-370 [PMID: 22473079 DOI: 10.1038/nrcardio.2012.45]

4 **Centers for Disease Control and Prevention (CDC)**. CDC Grand Rounds: the million hearts initiative. *MMWR Morb Mortal Wkly Rep* 2012; **61**: 1017-1021 [PMID: 23254255]

5 **Vazquez-Padron RI**, Mateu D, Rodriguez-Menocal L, Wei Y, Webster KA, Pham SM. Novel role of Egr-1 in nicotine-related neointimal formation. *Cardiovasc Res* 2010; **88**: 296-303 [PMID: 20615913 DOI: 10.1093/cvr/cvq213]

6 **You M**, Fischer M, Deeg MA, Crabb DW. Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). *J Biol Chem* 2002; **277**: 29342-29347 [PMID: 12036955]

7 **Nakada D**, Levi BP, Morrison SJ. Integrating physiological regulation with stem cell and tissue homeostasis. *Neuron* 2011; **70**: 703-718 [PMID: 21609826 DOI: 10.1016/j.neuron.2011.05.011]

8 **Mayr M**, Niederseer D, Niebauer J. From bench to bedside: what physicians need to know about endothelial progenitor cells. *Am J Med* 2011; **124**: 489-497 [PMID: 21605723 DOI: 10.1016/j.amjmed.2011.01.015]

9 **Zhang J**, Pan T, Liu Y, Wang JH. Mouse treadmill running enhances tendons by expanding the pool of tendon stem cells (TSCs) and TSC-related cellular production of collagen. *J Orthop Res* 2010; **28**: 1178-1183 [PMID: 20225313 DOI: 10.1002/jor.21123J]

10 **Brunner S**, Engelmann MG, Franz WM. Stem cell mobilisation for myocardial repair. *Expert Opin Biol Ther* 2008; **8**: 1675-1690 [PMID: 18847304 DOI: 10.1517/14712598.8.11.1675]

11 **Pereira AC**, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 2007; **104**: 5638-5643 [PMID: 17374720 DOI: 10.1073/pnas.0611721104]

12 **Mlinar B**, Marc J. New insights into adipose tissue dysfunction in insulin resistance. *Clin Chem Lab Med* 2011; **49**: 1925-1935 [PMID: 21892913 DOI: 10.1515/CCLM.2011.697]

13 **Ritchie SA**, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis* 2007; **17**: 319-326 [PMID: 17110092]

14 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/CIRCULATIONAHA.109.192644]

15 **Taube A**, Schlich R, Sell H, Eckardt K, Eckel J. Inflammation and metabolic dysfunction: links to cardiovascular diseases. *Am J Physiol Heart Circ Physiol* 2012; **302**: H2148-H2165 [PMID: 22447947 DOI: 10.1152/ajpheart.00907.2011]

16 **Walker CG**, Zariwala MG, Holness MJ, Sugden MC. Diet, obesity and diabetes: a current update. *Clin Sci* (Lond) 2007; **112**: 93-111 [PMID: 17155931 DOI: 10.1042/CS20060150]

17 **Steppan CM**, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. *Nature* 2001; **409**: 307-312 [PMID: 11201732]

18 **Wyne KL**. Free fatty acids and type 2 diabetes mellitus. *Am J Med* 2003; **115** Suppl 8A: 29S-36S [PMID: 14678863]

19 **Pittas AG**, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. *J Clin Endocrinol Metab* 2004; **89**: 447-452 [PMID: 14764746 DOI: 10.1210/jc.2003-031005]

20 **Rocha VZ**, Folco EJ. Inflammatory concepts of obesity. *Int J Inflam* 2011; **2011**: 529061 [PMID: 21837268 DOI: 10.4061/2011/529061]

21 **Matias I**, Di Marzo V. Endocannabinoids and the control of energy balance. *Trends Endocrinol Metab* 2007; **18**: 27-37 [PMID: 17141520]

22 **Getting SJ**. Targeting melanocortin receptors as potential novel therapeutics. *Pharmacol Ther* 2006; **111**: 1-15 [PMID: 16488018]

23 **Otero M**, Lago R, Gomez R, Dieguez C, Lago F, Gómez-Reino J, Gualillo O. Towards a pro-inflammatory and immunomodulatory emerging role of leptin. *Rheumatology* (Oxford) 2006; **45**: 944-950 [PMID: 16720637 DOI: 10.1093/rheumatology/kel157]

24 **Senolt L**, Housa D, Vernerová Z, Jirásek T, Svobodová R, Veigl D, Anderlová K, Müller-Ladner U, Pavelka K, Haluzík M. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* 2007; **66**: 458-463 [PMID: 17040961]

25 **Chitu V**, Stanley ER. Colony-stimulating factor-1 in immunity and inflammation. *Curr Opin Immunol* 2006; **18**: 39-48 [PMID: 16337366]

26 **Lowin T**, Zhu W, Gräber A, Neumann E, Müller-Ladner U, Straub RH. Cortisol-induced adhesion of synovial fibroblasts is mediated by the endocannabinoid system. *Brain Behav Immun* 2012; **26**: S6 [DOI: 10.1016/j.bbi.2012.07.043]

27 **Zhao LJ**, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. *J Clin Endocrinol Metab* 2007; **92**: 1640-1646 [PMID: 17299077 DOI: 10.1210/jc.2006-0572]

28 **Renehan AG**, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; **371**: 569-578 [PMID: 18280327 DOI: 10.1016/S0140-6736(08)60269-X]

29 **Feldman DE**, Chen C, Punj V, Tsukamoto H, Machida K. Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells. *Proc Natl Acad Sci USA* 2012; **109**: 829-834 [PMID: 22207628 DOI: 10.1073/pnas.1114438109]

30 **Adams Jr JD**. Design flaws in randomized, placebo controlled, double blind clinical trials. *World J Pharmacol* 2011; **1**: 4-9 [DOI: 10.5497/wjp.v1.i1.4]

31 **Rusch MD**, Andris D. Maladaptive eating patterns after weight-loss surgery. *Nutr Clin Pract* 2007; **22**: 41-49 [PMID: 17242453]

32 **Meguid MM**, Glade MJ, Middleton FA. Weight regain after Roux-en-Y: a significant 20% complication related to PYY. *Nutrition* 2008; **24**: 832-842 [PMID: 18725080 DOI: 10.1016/j.nut.2008.06.027]

33 **Matsumura S**, Eguchi A, Okafuji Y, Tatsu S, Mizushige T, Tsuzuki S, Inoue K, Fushiki T. Dietary fat ingestion activates β-endorphin neurons in the hypothalamus. *FEBS Lett* 2012; **586**: 1231-1235 [PMID: 22575661 DOI: 10.1016/j.febslet.2012.03.028]

34 **Bello NT**, Patinkin ZW, Moran TH. Opioidergic consequences of dietary-induced binge eating. *Physiol Behav* 2011; **104**: 98-104 [PMID: 21539852 DOI: 10.1016/j.physbeh.2011.04.032]

35 **South T**, Huang XF. Temporal and site-specific brain alterations in CB1 receptor binding in high fat diet-induced obesity in C57Bl/6 mice. *J Neuroendocrinol* 2008; **20**: 1288-1294 [PMID: 18752650 DOI: 10.1111/j.1365-2826.2008.01785.x]

36 **Saidpour A**, Kimiagar M, Zahediasl S, Ghasemi A, Vafa M, Abadi A, Daneshpour M, Zarkesh M. The modifying effects of fish oil on fasting ghrelin mRNA expression in weaned rats. *Gene* 2012; **507**: 44-49 [PMID: 22842192 DOI: 10.1016/j.gene.2012.07.015]

37 **Heran BS**, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011; CD001800 [PMID: 21735386 DOI: 10.1002/14651858.CD001800.pub2]

38 **Fries JF**, Singh G, Morfeld D, Hubert HB, Lane NE, Brown BW. Running and the development of disability with age. *Ann Intern Med* 1994; **121**: 502-509 [PMID: 8067647]

39 **Liemohn W**. Exercise and arthritis. Exercise and the back. *Rheum Dis Clin North Am* 1990; **16**: 945-970 [PMID: 2087586]

40 **Panush RS**. Does exercise cause arthritis? Long-term consequences of exercise on the musculoskeletal system. *Rheum Dis Clin North Am* 1990; **16**: 827-836 [PMID: 2087579]

41 **Elward K**, Larson E, Wagner E. Factors associated with regular aerobic exercise in an elderly population. *J Am Board Fam Pract* 1992; **5**: 467-474 [PMID: 1414447]

42 **Ward MM**, Hubert HB, Shi H, Bloch DA. Physical disability in older runners: prevalence, risk factors, and progression with age. *J Gerontol A Biol Sci Med Sci* 1995; **50**: M70-M77 [PMID: 7874592 DOI: 10.1093/gerona/50A.2.M70]

43 **Fries JF**, Singh G, Morfeld D, O'Driscoll P, Hubert H. Relationship of running to musculoskeletal pain with age. A six-year longitudinal study. *Arthritis Rheum* 1996; **39**: 64-72 [PMID: 8546740]

44 **Bruce B**, Fries JF, Lubeck DP. Aerobic exercise and its impact on musculoskeletal pain in older adults: a 14 year prospective, longitudinal study. *Arthritis Res Ther* 2005; **7**: R1263-R1270 [PMID: 16277679]

45 **Centers for Disease Control and Prevention (CDC)**. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation --- United States, 2007-2009. *MMWR Morb Mortal Wkly Rep* 2010; **59**: 1261-1265 [PMID: 20930703]

46 **Frohnauer A**, Neff A, Knechtle B. [Does running increase the risk of osteoarthritis?]. *Praxis (Bern 1994)* 2006; **95**: 1305-1316 [PMID: 16970140]

47 **Cymet TC**, Sinkov V. Does long-distance running cause osteoarthritis? *J Am Osteopath Assoc* 2006; **106**: 342-345 [PMID: 16790540]

48 **Tsai J**, Ford ES, Li C, Zhao G, Balluz LS. Physical activity and optimal self-rated health of adults with and without diabetes. *BMC Public Health* 2010; **10**: 365 [PMID: 20573237 DOI: 10.1186/1471-2458-10-365]

49 **Cuenca-García M**, Jago R, Shield JP, Burren CP. How does physical activity and fitness influence glycaemic control in young people with Type 1 diabetes? *Diabet Med* 2012; **29**: e369-e376 [PMID: 22803800 DOI: 10.1111/j.1464-5491.2012.03740.x]

50 **Coyle D**, Coyle K, Kenny GP, Boulé NG, Wells GA, Fortier M, Reid RD, Phillips P, Sigal RJ. Cost-effectiveness of exercise programs in type 2 diabetes. *Int J Technol Assess Health Care* 2012; **28**: 228-234 [PMID: 22980698 DOI: 10.1017/S0266462312000256]

51 **Ballard-Barbash R**, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012; **104**: 815-840 [PMID: 22570317 DOI: 10.1093/jnci/djs207]

52 **Adams JD**, Lien EJ. Traditional Chinese medicine: scientific basis for its use. London: Royal Society of Chemistry, 2013

53 **Adams JD**, Garcia C, Lien EJ. A comparison of chinese and american Indian (chumash) medicine. *Evid Based Complement Alternat Med* 2010; **7**: 219-225 [PMID: 18955312 DOI: 10.1093/ecam/nem188]

54 **Garcia C**, Adams JD. Healing with medicinal plants of the west: cultural and scientific basis for their use. 3rd ed. La Crescenta: Abedus Press, 2012

55 **Adams JD**, Garcia C. The Advantages of Traditional Chumash Healing. *Evid Based Complement Alternat Med* 2005; **2**: 19-23 [PMID: 15841273 DOI: 10.1093/ecam/neh072]

56 **El-Magboub A**, Garcia C, Adams JD. A revival of primary healing hypotheses: a comparison of traditional healing approaches of Arabs and American Indians. *TANG* 2012; **2**: 4.1-4.13 [DOI: 10.5667/tang.2011.0025]

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

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No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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