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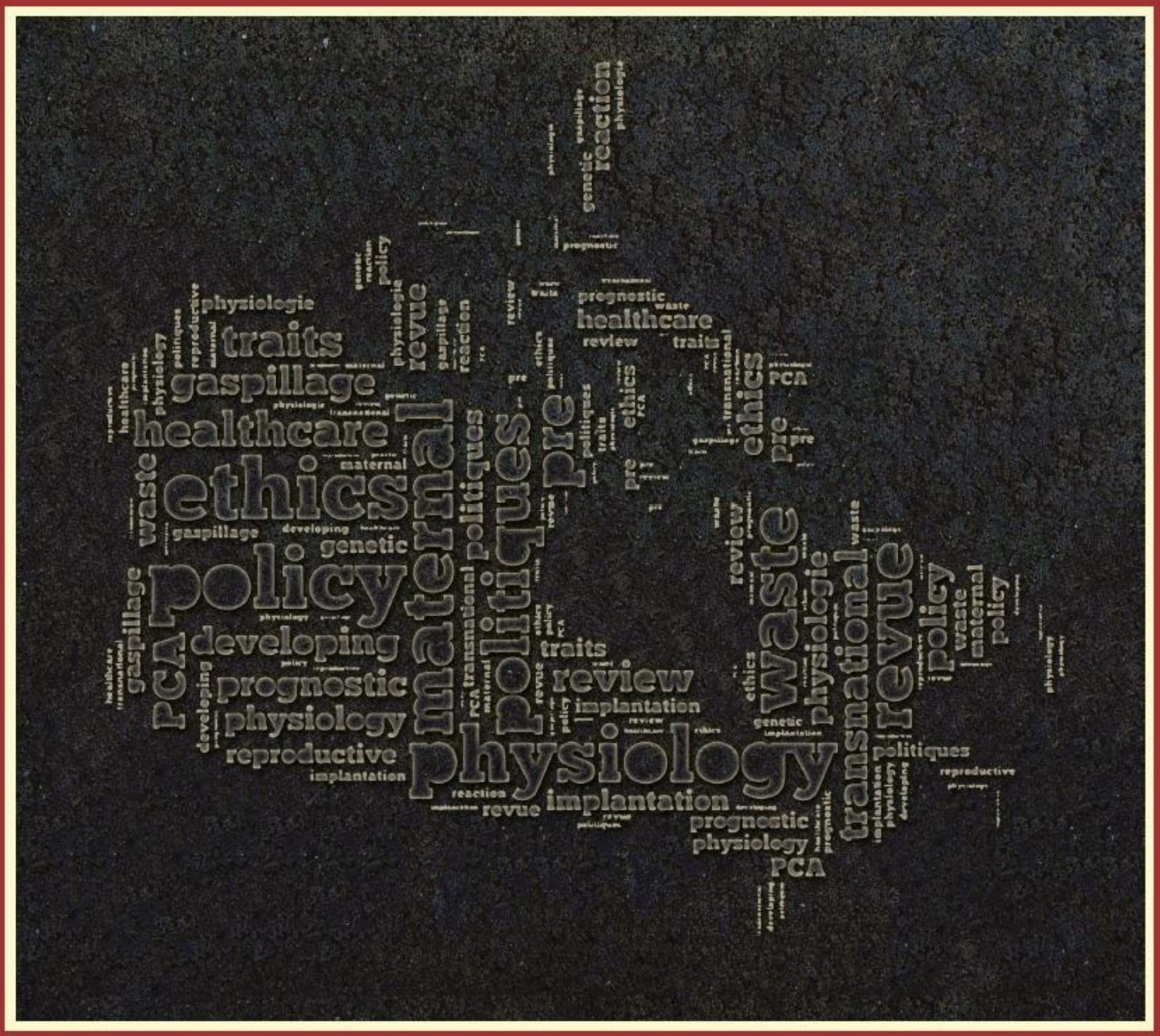

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Table des matières | Table of Contents

Comité Éditorial | Editorial Board

Avant-propos

Selam OGBALIDET Rédactrice en chef

Chère lectrice, cher lecteur,

Au nom de la RISS comité éditorial 2013-2014, je suis heureuse de vous présenter le premier numéro du 3e volume de la Revue Interdisciplinaire des Sciences de la Santé (RISS).

En accord avec le principe de collaboration interdisciplinaire, notre équipe s'est efforcée de fournir une représentation multidimensionnelle des déterminants de la santé en recrutant des collaborateurs des différentes facultés qui composent l'Université d'Ottawa. De plus, chaque résumé d'article dans ce numéro est traduit, dans le souci de préserver la tradition bilingue de la revue. Bien que la RISS ait évolué au fil des ans en ce qui concerne sa structure et sa gestion, notre engagement envers notre lectorat ne s'est jamais affaibli. Chers lecteurs, votre soutien continu a, à son tour, renforcé notre détermination et notre capacité à faire du bon travail d'édition.

Le comité éditorial de la RISS a été comblé de pouvoir compter sur le soutien d'un ensemble sans cesse croissant d'experts dévoués. Sans ces membres, la plupart affiliés à l'Université d'Ottawa et à d'autres organismes professionnels, nous ne serions pas en mesure de présenter des recherches étudiantes de qualité. Notre équipe est aussi redevable à Mirhad Lončar, le traducteur officiel de ce numéro, dont l'aide a été partie intégrante de la capacité de la revue pour mettre en valeur la recherche qui est le reflet de l'enseignement bilingue. Au professeur Raywat Deonandan qui supervise cette initiative dirigée par les étudiants, nous adressons nos plus vifs remerciements ainsi que notre sincère gratitude. Sans ses conseils, la RISS n'aurait pas mérité les éloges qu'elle a reçus depuis sa création en 2009. Enfin, le travail du comité éditorial, de ses éditeurs et éditrices seniors et associés, ne peut pas être surestimé. Leur enthousiasme pour le travail que nous faisons m'a laissé en admiration devant eux et, plus important encore, m'a assurée que leur dévouement ne doit pas être remis en question.

Mon temps avec la RISS a été une expérience remplie de défis mais bien enrichissante professionnellement. Au cours de mon mandat de deux ans, j'ai constaté comment les étudiants ont pu bénéficier, à la fois personnellement et professionnellement, de voir leur travail publié; j'ai eu le privilège de faire partie de leurs réalisations. Alors que mon équipe et moi avons tiré grand plaisir du processus de publication, les œuvres originales trouvées dans ces pages nous ont vraiment invités à savourer les délices de la recherche. En terminant, je souhaite que ce numéro fasse naître en vous un regain d'intérêt pour entreprendre un projet de recherche original de votre choix.

Cordialement,

Selam Ogbalidet, BHSc

Rédactrice en chef (2011-2013)

Foreword

Selam OGBALIDET Editor-in-Chief

Dear Reader,

On behalf of the 2013-2014 IJHS editorial board, I am happy to present to you the Volume 3 Issue 1 of the Interdisciplinary Journal of Health Sciences (IJHS).

In keeping with the true essence of interdisciplinary collaboration, our team has endeavoured to provide a multi-dimensional representation of the determinants of health by recruiting contributors from the different faculties that comprise the University of Ottawa. Furthermore, every abstract that appears in this issue is accompanied by a translated counterpart in an effort to preserve the journal's bilingual tradition. Although the IJHS has evolved over the years with respect to its structure and management, our commitment to our readership has never wavered. The continued support of our readership has, in turn, strengthened our resolve to continue to improve upon the work that we do.

The IJHS editorial board has been very fortunate to receive the support of a dedicated, and ever growing, peer review committee. Without its members, who are affiliated with the University of Ottawa and other professional bodies, we would not be able to make quality student research accessible to our readership. Our team is also indebted to Mirhad Lončar, the official translator for this issue, whose assistance has been integral to the journal's ability to showcase research that is reflective of bilingual education. To Raywat Deonandan, PhD, the supervising professor for this student-led initiative, we extend our warmest thanks along with our sincere gratitude. For without his guidance, the IJHS would not have achieved nor deserved the praise that it has enjoyed since its inception in 2009. Lastly, the contributions of the senior editorial committee as well as those of the associate editors cannot be overemphasized. Their excitement for the work that we do has left me in awe of them and, more importantly, has assured me that their dedication is not to be questioned.

My time with the IJHS has been a challenging yet richly rewarding experience. Over the course of my two-year term, I have seen how students have directly benefited, both personally and professionally, from having their work published and I have been privileged to be a part of their accomplishments. While my team and I have derived great pleasure from the publication process, the original works found within these pages have truly invited us to enjoy the delights of research. In closing, it is my hope that this issue will awaken in you a renewed interest to undertake an original research project of your own.

Sincerely,

Selam Ogbalidet, BHSc

Editor-in-Chief (2011-2013)

Transnational Trafficking of Hazardous Waste from Developed to Developing Nations: Policies and Recommendations

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Résumé :

(traduction)

La traite transnationale de déchets électroniques est devenue un problème de plus en plus préoccupant avec le temps alors que la quantité de déchets produits dans les pays développés continue à augmenter. Au fil du temps, l'accent s'est déplacé des moyens traditionnels d'élimination de déchets industriels vers la mise au rebut de déchets électroniques. Cette acceptation de déchets dangereux entraîne souvent des effets néfastes pour la santé dans le pays importateur. Dans le cadre d'une étude de cas, on examine l'histoire, les conséquences, les politiques actuelles et des recommandations pour le trafic de déchets dangereux dans le contexte de l'Afrique de l'Ouest. Suite à l'analyse, il est évident que, malgré des politiques rigoureuses de la part des importateurs, d'autres facteurs interviennent, notamment l'expansion économique et la corruption, qui continuent d'alimenter l'importation de déchets électroniques. Par conséquent, les recommandations s'adressent aux pays exportateurs qui disposent généralement d'une économie, de systèmes politiques, et de technologies bien développés, augmentant ainsi la probabilité d'une maîtrise de la situation.

Mots-clés :

E-gaspillage, gaspillage, trafic transnational, politique publique, Afrique de l'ouest

Abstract:

Transnational trafficking of e-waste has become a rising problem over time as the amount of waste produced in developed countries increases. Over time, the focus has moved from traditional industrial waste disposal to e-waste disposal. This acceptance of hazardous waste often leads to adverse health effects in the importing nation. As a case study, the history, consequences, current policies, and recommendations for hazardous waste trafficking are considered in the context of West Africa. Following the analysis, it is clear that despite strong policies on the importers part, there are confounding factors, such as economic expansion and corruption, which continue to drive the import of e-waste. Therefore, the recommendations are addressed to exporting nations which generally have well-developed economies, political systems, and technology thus increasing the likelihood of control over the situation.

Keywords:

E-waste, transnational trafficking, policy, West Africa

Introduction

As the global population continues to increase, accordingly, so does the amount of waste produced. In addition, there is often a lack of resources in industrialized nations to accommodate such waste expansion. As a result, many developed nations often look for alternatives such as exporting their waste to developing countries. Developing countries, despite experiencing adverse health effects, are often inclined to accept these exports in prospect of economic growth.

Traditionally, waste export has been focused on hazardous wastes such as radioactive material and sludge; while recently, e-waste has become center stage. "E-waste refers to end-of-life electronic products, including televisions, monitors, computers, audio and stereo equipment, video cameras, telephones, fax/photocopy machines and printers, mobile phones, wireless devices, chips, motherboards, cathode ray tubes and other peripheral items" (Frazzoli, Orisakwe, Dragone, & Mantovani, 2010, p. 388). Although extensive policies exist concerning transnational trafficking of hazardous waste, e-waste continues to be a problem for many developing nations. As a case study, the history, consequences, current policies, and recommendations for hazardous waste trafficking will be considered in the context of West Africa.

Hazardous Waste Trafficking in the Past

It is currently believed that toxic waste dumping from developed to developing nations began in the late 1980s (Lipman, 2011). From this period on, there have been numerous examples of hazardous waste dumping incidents. These incidents, although negative for the general health of the importing country, often resulted in the creation of policies which will be discussed later. Within this section, a few notable incidents will be described.

Kassa Island, Guinea (1988)

In March, 1988, a Norwegian shipping company dumped 15, 000 tonnes of incinerator ash from Philadelphia into a quarry on Kassa Island. This incident was discovered when the island's vegetation began to die (Vir, 1989). Subsequent investigations led to the discovery of a contract wherein Guinea was to receive a total of 85, 000 tonnes of waste (Vir, 1989).

Koko, Nigeria (1988)

In May, 1988, 900 tonnes of toxic waste was exported from Italy to Koko, Nigeria. Of these 900 tonnes of toxic waste, 150 tonnes were PCBs. Other imported chemicals included formaldehyde and methyl melamine, both of which are suspected carcinogens. This import of toxic waste from Italy was facilitated by a construction company, whose member, Gianfranco Rafaelli, had previously acquired land in Nigeria. As opposed to listing the chemicals that were actually being imported, the construction company applied for a permit to import mineral wax, polishing oil, cinder ash, and other industrial chemicals (Gbadegesin, 2001).

Abidjan, Ivory Coast (2006)

In 2006, 17 people died (United Nations Office on Drugs and Crime, 2009) and over 80, 000 were forced to seek medical attention due to vomiting, nosebleeds, and difficulty breathing in Abidjan, Ivory Coast (Mason, 2006). This was the result of 500 tonnes of toxic waste that was dumped by Trafigura management in 14 sites around the city— primarily sites near water and agricultural sources (Mason, 2006). Mason explains that "The waste from the ship had been brought in the hold of the Probo Koala along with a shipment of petroleum that was delivered to Nigeria [from Europe]" (Mason, 2006, para. 5). Mason describes that when the waste was analyzed, sulphur hydrocarbon was found. Sulphur hydrocarbon is highly toxic and is found in several types of crude oil. It is estimated that proper treatment of this waste would have cost the exporting country $250, 000 (Mason, 2006) while in Africa they were charged only $18, 500 (United Nations Office on Drugs and Crime, 2009).

Hazardous Waste Trafficking in the Present

Incidents of toxic waste dumping in developing countries prior to 1992 generally involved wastes that were by- products of industry (for example, petroleum refining and pesticide manufacturing industries) such as radioactive material, sludge, and heavy metals. Post-1992, there have been few cases of such toxic waste dumping; instead, the focus

has become e-waste (United Nations Office on Drugs and Crime, 2009). The United Nations Office on Drugs and Crime (UNODC) (2009) estimates that 94, 900 tonnes of e-waste is trafficked from developed to developing nations annually. Transnational trafficking of e-waste, similarly, is not always straightforward.

"US legislation authorizes the export of second-hand goods [electronics] for reuse or recycling operations" (UNODC, 2009, p. 57); however, recycling operations in developing countries are generally primitive or non-existent (Frazzoli et al., 2010). Common methods of crude recycling include:

i. stripping of metals in open-pit acid baths to recover valuable metals [such] as Ag [silver], Au [gold], Cu [copper] and Pt [platinum],

ii. removing electronic components from printed circuit boards by heating over a grill using

iii. honeycomb coal blocks (coal mixed with river sediment which is contaminated) as fuel,

iv. chipping and melting plastics without proper ventilation,

v. burning cables for recovering metals, and also burning unwanted materials in open air,

vi. disposing unsalvageable materials in fields and riverbanks,

vii. toner sweeping[1], and

viii. dismantling electronic equipment (Frazzoli et al., 2010).

Alter (1997) argues that importing hazardous wastes from developed countries can actually be beneficial to developing countries as it conserves natural resources, reduces energy demand, removes hazardous components, and provides raw materials for industrial growth; however, this is questionable when considering the crude recycling methods mentioned above.

European law, as opposed to US law, prohibits the export of non-functioning electronics to non-Organization for Economic Co-Operation and Development (OECD) countries; however, there are currently no regulations to ensure that all second-hand electronics being exported are functioning (UNODC, 2009). This often results in e-waste being exported to developing countries under the title of 'functioning electronics intended for second hand use'. According to the Basel Action Network (BAN) (2006), in general, 25% of exported electronics are functional and 75% is e-waste.

Frazzoli et al. (2010) support this by explaining that in Africa, e-waste is often discarded by riverbanks where it is subsequently manually disassembled to acquire working pieces, leaving those pieces that are non-functional to be burned. Consequently, residents frequently use the water that resides next to these landfills and open burning sites for washing, cooking, and drinking (Frazzoli et al., 2010). The direct use of water contaminated by toxic waste and their by-products often leads to adverse health effects. Despite the health consequences of importing hazardous wastes, "economic compulsions, the generation of employment opportunities, and the short-sightedness of national governments create[s] incentives" (Sonak, Sonak, & Giriyan, 2008, p. 144).

E-waste and Health

Various forms of e-waste may include chemical compounds such as PCBs and persistent organic pollutants (POPs), as well as chemical elements such as barium, cadmium, mercury, nickel, lead, zinc, lithium, chromium, and beryllium in their components. Additional chemicals such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated dibenzo-p-dioxins and furans (PCDD/Fs), and dioxin-like polychlorinated biphenyls (DL PCBs) may be released as a result of incineration (Frazzoli, et al., 2010). Frazzoli et al. explain that POPs, aluminum, mercury, manganese, and lead affect children's neurological development while chromium, arsenic, and PAHs increase the risk of cancer. Furthermore, POPs (Frazzoli et al., 2010) and DL PCBs (National Institute of Environmental Health Sciences, 2011) have been classified as endocrine disruptors. Endocrine disruptors are chemicals that interfere with the body's endocrine, or hormone, system and may result in undesirable effects experienced in the neurological, immunological, and reproductive systems (such as reduced fertility) (National Institute of Environmental Health Sciences, 2011).

Many of the above-mentioned chemicals, in addition to their adverse effects, are prone to bioaccumulation and often resist biodegradation (Frazzoli et al., 2010). This co-bioaccumulation of multiple chemicals may result in unpredicted health consequences, as the study of mixture effects is still a challenge (Frazzoli et al., 2010). Further-

more, bioaccumulation facilitates the spreading of chemicals as levels are often amplified in food sources and are able to be passed from mother to child through breastfeeding. A lack of health care services and resources, often experienced in developing countries, typically results in the inability to mitigate the health consequences of e-waste (Sonak et al., 2008) which are most often cancer, congenital malformations (Musmeci et al., 2010) endocrine disruption, and neurotoxicity (Frazzoli et al., 2010).

Current Policies

Harmful Wastes (Special Criminal Provisions) Act No. 42 Chapter 165 (1988)

This act prohibits the "carrying, depositing and dumping of harmful waste on any land, territorial waters and matter relating thereto" in Nigeria (p.1) and was enacted as a "response to the dumping of toxic waste in Koko, Delta State, Nigeria in 1988" (Onyenekenwa, 2011).

Bamako Convention on the Ban on the Import into Africa and the Control of Transboundary Movement and Management of Hazardous Wastes within Africa (1991)

This convention bans the import of hazardous waste into many West African countries; however, Nigeria and Ghana are not signatories (UNODC, 2009).

Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (1989) and the Basel Ban (1995) amendment to the Basel Convention

The Basel Convention made it possible for countries to track and monitor the flow of hazardous waste globally; however, it was not able to stop the flow (UNODC, 2009). The Basel Ban amendment to the convention reduced levels of trafficking by prohibiting OECD countries from exporting their hazardous waste to non-OECD countries (UNODC, 2009). This, in turn, placed the responsibility on the exporter rather than the importer in an attempt to address the imbalance of power between developed and developing countries (Sonak et al., 2008). Sonak et al. state that "The exporting State is obliged not to permit any exporter of hazardous wastes to commence transboundary movement without written consent from the importing State, as well as any State of transit" (p. 147). Many countries refused to sign this convention, notably the USA, despite their role as one of the largest producers of hazardous waste (Sonak et al., 2008).

US Environmental Protection Agency (EPA)'s Import-Export Program: International Trade in Hazardous Waste (1998)

This regulation requires US exporters to submit documents, or notifications, in three phases of an export: before a shipment proceeds, while a shipment is in transit, and annually. The US currently has multiple agreements between itself and international countries which all include "the basic principles of notification to the government of the exporting country, government-to-government notification to the importing government, and the consent of the importing government for exports and imports of hazardous wastes" (EPA, 1998, para. 6).

Recommendations

The following recommendations are made in consideration of the US government as the US is currently one of the largest producers of e-waste in the world (Sonak et al., 2008).

Recommendation #1: create sustainable products

As previously mentioned, it is estimated that 94, 900 tonnes of e-waste is trafficked annually (UNODC, 2009). Such a large quantity of e-waste can likely be attributed to short product lives—a quality of technology that is becoming familiar throughout the developed world. Many of the electronics that contribute to e-waste, such as cameras, cell phones, computers, etc. become obsolete quickly due to rapid technological advances. Therefore, it is clear that developing sustainable electronics would likely reduce the amount of e-waste produced. This can be challenging considering that American society is primarily economically driven and any increases in product lives would likely reduce profit.

Recommendation #2: create a federal policy concerning e-waste specifically

In reviewing the current policies that exist pertaining to Nigeria, primarily the *Harmful Wastes Act* and the *Basel Convention*, it is clear that regardless of strong policies,

transnational trafficking of e-waste into Nigeria still occurs. Onyenekenwa (2011) explains that "Corruption makes a mess of implementation of even faultless policies in Nigeria and puts to waste resources employed in producing them" (p. 258).

Therefore, with the knowledge that corruption exists in Nigeria, the responsibility should be placed on the exporting nation to ensure that exported electronics intended for second hand use are indeed functional. Currently, according to the EPA's *Import-Export Program*, the US is permitted to export e-waste to developing nations with their consent. This is not pragmatic when considering the crude recycling methods often employed by developing nations as well as the high levels of corruption previously mentioned. Nigeria, for example, is likely to consent to importing e-waste regardless of health consequences and a lack of proper recycling techniques in prospect of economic gain.

Moreover, there are policies for which either the US or certain developing nations are not party to, principally the *Basel Convention* and *Bamako Convention*. These conventions both protect developing nations from e-waste trafficking; therefore, signing these conventions would likely decrease e-waste trafficking. This is clearly not all that is required to solve the problem, as e-waste trafficking is still prevalent among signatories. This is to be expected when considering the corruption and the promise of economic gain in developing countries as mentioned above.

In order to avoid such corruption, it falls upon the exporting country to restrict exporting e-waste to developing countries that are incapable of properly processing them. In the US, there is currently no federal policy concerning e-waste specifically. The EPA's *Import-Export Program* addresses hazardous waste as a whole; however, this program does not account for the distinctive characteristics of e-waste, such as their potential use as second hand goods, which allows them to be imported through unique channels. The US, in response to growing e-waste, has delegated the responsibility to the states as opposed to creating a federal legislation. Greenemeier (2009) explains that in 2009, only 19 states had enacted e- waste laws while 14 states had e-waste laws pending. This leaves many states with no laws regarding e-waste and also creates confusion among manufacturers. Different regulations concerning e-waste across states require manufacturers to continuously alter their production, ultimately increasing production costs (Greenemeier, 2009).

In formulating a federal policy regarding e-waste explicitly, the US may look to Europe as an example. In Europe, there are currently several laws which address e- waste. The EU's *Restriction on the Use of Hazardous Substances (RoHS)*, for example, is a policy that "bans new electronics containing more than agreed-to levels of lead, cadmium, mercury, hexavalent chromium, and polybrominated biphenyl (PBB) as well as polybrominated diphenyl ether (PBDE) flame retardants" (Greenemeier, 2009, para. 5). Greenemeier (2009) explains that the EU also has *The European Community's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program* which "addresses manufacturers' responsibilities to manage risks from chemicals in their products" (para. 5) and the EU's *Waste Electrical and Electronic Equipment (WEEE)* which "directs e-waste management" (para. 5). A comprehensive, well-implemented, federal policy would likely reduce confusion in the US regarding e- waste as well as reduce overall production and export.

Recommendation #3: invest in local e- waste recycling programs

Presently, the US, like many other developed nations, creates more e-waste than they can physically dispose of. In addition, it is often cheaper to export this large amount of e -waste for recycling than it is to dispose of it in the developed nation. This option, despite economic benefits, often leads to adverse health effects for the importing nation if recycling methods are not current. In order to avoid this, exporting nations might invest in local e-waste recycling programs. Local recycling programs would reduce the cost of transportation, reduce the time needed for proper documentation and communication between countries, and reduce the cost associated with fines for taking part in illegal waste dumping. Quan (2011) describes how a Canadian company in Toronto was fined $30, 000 for transporting 1, 200 used lead acid batteries and 7 cathode ray tube monitors to Hong Kong without China's consent.

Furthermore, if local companies are paid to properly dispose of their e-waste, in theory, the economy of the nation may improve. This would occur by creating job opportunities and possibilities for importing other nations' e-waste. Overall, disposing of e-waste locally ensures that recycling processes are modern, legal, and encouraged.

Recommendation #4: develop partnerships with developing nations

As Alter (1997) previously mentioned, recycling can be beneficial for developing nations if they have appropriate recycling techniques, which currently they do not. If developed nations were to partner with developing nations to create sustainable recycling centers for hazardous waste, it would likely benefit both the exporting and importing nations. Exporting waste to a developing nation would likely remain cheaper than disposing of waste in a developed nation (due to variations in nations' economies), while partnerships would ensure legality, safety, and economic growth in the developing nation.

Conclusion

Transnational trafficking of hazardous wastes, believed to have commenced in the late 1980s, has undergone substantial changes with advances in technology. Over time, the focus has moved from traditional industrial waste disposal to e- waste disposal. More often than not, e- waste is trafficked from developed nations to developing nations through third parties for disposal. This is in part motivated by a lack of resources in the exporting nation to properly dispose of e- waste as well as the reduced cost associated with trafficking. However, due to the crude recycling methods currently in place in developing countries, this transfer of e-waste often leads to adverse health effects—most often cancer, congenital malformations, endocrine disruption, and neurotoxicity in the importing nation. In order to prevent such health outcomes and inequity, multiple policies have been implemented by both the developing nations and the developed nations involved. In analyzing these policies, it is clear that despite strong policies on the importers part, there are confounding factors, such as economic expansion and corruption, which continue to drive the import of e-waste. Therefore, the above recommendations are addressed to exporting nations which generally have well-developed economies, political systems, and technology thus increasing the likelihood of control over the situation. Finally, as e-waste disposal is a comparatively new concern, it is recommended that more research be completed in this topic.

Notes

[1] A method where by workers without any protective respiratory equipment open cartridges with screw drivers and use paint brushes and bare hands to wipe toner into a bucket. In this process, constant clouds of toner are created and inhaled. Material Safety Data Sheets (MSDS) for carbon black and other ingredients indicate that they may cause lung and respiratory irritation while other documentation suggests that they may be a carcinogenic (Puckett et al., 2002).

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Under-reporting of Adverse Drug Reactions: The Need for an Automated Reporting System

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Résumé :

(traduction)

Bien que plus de 32 000 réactions indésirables aux médicaments soient déclarées annuellement à Santé Canada, cela ne représente qu'environ 5% des cas vécus par les Canadiens chaque année. Cet affichage frappant de sous-déclaration aboutit non seulement à des résultats non représentatifs en ce qui concerne les effets indésirables des médicaments, mais jette également le discrédit sur les bases de données utilisées par les professionnels de la santé, ce qui, à son tour, présente un danger pour la santé et la sécurité des Canadiens. Les principales causes de la sous-déclaration que l'on trouve dans la littérature sont l'ignorance, la méfiance et la léthargie de la part des professionnels de la santé. Bien que Santé Canada se fie à ces professionnels pour signaler volontairement les effets indésirables, il existe le potentiel d'un système de déclaration automatisé pour éliminer les causes de sous-déclaration. L'intégration d'un tel système avec des technologies de l'informatique de la santé actuelles, tels que le dossier de santé électronique et l'utilisation des technologies de communication existantes dans le cadre du système de santé, permettra aux professionnels de la santé d'utiliser des données représentatives sur les réactions indésirables aux médicaments au Canada, ce qui, à son tour, les aidera à mieux servir leurs patients.

Mots-clés :

Réactions indésirables médicamenteuses, Bulletin Canadien des Effets Indésirables, BCEI, e-sante, dossier médical électronique, informatique de la sante, systèmes de sante, pharmacovigilance, déclaration, déclaration volontaire

Abstract:

Although upwards of 32,000 adverse drug reactions are reported to Health Canada annually, this represents only approximately 5% of cases experienced by Canadians every year. This gross display of underreporting not only results in unrepresentative data in regards to adverse drug reactions, but further discredits databases used by healthcare professionals and in turn compromises the health and safety of Canadians. Major causes of underreporting seen in the literature are ignorance, diffidence and lethargy displayed by healthcare professionals. While Health Canada relies on these professionals to voluntarily report adverse drug reactions, the potential exists for an automated reporting system to remove causes of underreporting. Through integrating such a system with current health informatics technologies such as the electronic health record and utilizing existing health system communication technologies, healthcare professionals will be provided with representative data of adverse drug reactions in Canada and in turn be able to better serve their patients.

Keywords:

Adverse drug reactions, Canadian Adverse Reaction Newsletter, CARN, e-Health, electronic patient record, health informatics, health systems, pharmacovigilance, reporting, voluntary reporting

Introduction

Adverse drug reactions (ADRs) are undesirable effects to health products including drugs, medical devices and natural health products (Health Canada, 2012). While an overdose can be seen as an adverse drug reaction, such reactions are typically observed and reported at standard dosage. Over 32,500 adverse drug reaction reports were received by Health Canada in 2010 (Health Canada, 2011a), however this may be an underrepresentation of the true number of cases. Currently, ADRs are reported on a voluntary basis by health care professionals, manufacturers and consumers via www.medeffect.ca. This Health Canada website gives consumers, health care professionals and the industry opportunities to report adverse drug reactions that are either witnessed or experienced personally. Methods of submission include an online reporting option, a printable form that can be faxed and/or mailed and lastly a telephone number allowing reporting over the phone. Regional offices of Health Canada receive these reports before they are processed and sent to the national office. All reports are recorded in Health Canada's Canada Vigilance Database, from where the public is able to search them online. This not only provides physicians with a database to compare adverse reactions they witness, but also provides consumers with a research tool for health products that themselves, friends or family members may have been prescribed. Furthermore, frequent health product appearances and serious cases are published in the *Canadian Adverse Reaction Newsletter* (CARN). This publication is distributed to a mailing list of over 20,000 subscribers (Health Canada, 2014).

Operational Challenge

While the current operational model of adverse drug reaction reporting provides useful tools to Canadians such as the CARN and Canada Vigilance Database, it relies completely on physicians and consumers alike to voluntarily report ADRs. This leads one to speculate about whether 32,500 adverse drug reaction reports is representative of cases experienced in Canada. Furthermore, it raises questions of under-reporting.

In a systematic review conducted by Hazell and Shakir (2006), determinants of under-reporting were examined. Factors associated with under-reporting included ignorance (95%), diffidence (72%) and lethargy (77%). In cases in which lethargy was listed as a reason, physicians displayed a lack of interest in finding a reporting form or stated other excuses (Hazell & Shakir, 2006). This shows that physician's beliefs and attitudes greatly affect the outcome of adverse drug reaction reporting. Furthermore, a voluntary system that relies on these physicians leaves room for error due to personal biases.

Another study, carried out by Lopez-Gonzalez, Herdeiro, & Figueiras (2009), estimated the extent of ADR underreporting. Across 12 countries, adverse drug reactions were under-reported at a median rate of 94%. When further examined between standard reactions and those deemed serious, the rate of under-reporting was still significant at a median of 85% (Lopez-Gonzalez, Herdeiro, & Figueiras, 2009). This indicates that a gross portion of adverse drug reactions are being left unreported and raises concern for the representativeness of ADRs experienced by Canadians in the current databases.

To date, no legislation or regulations exist that require health professionals to report adverse drug reactions. However regulations are in place for market authorization holders (MAHs), otherwise known as industry stakeholders, making reporting mandatory in the event of an incident regarding one of their own marketed products (Health Canada, 2011b). While regulations such as these may be difficult and time-consuming to impose on health professionals, a gap is left to be filled by a health informatics solution.

Proposed Informatics Application

Throughout the current literature regarding underreporting of ADRs, it can be seen that a strictly voluntary model provides fundamental information through reports, but also hinders the quantity and accuracy of information that is being provided to Canadians.

Currently, adverse reaction reports come from three sources– consumers, health care professionals and MAHs. The latter of the three sources is regulated by government legislation, and is thus required to report cases to Health Canada. Consumers and health care professionals however, are not required to report reactions

Based on this knowledge, the most effective means of increasing adverse reaction reporting lies in the field of the health care professional. This includes but is not limited to health clinics, hospitals and pharmacies. It is clear that

while a voluntary reporting system is effective for the needs of market authorization holders and consumers, it is not adequate to ensure representative reporting in health care settings.

When proposing a solution for such a case, one must take into consideration determinants that lead to under-reporting in physicians. As discussed previously, ignorance, diffidence and lethargy were all factors affecting physicians reporting habits (Hazell & Shakir, 2006). While a voluntary system requires physicians to manually input adverse reactions into the reporting means provided, an automated reporting system eliminates the need for health professional participation. This in turn, would leave no room for these three determinants of under-reporting to skew data.

As we shift towards steady integration of technology into healthcare administration and practice (Coiera, 2003), adverse drug reaction reporting and monitoring systems are being developed and implemented around the world. The Health Evaluation through Logical Processing (HELP) system currently in place at the Latter Day Saints (LDS) Hospital in Salt Lake City, USA, is an early front-runner of such technology. This system, however, does not completely eradicate the role of the doctor in ADR reporting. First, it gathers information from the laboratory, radiology department and the hospital pharmacy. Then, using predetermined parameters, the system signals to a healthcare professional that an adverse drug reaction has occurred. It is up to the doctor's discretion at this point to either confirm or reject the adverse drug reaction (Thürmann, 2001).

However in a study by Dormann et al. (2000), a similar automated system was compared to standard manual reporting. In this case, thirty-four adverse drug reactions were detected by the automated system, however physicians only reported seventeen. Thus, the automated system was associated with a 100% increase in ARs captured.

In Brent, United Kingdom, a team of health informaticians developed a method of information extraction in order to trend adverse drug reactions. General practices under examination used a Clinical Information Management System (CIMS) to code details of patient treatment and prescribing using the Read classification system. These Read

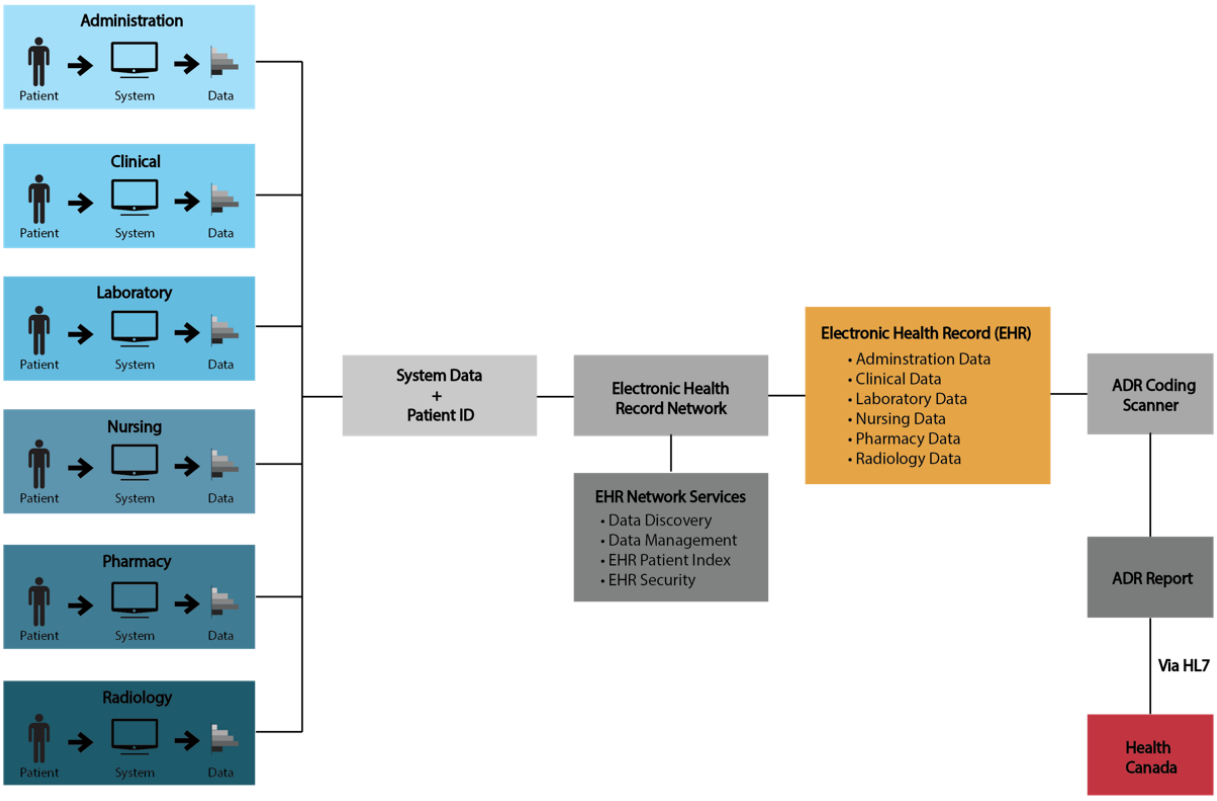

Figure 1

Electronic Health Record and automated ADR reporting system interoperation. This model illustrates the potential interactions of a proposed informatics system (adapted from lecture on Electronic Health Record, 30 September, 2011).

codes could then be analyzed by an informatics system in order to recognize adverse drug reactions and further trend them based upon age, ethnicity and sex (Tsang, Majeed, Banarsee, Gnani, & Aylin, 2010).

While the system observed in Brent was not specifically used for adverse drug reaction reporting to a government authority, it was able to use procedural codes and classifications in order to recognize adverse reactions in an electronic information setting. A system such as this, once refined, could potentially act as a solution to under-reporting of ADRs.

The Electronic Health Record (EHR) provides an opportunity for the implementation of an automated adverse drug reaction reporting system. Defined by the Government of Canada as "secure and private lifetime record that describe[s] a person's health history and care," their implementation is currently a pan-Canadian initiative, with all provinces having established at least one core EHR system (Office of the Auditor General of Canada, 2010).

Through the usage of standardized vocabularies, clinical systems such as an automated reporting system and an EHR are able to interoperate in a meaningful way. The Systemized Nomenclature of Medicine Clinical Terms (SNOMED-CT) is currently used as a standard for clinical terminology, and is seen as a first choice due to its comprehensive clinical terminology system (Héja, Surján, & Varga, 2008). Another medical classification currently used in Canada is the ICD-10-CA, a coding system that permits coding of signs, symptoms, abnormal finds, causes of disease and most importantly under our circumstances – adverse effects of drugs in therapeutic use (Canadian Institute for Health Information, 2009). The use and implementation of vocabularies such as these, would allow ease of automated reporting across multiple systems.

Figure 1 demonstrates a model of the proposed automated adverse drug reaction reporting system. It can clearly be seen through the model that this system works very closely with the EHR. Once information is compiled from all regions of a healthcare setting as seen on the left of the model, an electronic health record is created. This allows simplified access by health care professionals to the most current and widespread patient clinical data. Furthermore, this data is coded using terminology from standard nomenclature or structured vocabulary including, but not limited to, SNOMED-CT and ICD-10-CA.

In order to classify an adverse drug reaction, SNOMED-CT uses the term "adverse reaction to drug (disorder)," and labels it with the Concept ID: 62014003 and SNOMEDID: DF-10010. Under this grouping, adverse drug effect, adverse drug reaction and ADR are also classified (International Health Terminology Standards Development Organization, 2008).

The ICD-10-CA classification system, like SNOMED-CT, also uses codes in order to establish a classification. "Drugs, medicaments and biological substances causing adverse effects in therapeutic use" are classified under the codes Y40-Y59 (Canadian Institute for Health Information, 2009, p. XX-89). Furthermore, the code T88.7 classifies "unspecified adverse effect[s] of drug[s] or medicament[s]" (p. XIX-130).

While cross mapping exists between SNOMED-CT and ICD-10-CM, it does not yet exist for ICD-10-CA (Canada Health Infoway, 2013b). Thus, the proposed automated reporting system would be required to scan the electronic health record for both SNOMED-CT and ICD-10-CA codes related to adverse drug reactions.

Once the aforementioned scan is completed by the automated system, it would either flag an electronic health record as being ADR-positive or ADR-negative. ADR-positive results, results containing one or more adverse drug reactions, would then be flagged for conversion of relevant information into an ADR report. A copy of the current Health Canada adverse reaction reporting form can be found at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/report-declaration/ar-ei_cons_form-eng.pdf . Reports include information such as age, sex, health outcomes, drug prescriptions and treatment – all of which can be found in an electronic health record. Procedure codes such as ICD-10-CA and SNOMED-CT would be used to scan and extract this information into meaningful and complete reports.

Upon creation, these reports would be automatically sent to Health Canada using Health Level 7 (HL7). This international set of open standards allows automatic communication between health systems developed independently (Coeira, 2003). In our case the systems communicating would be the Electronic Health Record based adverse reaction report and the adverse reaction database in place at Health Canada, which would be receiving the reports. Through the implementation of Health Level 7 based intersystem communication, labor and time involved negotiat-

ing application-to-application interfaces would be reduced, along with the elimination of the need for custom developed programming and interface maintenance (Canada Health Infoway, 2013a). With infrastructure already in place at Health Canada to deal with incoming ADR reports, there is no need for any additional elements to the system. This proposed solution is not only simple in concept, but is able to deliver results in harmony with existing medical information technologies.

Since EHRs are not in place across all health care facilities in Canada, it must be understood that this system cannot be implemented throughout the country immediately. As EHR utilization across the country develops, so would the proposed automated adverse reaction reporting system. The first step is to implement the system into current EHR -based set ups such as Alberta Netcare, in order to serve as a model for other provinces (Graham et al., 2008). This implementation would then serve as pilot study for further expansion and development.

While the use of electronic health records is limited under privacy laws, precedent already exists in which they have been used for research purposes (Hodge, Gostin, & Jacobson, 1999). The Electronic Primary Care Research Network, being an example, enables healthcare institutions to safely transfer information such as EHRs (University of Minnesota, 2010). Furthermore, EHRs contain a unique patient identifier that is unidentifiable outside the organization in which it serves, thus alleviating ethical issues such as privacy of information.

As mentioned previously, Health Canada currently provides feedback regarding ADRs to healthcare professionals through the Canadian Adverse Reaction Newsletter, eNotices and the Canada Vigilance Database. Feedback from regulatory agencies plays a crucial role in the reduction of adverse reactions, especially in those related to concomitant drug use and serious adverse reactions (Brewer & Colditz, 1999). A study in Germany conducted by *Pharmacoepidemiology and Drug Safety* found that adverse drug reactions resulted in direct costs of over 740 million dollars, assuming that ADRs were responsible for 5.8% of hospital admissions. With 30% of ADRs deemed to be preventable through mechanisms such as monitoring, reporting and feedback systems, potential savings of just fewer than 250 million dollars are displayed (Rottenkobler et al., 2011). While the entirety of these savings cannot be attributed to an automated reporting system, it goes to show the potential for economic savings after the implementation of such a system.

Conclusion

While a voluntary adverse drug reaction reporting system, such as that currently in place in Canada, is cost-efficient, it is not effective and does not accurately represent ADRs experienced by Canadians consumers, health professionals and market authorization holders alike. Under-reporting of ADRs due to voluntary systems has been exhibited in Canada, as well as other countries across the globe.

The implementation of an automated adverse drug reaction reporting system would not only provide Health Canada with more representative data, but brings with it increased health and safety to Canadians and vast economic benefits. Unlike campaigns focused on change in habits of the physician to eradicate ignorance, diffidence and lethargy, this system achieves a solution without new legislation or behavioral change.

Although an automated reporting system will not be introduced and deemed effective overnight, its development and gradual implementation is a step towards an informatics solution. Once integrated with widespread electronic medical records, it will provide health administrators and regulators a powerful tool leading to a healthier future for Canadians.

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Access to Maternal Health Care for Native Canadians on Reserves in Northern Canada

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Résumé :

(traduction)

L'historique de violence et d'isolement des populations autochtones du Canada a créé un écart dans les soins de santé maternelle, entraînant des taux de mortalité infantile (TMI) de 12 décès pour 1000 naissances pour les populations des réserves par rapport à 5,8 décès pour 1000 naissances pour la population canadienne en général. Cet écart est considéré comme un sérieux enjeu de santé des populations puisque les Autochtones, qui représentent environ 3% de la population canadienne, ont des taux de mortalité infantile similaires à des pays du « tiers monde ». Actuellement, il existe de multiples organisations gouvernementales et non-gouvernementales en charge de la prestation des soins de santé maternelle auprès des populations des réserves. L'absence d'un système de communication unifié reliant ces organisations entre elles provoque des lacunes importantes dans la prestation de services de soins et compromet les soins prénataux chez les Canadiens autochtones. La méthode actuelle de prise en charge des grossesses à haut risque dans les réserves du Nord canadien consiste à transporter par voie aérienne les mères depuis leur communauté d'origine jusqu'à un hôpital qui se trouve être à la fois loin de leur famille et complètement étranger pour elles. Cette pratique contraste avec les normes culturelles de la population autochtone du Canada où les femmes reçoivent normalement des soins prénataux dispensés par des femmes plus âgées au sein de leur communauté. De nouveaux modèles de soins, dans lesquels les sages-femmes sont les principales dispensatrices de soins prénataux au sein d'une communauté donnée, ont récemment été mis en œuvre dans le nord du Québec et dans d'autres régions isolées du Canada. Les sages-femmes travaillent avec les aînées de la communauté pour fournir un système complet de soins de santé maternelle. Ces nouveaux modèles sont très prometteurs quant à l'amélioration de notre système actuel de soins de santé maternelle pour les Canadiens autochtones en fournissant des soins prénataux potentiellement plus efficaces et plus accessibles tout en intégrant les normes culturelles des communautés.

Mots-clés :

Santé maternelle, Autochtones canadiens, réserves Autochtones, programmes prénataux, santé Autochtone

Abstract:

The history of abuse and isolation of Native Canadian populations has created a gap in maternal health care, resulting in infant mortality rates (IMRs) of 12 per 1000 births for on-reserve populations compared to 5.8 per 1000 births for the general Canadian population. This discrepancy is deemed a population health issue, as Native Canadian people constitute roughly 3% of the Canadian population, but have infant mortality rates similar to other third world countries.

Currently, there are multiple government and non-government organizations in charge of providing maternal health care for on-reserve populations. A lack of a unified communication system linking these organizations creates a gap in the delivery of services and compromises the prenatal care in Native Canadians. The current method of caring for high risk pregnancies on Northern Canadian reserves is to fly the mothers out of their home community to a hospital that is both far away from their families and completely foreign to them. This practice contrasts with the cultural norms of the Native Canadian population, where expecting women receive antenatal care from elder women within their community. New models of care, in which midwives are the primary providers of antenatal care within a given community, have recently been implemented in Northern Quebec and other isolated areas of Canada. The midwives work with women elders of the community to provide a full system of maternal care. These new models show great promise in improving our current system of maternal health care for Native Canadians by providing more efficient and accessible antenatal care while also incorporating cultural norms of the communities.

Keywords: Maternal health, Native Canadians, Aboriginal reserves, prenatal programs, Aboriginal health

Introduction

The current practice in maternal health care for on-reserve Native Canadian populations (ORNCs) is rooted in the history of the community and the key decision makers involved in health care structuring. Historically, in native communities, the Canadian government has provided universal health care since the late 1960s; however, due to inefficiencies in its delivery and internal colonization of Native Canadian populations, there has been an ever-widening gap between the health care services provided on -reserve and off-reserve (Adelson, 2005).

The internal colonization of Native Canadian populations, defined as the encroachment and subjugation of Aboriginal people since the arrival of Europeans has isolated these populations from political focus, which has resulted in less access to health care funding and services offered to the general population (Adelson, 2005). These political and economic disadvantages are part of the long-standing history of European settlement in Canada. The movement of Native Canadians to onto reserves, the abuse of students in residential schools, and the neglect of the federal government to provide adequate and effective health care have further amplified the health disparities for Native Canadian populations (Adelson, 2005).

According to Smith (2003), current Canadian maternal health practice says that a native Canadian woman nearing the end of gestation must be transferred to Southern Canada to ensure a medically safe birth. This means that pregnant women are absent from their family and community to give birth in unfamiliar environments with no social support network (Smith, 2003). Up to 40% of women on-reserve in Northern communities travel more than 100 km to give birth, and 77% of these women were also away from their community overnight for the first time (Butler-Jones, 2009).

According to Smith (2003), remote Northern Canadian communities are strained by a shortage of resources, especially qualified human resources or health care professionals. In many isolated communities, the medical staff turnover rate is over 40% during an 18-month period, and over 50% of positions are persistently vacant. Due to the strain put on the existing staff, emergency care is the priority among health care providers. With the resources to only provide emergency care, other areas of medicine such as health promotion and prevention are neglected and comprehensive maternal care may not be provided (Smith, 2003).

Population Health Issues

Statistics Canada data show that roughly one million people (3% of the population) in Canada identify themselves as Native Canadian, including First Nations, Métis and Inuit peoples (Statistics Canada, 2008). This number is thought to be an underestimate since many individuals, especially in more remote areas of the country, do not report their ethnic status to Statistics Canada. This visible minority group constitutes a significant portion of the Canadian population and their poor health status produces a substantial problem for the nation's health care system (Adelson, 2005).

In maternal health, infant mortality rate (IMR) is a universally accurate and reliable indicator of the country's current maternal health status. The on-reserve IMR is 12 per 1000 as compared to 5.8 per 1000 in the general populations (Smith, 2003). This twofold difference between on-reserve and general population IMR has been consistent over two decades, with no reduction in the IMR between the populations. As the IMR is a widely used indicator for the health status of a population, the great difference in rates between the general Canadian population and on-reserve populations point to a lack of access for maternal care on-reserve (Smylie, Fell, & Ohlsson, 2010).

The isolation of Northern reserves, limited access to maternal care, and great distances travelled to give birth all contribute to an IMR that is more than double that of the rest of Canada. Barriers to easily accessible maternal care is thus a significant population health concern and should be addressed by the federal government, a key organization charged with providing care to on-reserve Native Canadian women.

Key Drivers of the Issue

The First Nations and Inuit Health Branch (FNIHB) of Health Canada is the main organization responsible for providing health care to on-reserve populations. The Native Canadian populations have requested an autonomous, locally accountable system of health care delivery body that would be separate from the federal government. This re-

quest has been denied based on the Indian Act of 1876, which was amended in 1939. The Indian Act is a treaty that was signed by both parties to define the governance of Native Canadians. This act placed Native Canadians under the control of the federal government of Canada and did not leave room for self-governance. As a result, the current health care system for Native Canadians is fragmented between many different governing bodies (Adelson, 2005).

There are multiple government agencies that directly or indirectly target maternal health for on-reserve women in Canada: Human Resources Development Canada, Indian and Northern Affairs Canada, local Native Canadian governments, and the FNIHB of Health Canada. As a result of these independent governing bodies, there is a lack of unified communication between maternal health programs. This disconnect of communication between organizations creates inconsistencies in program governance and duplication or neglect of certain health care coverage may occur. The lack of a coherent, integrated health network slows down and ultimately prevents the process of improvement for maternal health coverage on-reserves (Smith & Davis, 2006).

Potential Solutions and Barriers

According to O'Driscoll et al. (2011), Native Canadian women who give birth and raise a family are viewed as community leaders and are expected to pass down their knowledge of birthing and mothering to the younger generation of women. Most girls living on reserves learn how to care for themselves and their future families from elder women and extended family in their communities. However, the current maternal health system isolates some women from their families during birth, depriving them of the social support and maternal education that their elders can provide.

Programs on the Northern Quebec Inuit reserve of Povungnituk have combined traditional birthing methods with safe modern practices of birthing to improve the overall maternal health of women in their community. The programs aim to put the responsibility of women's health care services into the hands of fellow Inuit women. Female elders are recruited from the community and trained to work in collaboration with midwives trained in modern birthing techniques. This model of providing culturally sensitive and safe care in the community reduces the need to transport pregnant women out of the community to a hospital (Smith, 2003).

According to Miller et al. (2012), evidence shows that maternal outcomes are better when women do not have to travel away from their community but are provided care through an integrated antenatal care system. Training programs that are offered in the community and combine modern birthing techniques with traditional Native Canadian healing techniques are ideal models of integrated antenatal care. The combination of the two health care approaches encourages cultural sensitivity and can greatly improve access to maternal health care on isolated reserves. In 2008, the Nunavut Arctic College was one of the first programs in the Northern Territories to graduate midwifes who were trained under a curriculum partially designed by local Elders and containing a traditional component. This program regularly includes traditional midwives in seminars and develops a connection with the communities to incorporate a cultural component to their training in midwifery (Stout & Harp, 2009).

The collaboration of traditional and modern practices addresses many of the issues associated with current birthing practices on reserves. This collaborative approach allows the women to give birth in their community where their family and support network can assist alongside health care professionals. Their social and emotional needs can be met within the social network of their community. This collaborative model creates less of a need for relocation to southern Canada to give birth in an unfamiliar environment and that community support has been shown to improve maternal outcomes (Miller et al., 2012).

The collaborative model is an ideal system for providing high quality maternal care to Native Canadian women in isolated regions of Canada. The various agencies and organizations that are in charge of providing maternal health services to women on-reserve should address the various barriers of improved access to these services. The FNIHB of Health Canada should take the lead to implement a unified system of communication between the different federal government departments that directly or indirectly influence provision of maternal care so that more efficient programs are provided. With on-reserve, culturally sensitive maternal health care the discrepancy in maternal mortality rates between on-reserve and off-reserve populations can be bridged which leads to improved maternal health outcomes. On a population health level, improved care for on-reserve Native Canadians reduces the health inequities that

are perpetuated by the remoteness of many Northern Canadian communities.

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Commentary: Obamacare and American National Identity

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On March 23, 2010, US President Barack Obama signed into law the Patient Protection and Affordable Care Act (PPACA) (United States of America, 2010), commonly called "Obamacare." Representing the most significant revision of the American health care system in over four decades, PPACA is aimed primarily at decreasing the number of uninsured Americans and reducing the overall out-of-pocket costs of individual health care.

The Act has been characterized by its opponents as an American version of socialized medicine (Faria, 2012). Generally defined as a system of medical care that is publicly financed and government administered, socialized medicine manifests in a variety of forms around the world. American experiences with it include the Veterans Health Administration, the military health care system, and the Indian Health Service, to the extent that these services are government-administered care, albeit reserved for a specialized demographic in each case (Boffey, 2007). In addition, Medicare and Medicaid are forms of publicly funded health services, though the individual shares some degree of cost.

In a sense, the adoption of PPACA constitutes a national paradigm shift in American culture. Long self-characterized as a society of rugged individualists, the USA has put forth a public face of risk-taking and the acceptance of individual responsibility for individual lifestyle choices, however unhealthy those choices might be. Described by some as a mythic identity, the extent to which this characterization is seated in reality is open to debate (McDonald, 2010). But its prevalence in American media, art, and expressions of nationalism suggest a strong vein of symbolic individualism that percolates through Americans' values and self-perception (Harms, 2007). It is therefore not surprising that the opposition to PPACA came from Republicans, whose public values espoused extreme versions of the individualistic motif, including a minimal governmental role in public life, looser firearm regulations, and greater freedom from state-directed education.

With the advent of PPACA, it will be interesting to see the extent to which American self-identification with individualistic values may diminish. In a society with socialized medicine, it quickly becomes apparent that individual actions have a direct impact on the wherewithal of the group, usually through finances. If population health costs, as reflected through either taxation or individual co-payments, are responsive to the perturbations of individual extremes, then a minority's decision to engage in risky behaviours may affect the affordability of health care for the greater population.

Some of the more obvious examples of where this conflict in values may arise include attitudes around smoking and helmet wearing. Presently, laws requiring all motorcycle riders to wear helmets are in place in 19 states and the District of Columbia, while 28 states require some motorcyclists to wear helmets; and three states (Illinois, Iowa, and New Hampshire) have no helmet laws whatsoever (Insurance Institute for Highway Safety, 2013). If, in those latter states in particular, serious head accidents related to a failure to use helmets results in a measurable financial burden on the new public health insurance plan, it will be interesting to note whether political and social pressure will be applied to legislators to enact strict helmet laws.

Currently, nine states have bans on smoking in restaurants, bars, or non-hospitality workplaces (Wikipedia, 2013). Arguments for restricting public smoking range from comfort to individual health to public health. Under PPACA and the possibility that public health may be perceived to migrate from a state responsibility to a public responsibility, there may evolve a greater push to enact public smoking bans under the banner of cost control, as lessened exposure to tobacco products may minimize claims on the public health insurance system. It is commonly noted that the overall economic costs to the US economy are over $50 billion annually (Morreale, 1998). However, health costs are actually lower, since smokers have shortened lifespans (Morreale, 1998). That

may change if PPACA allows previously unaffordable extreme and costly end-of-life measures to be attempted on this population.

As Canadians have long noted, systematized health care can be intimately associated with national identity. The potential exists for "Obamacare" to contribute to the dynamic definition of American national identity, veering from its frontiersman iconography toward something more akin to a web of social responsibilities.

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The Ethics of Pre-implantation Genetic Diagnosis: An Opinion Piece Examining the Moral Distinction Between Positive and Negative Selection of Traits Using PGD

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Résumé :

(traduction)

Le diagnostic préimplantatoire (DPI) suit la fécondation *in vitro* (FIV) de plusieurs ovules. Dans ce cadre, la sélection négative (SN), ou le rejet d'embryons contenant des allèles indésirables, est actuellement une pratique courante dans les cliniques de FIV. La sélection positive (SP), quant à elle, est le rejet d'embryons qui *ne* contiennent *pas* un allèle désirable – en d'autres termes, la SP conserve un embryon car il renferme un profil génétique souhaitable.

De nombreux groupes sont en faveur de la SN, mais il y a beaucoup moins de partisans de la SP. La philosophie bio-conservatrice, dirigée par des philosophes tels que Leon Kass, s'oppose à la SP et au bio-libéralisme en général. À l'inverse, la SN (et SP) d'embryons résonne mieux avec la philosophie bio-libérale, plus précisément avec un sous-ensemble du bio-libéralisme appelé le « transhumanisme ».

Pour pouvoir considérer que la SN est moralement admissible et que la SP est moralement inacceptable, il faut soutenir sa position en faisant une distinction entre les deux types de sélection. Les réclamations majeures contre la SP comprennent le fait que ce n'est pas médicalement grave, qu'elle répand l'eugénisme, qu'elle propage la sélection du sexe et qu'elle suscite une aversion morale qui prouve son immoralité. Dans l'analyse de ces arguments, j'espère démontrer qu'aucun d'entre eux n'est cohérent dans leur application, et que leur incapacité à être appliqués de manière universelle mine leur propre cause.

Mots-clés :

N/A

Abstract:

Pre-implantation genetic diagnosis (PGD) follows *in vitro* fertilization (IVF) of several ova. Negative selection (NS), or the discarding of embryos containing undesirable alleles, is currently being performed in IVF clinics. Conversely, positive selection (PS) is the discarding of embryos that do *not* contain a desirable allele. In other words, PS keeps an embryo because it contains a desirable genetic profile.

There are many groups that support NS but there are far fewer who support PS. The bioconservative philosophy, led by philosophers such as Leon Kass, opposes PS and bioliberalism in general. Conversely, NS (and PS) of embryos resonates best of all with the bioliberalism philosophy. More specifically, a subset of bioliberalism, called transhumanism.

In order to find NS morally permissible and PS morally unacceptable, one must support one's position by making a moral distinction between the two types of selection.

The major claims against PS include that it is not medically serious, that it propagates eugenics, that it propagates sex selection and that it elicits a moral repugnance which proves its immorality. In analyzing these arguments, I hope to show that none of them are consistent in their application, and that their inability to be applied universally significantly weakens their case.

Keywords: N/A

Introduction to Pre-implantation Genetic Diagnosis and its Uses

Pre-implantation genetic diagnosis (PGD) follows *in vitro* fertilization (IVF) of several ova[1]. Negative selection (NS), or the discarding of embryos containing undesirable alleles[2], is currently being performed in IVF clinics (Purdy, 1996). Conversely, positive selection (PS) is the act of selecting embryos because they *do* contain desirable alleles. In other words, PS keeps an embryo because it contains a desirable genetic profile[3].

I will begin by presenting a summary of the support for NS, which is widely accepted for diseases such as Huntington's (Abraham, 2012; Glover, 1984). As far as severely painful diseases go, or those that give the infant a very low life expectancy, NS is an attractive technology, even surviving the abortion debate as some anti-abortionists condone its use[4]. NS of embryos is also attractive to supporters of Judith Jarvis Thomson's autonomy-based philosophy[5] (Thompson, 1971). If this is true, NS simply allows parents to exercise their autonomy if they decide that they are not prepared to raise a child with a debilitating or life threatening genetic condition. Utilitarian philosophers such as Peter Singer would offer a third rationale for supporting NS of embryos[6] (Singer, 1974). In that light, it may be beneficial to the world as a whole (or the sum of the world's persons) to refrain from bringing more children into the world who will live in pain and/or psychological distress (Purdy, 1996), who will require very costly treatments that put a strain on the health care system, and who will have lower utility in society. It is likely that the NS (and PS) of embryos resonates best of all with the bioliberalism philosophy; more specifically, a subset of bioliberalism, called transhumanism[7]. Transhumanists argue that genetic selection of embryos could benefit the future individual by improving physical wellbeing, intelligence, emotional stability and resiliency to stressors. To a transhumanist, the failure to use such technologies would be a failure to move humanity forward (Roache & Clarke, 2009).

Overall, the numerous philosophies that permit the NS of embryos containing several disease genes seem to be supported and put to practice by Canadian society[8] (Abraham, 2012). Of course, it does not follow that widespread desire for PS will necessarily drive its global acceptance[9] (Abraham, 2012). The bioconservative philosophy, led by philosophers such as Leon Kass, opposes PS and bioliberalism in general. There is also continual opposition against all forms of PGD – and IVF in general – from those who believe that embryos have a right to life[10]. I will not get into that particular debate in this essay. As we will see, there are many lines of opposition to PS from outside the anti-abortionist philosophy. My interest here is the distinctive line that may or may not be drawn between different forms of embryo selection using PGD (which IVF). For ease of discussion, it will be assumed that embryos are not persons and have no right to life.

From here, I would like to address the following questions within the context of PGD. There are many groups that support NS, but far fewer who support PS as well (Roache & Clarke, 2009; Bostrom & Savulescu, 2008). In order to find NS morally permissible and PS morally unacceptable, one must support one's position by making a moral distinction between the two types of selection. I will make the claim that the majority of such arguments are weak, and do not make a satisfactory case against PS. If there is no satisfactory argument to morally differentiate NS from PS, I would argue that in accepting the former, we must also accept the latter. To begin, I would like to address several arguments made against PS by supporters of NS. In order to hold PS impermissible while NS permissible, they must create a morally relevant distinction between PS and NS. Either PS must possess some morally relevant element that NS does not, or vice versa. In analyzing these arguments, I hope to show that none of them are consistent in their application to real-life situations, and that their inability to be applied universally significantly weakens their case.

Argument 1 – NS is always to avoid medically serious traits, while PS focuses on genes for trivial traits:

The 'medical seriousness' argument refers to the application of NS only to embryos containing a dangerous, debilitating, or pain-causing gene. The problem with PS is that its focus is on genes for traits that are not medically serious or dangerous (Glover, 1984). This results in the creation 'designer babies' because there is picking and choosing of non-critical, also called 'trivial' traits. Proponents of this claim are religious bodies, geneticists, and physicians who believe that removing life-threatening genes is the moral limit for PGD application (Abraham, 2012).

This claim is too narrow. There are as many trivial or designer traits that could undergo NS as there are those that are medically serious. If the presence of a gene coding for

shortness, dark hair, brown eyes or creative intelligence (versus mathematics/logical intelligence) causes an embryo to be discarded, then this is no doubt an example of NS being used for 'trivial' traits. Consider some less extreme trait examples that are already undergoing NS in some fertility clinics. Genes for psoriasis, albinism, cleft palate, none of which are life threatening, are some examples of genes that undergo NS by parents (Abraham, 2012). Although perhaps less trivial than height, can these traits be considered medically serious? Moreover, there may be 'serious' traits that, upon closer consideration, actually require PS. Consider a rare gene allele that makes one immune to an infectious disease: malaria, tuberculosis or influenza. Would PS of such a trait not be on equally medically serious grounds as NS of a gene for Huntingon's? The answer is clearly "yes."

If we accept that some traits, possessing some degree of triviality, may undergo NS, then the medical seriousness claim is moot. Similarly, if some traits possessing some degree of seriousness can be accomplished using PS then the medical seriousness claim is also moot. A distinction between NS and PS is inadequate because we cannot be sure that only serious traits will require NS and only trivial ones will require PS. If the medical seriousness claim is moot, then for the remainder of this essay I will abandon the NS/PS distinction altogether and focus on the more relevant distinction: "serious" selection using PGD which I will refer to as genetic therapy (GT), and 'trivial' selection using PGD, which I will refer to as genetic enhancement (GE).

Argument 2 – GT is the progression of medicine. GE is eugenics, and eugenics is wrong, as exemplified by the early 20th century eugenics movement and Nazi Germany:

It is true that very serious infringements of human rights have been committed in the name of eugenics. The eugenics movement of the early 20th century saw massive sterilization of disabled persons in North America and Europe. Nazi Germany saw the murder of millions of 'inferior' citizens: the old, disabled, homosexuals, Jews and other minorities (Bostrom, 2005). Those who support GT and wish to differentiate between GT and GE often invoke the history of eugenics. They seek to make connections between GE and the eugenic practices of Nazi Germany: if GE belongs in the category of eugenics, and all eugenics is immoral, then GE is immoral. However, I disagree with the 'eugenics' claim and would assert that just because there are *some* applications of eugenics that are morally wrong, it doesn't mean that *all* applications, including GE, are morally wrong. I will try to differentiate GE from historical eugenics by pointing to a number of differences.

Arthur Caplan *et al.* (1999) delineate three distinguishing factors between 'Nazi-style' eugenics and GE. The first is coercion, which manifests itself in two immoral ways. In both the 20th century and specifically, the Nazi eugenics practices, an overruling regime decided which phenotype was desirable and which was not. Those possessing an undesirable trait were sterilized or killed, both of which satisfied the eugenic principle of eliminating undesirable genes from the population (Caplan, McGee, & Magnus, 1999). The first aspect of coercion is that all those under that regime were subjected to the same discrimination framework, which was not decided by the citizens but by the regime rulers. The second aspect of coercion was that the application of eugenics was a massive violation of a person's rights: the right to reproductive autonomy (in the case of sterilization) and the right to life (in the case of the murders). However, neither of these coercive phenomena need be present with the application of GE. Each set of parents will determine, on their own, if and how to discriminate between desirable and undesirable traits, and no person's rights will be infringed upon if embryos that don't possess desirable traits are killed (Glover, 1984). Instead, parents will simply be exercising their reproductive autonomy by choosing whatever qualities they wish to have in their offspring[11] (Glover, 1984).

This is the second distinguishing factor of GE proposed by Caplan *et al.* (1999), which is the absence of 'subjective perfection' or a single ideal human form. This factor is similar to that of the first manifestation of coercion mentioned above, but it does not require a state to *impose* the 'subjective perfection' standard. Instead, it is simply the *presence* of such a homogenous standard. In Nazi Germany, for example, the homogenous standard for perfection was the 'Aryan race': Caucasian, blonde and blue eyed. GE however, would accommodate a myriad of different desirable traits if available worldwide. Some of these traits may be concentrated in some regions, as different cultures may traditionally value different characteristics, and there may be some prevailing tendencies in a given decade (Glover, 1984). These culture-related preferences, however, are already being selected for. Selection of preferred traits is not something owed only to PGD; conversely, peo-

ple have long been choosing their mates based on biological or societal fitness characteristics. In this light, there is no comparison between Nazi-style eugenics, which aimed to homogenize the population to fit one subjective standard and GE to satisfy individual reproductive choice.

I recognize that with increased abilities to exercise reproductive choice come certain stipulations. Imagine a cult who desired to distinguish themselves by having children who all had a serious physical disability. GE for such traits would jeopardize the child's wellbeing and quality of life, and even subject him or her to discrimination (Glover, 1984). If children are protected from parental cruelty after they are born, should they not also have such protection before they yet exist? As with other policies currently in place to protect unborn children from parental abuse, such as restrictions on abusive first names, policy can and should be implemented to reflect an appropriate spectrum of GE outcomes in a given political system (Glover, 1984). It does not follow, however, that the need for regulation of a technology makes such a technology immoral. The crucial distinction between regulated GE and Nazi-style eugenics is, again, that coercion is absent in the former and central to the latter. As long as parents have the choice to opt in or opt out of PGD, human rights have not been infringed upon.

Another argument against GE focuses on the implications of enhancement in a more objective sense. It goes as follows: instead of the array of subjective traits produced by reproductive choice, selection for objective traits such as intelligence, athleticism, or memory will produce homogeny among the enhanced population, resulting in an 'overclass' (Caplan et al., 1999). GE will give advantages to those people who had rich enough parents to afford it. Inequality is immoral; therefore, GE is immoral. I agree that inequality is immoral, but such an argument falls prey to inconsistencies because children whose parents can afford many other things (good food, comfortable living, health care, private schools, university education) are also given unequal advantages over others. What is highlighted by this argument and its inconsistencies is that socioeconomic disparity is a major issue in societies; both in the developing and developed world (Caplan et al., 1999). This indeed results in inequality in children's futures, and I recognize that this is a major problem, but not one that can be blamed solely on PGD. If one is concerned with preserving equality, then one can start by providing all parents equal access to resources for their children. If GE becomes a reality, then equality could continue to be preserved by providing it to all parents who desire it. As Caplan *et al.* (1999) describe, the bottom line is providing additional development and educational resources to make up for "differences in biological endowment" (Caplan et al., 1999, p. 337), whether genetically derived or not. This illustrates his third distinguishing factor: GE need not create inequality the way that Nazi-style eugenics did (Caplan et al., 1999). Rather, inequality should be looked at as a separate issue, one that will have negative consequences on society that are more far-reaching than in the context of GE (Caplan et al., 1999).

It seems that, upon closer inspection, that co-classification of Nazi-style eugenics and GE cannot rely on three immoral characteristics of historical eugenics: coercion, subjective definition of perfection, and inequality, as none of these three apply to GE. It also seems then, that historical examples of eugenics and eugenics derived from GE cannot be equated. This opens the possibility that, while eugenics such as the historical examples provided is definitely immoral, GE may not be. If other appeals are necessary to make a convincing argument that all eugenics is immoral, then GT advocates can no longer use the 'eugenics' claim to try and morally differentiate GT from GE. Thus, we continue the debate from the end of the second claim.

Argument 3 – GE is wrong because it will perpetuate the immoral practice of sex selection:

Perhaps the fiercest debate surrounding GE concerns the alleged danger that sex selection will perpetuate gender imbalance and subjugation of women. Those who oppose GE on the grounds that sex selection is immoral often point to Asian countries to exemplify the negative consequences that stem from reproductive power over gender (Savulescu, 1999; Ganatra, 2008). Late abortions and infanticide of female offspring are seen as cruel practices for they kill unjustly – solely based on sex (Ganatra, 2008). Abandonment, neglect or simply discarding the child at an orphanage are very much immoral and grave consequences of gender discrimination (Ganatra, 2008).

The issue I take with the 'sex selection' claim, based on the perpetuation of cruelty, is that it is not clear to me how *cruelty* itself would increase as a result of GE. Allowing PGD could actually decrease the frequency of such cruel practices. If parents could select the sex of a desired offspring before implantation, they would not have to resort to often unsafe abortions (Ganatra, 2008), infanticide or

abandonment. Fewer rights would be infringed upon, as the embryo is a non-person in this debate, and fewer children would be destined to grow up in destitution as a result of their gender.

Of course, removing the more cruel practices associated with gender discrimination does not remove the discrimination itself; parents will still be subjectively choosing one gender over another. This type of discrimination, similar to discrimination based on race and disability, runs deep in many societies. Despite continuous global efforts to change people's mentalities on race and gender, we are debatably still close to the beginning of the long road to equality ("Women in the Workforce", 2009). If we are faced with the reality that, at least for the time being, such sexist mentalities prevail in the world, is it not our duty to minimize the casualties?[12]

Another issue I take with the sex selection claim is that it over-generalizes parents' intentions. Certainly, areas of the world such as China and India do show gender discrimination, but this does not necessarily apply everywhere (Savulescu, 1999). One study found that just over half of the parents who underwent sex selection during PGD in the US and the UK opted for girls (Savulescu, 1999). Another found that most Canadian parents actually chose girls (Savulescu, 1999). Perhaps most encouraging is that 90% of American sex-selecting couples chose the gender that would balance the sex ratio between their offspring (Savulescu, 1999). It seems that such scenarios are unlikely to result in the human rights abuses discussed previously and that GE may not produce or exacerbate unhealthy parenting choices about sex.

In countries such as Canada, where an increasing percentage of the population is made up of South and East-Asian immigrants, there has been debate over whether cultural gender discrimination will threaten the balanced gender selection that has been recorded (Vogel, 2012). Statistics from highly concentrated South and East-Asian immigrant communities in various Canadian cities show a significant imbalance in the offspring gender ratio – and the suggested mode of sex selection is abortion (Vogel, 2012). Does this mean that, due to our large influx of immigrants, that PGD will be increasingly exploited for sex selection, and is thus to be prevented from being applied altogether? First of all, PGD would remove the female feticide practices and replace them with safer, earlier termination of embryos (see earlier discussion on casualties). Second of all, such an assumption discredits the education and open-mindedness of the second and third generations – the children of first-generation immigrants. These children will enter the Canadian school system, many will pursue college or university degrees, and will be exposed to direct and indirect education about gender roles, gender equality, human rights, and social structure as it is in Canada. To assume that all these children will preserve the sexist values of their parents is insulting, and untrue. Even if a boy is still desired, better socioeconomic conditions combined with PGD could mean that parents can select a boy, and be able to afford having another child – boy or girl – as well.

One Canadian case highlights an interesting biological limitation to sex selection using PGD. One Canadian mother, who underwent IVF with the hopes of producing a fifth-generation namesake for her husband, was told that all her healthy embryos were female (Abraham, 2012). This can be related back to the concern about East-Asian sex selection: instead of blindly trying to produce a boy and disposing of an undesirable girl in a number of very cruel ways, parents could be told their options before undergoing implantation and gestation. If they know that their only chance of having a healthy child means that it will be female, then they can decide against conception altogether or make the decision to keep a female embryo. I believe that, psychologically, the act of consciously choosing a girl may foster a more healthy perspective of the coming baby, and result in better parenting and care for girls.

In light of these arguments, it seems that the only thing accomplished by sex selection is giving parents more freedom to choose which children they will have at an earlier stage. At the very least, GE would make it possible to eliminate the cruel practices associated with sex selection today and allow parents a safe and humane way to opt out of bringing a pregnancy to term if their healthy embryos do not include a given sex. As seen with the American statistic stated above, it is possible that in some parts of the world, sex selection may actually work towards equalizing the gender ratio (Abraham, 2012). It is unclear to me, therefore, how GE would necessitate any cruelty or rights abuse practices related to sex selection, nor how it would exacerbate sex selection where it already exists, nor again how it would produce gender imbalance.

Argument 4 – GE is wrong. Our intuition tells us so, because human enhancement is repugnant to us:

There are certainly many cases in which humans use some innate feeling, or intuition, to guide their moral thoughts and practices. There are certain things that most people will inherently feel good about and other things that will induce the so-called 'yuck factor' (Bostrom, 2005). This intuitive moral repugnance is often activated in reaction to concepts such as rape, incest, pedophilia or torture (Bostrom, 2005). Bioconservative philosophers such as Leon Kass often invoke this moral repugnance as proof that GE is immoral (Roache & Clark, 2009). Thus, we find ourselves facing another claim against GE. This one seeks to identify negative intuitions as a morally relevant quality of human enhancement, in order to distinguish GE from GT.

In order to build an objection to the 'intuition' claim, I will make the following arguments: 1) intuitions about GE are inconsistent, 2) the bioconservative definition of the immoral element of repugnance is weak, and 3) in general, intuitions may be poor moral compasses.

If our moral repugnance of human enhancement is to carry moral weight, it should be trustworthy across all forms of GE; that is, all examples of congenital alteration of human phenotypes. Many forms of accepted human enhancement, such as those driven by social mating behaviours, *are* genetic in nature (Glover, 1985). Consider the forces that influence some people to have many offspring and others to have none (such as policies or culture) and those that drive sexual selection (who is an attractive mate and who is not). Both forces have an impact on whose genes get passed on and in which combination. In most countries, rich people can generally afford to have more children, and career-driven women often have fewer children ("Women in the Workforce", 2009), whether by choice or necessity. These practices do not elicit moral repugnance, yet they accomplish genetic enhancement. No one tries to prevent two smart people from choosing each other as mates, nor two blue-eyed people, nor two professional basketball players. Yet such selection can no doubt have the same outcome as enhancement using PGD; increasing the *probability* of achieving a particular trait (nature can only do so much by way of ensuring a given phenotype). To conclude, if one can engage in many forms of non-genetic *and* genetic human enhancement without an onslaught of negative moral intuitions then the immorality of GE using PGD based on intuition loses its logic. If our intuitions speak out against GE, then why don't they speak out against all over forms of genetic enhancement?

The inconsistencies that become obvious when the intuition claim is applied to GE are compounded by the weakness of the definition of moral repugnance itself. This is my second argument against the intuition claim. When asked to describe in analytical terms the 'wrongness' – that element that our intuition identifies and repulses – philosophers such as Kass counter that most of us cannot give "argument fully adequate to the horror" (Roache & Clark, 2009, p. 5) of acts like rape, incest, of pedophilia, yet it doesn't follow that our repugnance can therefore be dismissed as incorrect (Roache & Clark, 2009).

Martha Nussbaum critiques Kass' repugnance argument by pointing out that every example he gives involves repugnance *but also* harm to others. Rape and pedophilia violates one's right to consent, to sexual autonomy and to live violence-free, and incest is often both rape and pedophilia (Nussbaum, 2004). What we are really feeling in scenarios such as rape or pedophilia is the revulsion at the major breach of rights (Nussbaum, 2004).

What Kass fails to do is produce an example of something that 1) elicits repugnance, 2) is immoral, but 3) that does *not* violate someone's rights (Nussbaum, 2004). If he could do that, he could prove that repugnance *can* work as a moral compass independently from rights-based analyses. Instead, what Kass is doing is conflating repugnance in general with *rights-based intuition*.

To exemplify this, I offer the following two scenarios. The first considers incest, for example between a father and a daughter. Kass would say that our moral repugnance expresses the wisdom that incest is immoral. Nussbaum would say that incest is immoral because it is a violation of the daughter's rights. Now, imagine removing the rights violations by replacing the father-daughter couple with an adult, consenting brother-sister couple. Do we feel repulsed now? If yes, our repulsion cannot be due to a rights-based intuition (Nussbaum, 2004). It would need to be due to some general 'yuck factor', or as Nussbaum calls it, disgust (Nussbaum, 2004). For example, it could be because we are personally disgusted at the thought of being intimate with our own sibling. Alternately, many of us may feel significantly less repugnance to cases of brother-sister incest: as Nussbaum points out, consensual incest was rampant among historical royal families, yet we continue to celebrate them and cherish their legacies (Nussbaum, 2004). To conclude, in the case of incest, once rights violations are removed from a scenario and rights-based intuitions disappear, general repugnance (disgust) could still

exist, but for reasons other than immorality (Nussbaum, 2004).

My second example illustrates how general repugnance can be applied in morally irrelevant ways, thus distinguishing it even more from rights-based intuitions. Nussbaum asks us to consider our repugnance to things like feces, semen, or nasal mucous (Nussbaum, 2004). Does our repugnance signify that these things are violating someone's rights? More importantly, consider some people's repugnance to the "handicapped, the deformed, or the morbidly obese" (Nussbaum, 2004). Is their existence immoral? Does it violate anyone's rights? I believe that Nussbaum exposes a fatal implication of Kass' argument. Either repugnance is a completely useless moral compass and can *at most* supplement our rights-based intuitions, or our repugnance toward the handicapped is well-founded and they should receive moral and legal judgment similar to that of rapists and pedophiles.

To formulate my third opposition against the intuition claim, I echo Peter Singer, another opponent of Kass' repugnance argument, who proposes that reasoning should always win over intuition. Singer questions the validity of our intuitions in general on the basis that they, being inborn psychological reactions based on neurological pathways, are products of the evolution of our central nervous system (Roache & Clark, 2009). Selective pressures on our ancestors favoured repugnance to something like incest, says Singer, because the small social groups we lived in made inbreeding (and the resulting decrease in evolutionary fitness) a high probability unless it was consciously avoided (Roache & Clark, 2009). Roache and Clark (2009) build on Singer's postulate by suggesting that intuitions may have *some* value, but not when they are about something with which we have no experience or historical groundwork. Why are intuitions about novel circumstances untrustworthy? Firstly, we may be predisposed to doubt the morality of *all* new scientific advancements (Bostrom, 2005). Many of these predisposed moral doubts, as history shows us, were eventually dropped. As biochemist J.B.S. Haldane observed,

"The chemical or physical inventor is always a Prometheus. There is no great invention, from fire to flying, which has not been hailed as an insult to some god. But if every physical and chemical invention is a blasphemy, every biological invention is a perversion. There is hardly one which, of first being brought to the notice of an observer from any nation which has not previously heard of their existence, would not appear to him as indecent and unnatural" (Haldane, 1923).

In addition, it is certainly true that our early moral intuitions about the morality of issues pertaining to our social interactions or perceptions have proven to be wrong. Slavery, gender equality, gay marriage and interracial marriage were also, at one time, considered immoral (Nussbaum, 2004) – and unfortunately still are in some areas of the world. In light of these two arguments, it seems that GE may fit both descriptions: because it is a novel technology we may have a (possibly incorrect) predisposition to judge it, and because it pertains to human society and our perception of humanity our intuitions about its morality reflect a poor track record and are likely to be unsustainable. If all this is added to the proof that intuitions on this particular subject are fraught with inconsistencies (as shown earlier) and the reliance on repugnance a moral compass is largely useless, it seems that the intuition claim is a poor candidate to morally distinguish GE from GT.

Considerations of Human Virtue: An impasse, or a cautious way forward?

Negative selection is accepted on the basis of duty to prevent pain and suffering, and due to the moral rightness of practices, even those that are genetic, that restore baseline human functioning. Negative selection has subsequently been proven to be indistinguishable from positive selection on the basis that there are many serious traits that can be positively selected, and many trivial traits that can be negatively selected. Moving forward from the positive-negative debate, we can call the selection of all 'serious' traits GT, and the selection of all 'trivial' traits GE. The distinction between therapy and enhancement, however, is also difficult to make in any meaningful way. As we saw, there were a number of weak claims, that GE is either a purely selfish parental wish, a form of eugenics comparable to the Nazi regime, or an evil process that will perpetuate immoral sex selection, which do not hold true universally. In addition, we cannot rely on our intuitive repugnance to GE to guide debate of its morality.

Where does that leave us? Is bioconservatism a worthless philosophy when applied to GE by PGD? Are we to adopt the opposite view, transhumanism, and enforce all forms of GE using PGD? Before defending my own conclusions to this impasse, I would like to present one final argument made by bioconservatives. I believe this argument to be the

most important in influencing my conclusion because it shifts the perspective of the debate. Instead of assessing the objective morality of GE using PGD, it addresses the more subjective consideration that must be made of the moral agents who will be applying it. It also addresses the pervasive theme of regulation, and demonstrates how the need for regulation reflects the questionable morality of the *agents*, and not of the technology itself.

Much of the bioconservative philosophy, in addition to its concern with intuitive repugnance, attacks GE on the basis that it threatens a certain 'humanness', or human dignity (Bostrom & Savulescu, 2008; Vallor, 2009). Although the debate about human dignity is an interesting one, I have chosen not to include it in this essay. I have found that debates about human enhancement largely look beyond PGD, as germ line genetic alterations and human cloning become ever more tangible. The idea proposed by the bioconservatives that does influence PGD specifically, and which I think is relevant to the current debate, concerns not the process of GE itself, but the virtue of the moral agents who will be responsible for executing the enhancement. As Shannon Vallor describes, the bioconservative position rests in large part on a "deep uncertainty about the intellectual ability and moral will of today's humans to transform themselves wisely and well… do we today possess the extraordinary ambition, moral imagination and prudential insight needed to wisely and effectively implement such a radical program?" (Vallor, 2009, p. 41). The pessimistic answer, she says, is that our actions have proven that we are lacking the virtue to use technologies such as PGD in a moral way, regardless of whether it is moral or not (Vallor, 2009). We need look no further than the genocide, rape, sex slavery or terrorism that go on today to feel compelled to deeply distrust at least some people with the power of selecting embryos for enhancement reasons (Roache & Clarke, 2009). What bodes worse for human virtue is our apparent inability to learn from our mistakes. A major resistance to GE using PGD lies, as we have seen, in our deep desire to avoid anything related to Nazi Germany. Transhumanist philosopher Nick Bostrom describes it as a defense mechanism set against repeating the history of genocide (Bostrom, 2005). The question is, did we assimilate anything at all from our experiences if we stood by and allowed history to repeat itself less than fifty years later in Rwanda? (Bostrom, 2005).

Such doubt about human virtue leads to apprehensive thoughts about the employment of PGD for GE. As Vallor recognizes, however, a resolution may not be available, for current doubt can neither be "rejected on the grounds of cynicism alone, as transhumanists have done" nor "confirmed by mere intuition" (2009, p. 41), as many bioconservatives would prefer. This, says Vallor, leaves the virtue debate at an impasse until either hypothesis can be proven (2009).

So far, this dissertation has been progressing steadily in the defense of the moral soundness of GE using PGD. Vallor's impasse, however, is unsatisfactory. Although unrelated to the morality of GE itself, the human virtue debate is intimately tied to this discussion due to the fact that PGD relies on moral agents for its execution. An impasse is of no use to applied ethics, which seek to guide practices that are already happening. Wise decisions about policy need to be made now, and cannot afford to risk the consequences of waiting until the impasse is resolved. The last question I must ask is this: is there some way to resolve the impasse without concluding that GE is a lost cause, that its morality has been undone by its moral agents?

Bioliberalist Jonathan Glover proposes an attractive formula for implementation of GE. Firstly, it acknowledges the distinction between the morality of GE itself and of its moral agents. Secondly, it gives some merit to our intuitions about PGD while also accommodating their transient nature. Thirdly and most importantly, it provides a practical solution to the impasse.

Glover supports GE on the basis that it is morally indistinguishable from GT and on the basis that it will benefit humanity (Glover, 1984). He also echoes the concern about moral agents and their threat to the applicability of an otherwise moral enhancement: "the trouble lies not with techniques for enhancement…but with a society's commitment to equality" (Baldwin, 2006, p. 673). As much as our intuitions can be problematic, they should not be completely discarded in this matter. Where does that leave us with regards to implementation of GE? Perhaps the dogma "optimism in principle, caution in practice" (Baldwin, 2006, p. 673) is the best way to summarize the two mutually crucial components of GE implementations. As with other new or powerful technologies such as virus engineering, geo-mapping or social media, I believe that regulation of GE is not only appropriate, but it is necessary if we are to benefit from such powerful (and otherwise morally sound) technologies while restricting their exploitation by those of poor virtue.

I recognize the disadvantage of implementing regulations: one has replaced the problem of power given to a morally suspect humanity with power given to a morally suspect few. Who will enforce the regulations? More importantly, who will decide which to enforce? These questions could be answered in the cynical perspective of the virtue debate. We could say that it is doubtful if *any* body of power will prove to have moral virtue, and that the powerful few will exploit GE in immoral ways, and that all potential for GE to benefit humanity will be lost.

One of Glover's central points in his analysis of GE implementation is that the demand for caution does not infer that outright ban on enhancement is the answer (Glover, 2006). As we have seen throughout this discussion, acknowledging regulation as a necessary concession does not preclude the possibility that PGD is both moral and beneficial to humanity. Should we destroy all the viral vectors we are developing for the delivery of drugs because centralized bodies restrict its use for biowarfare? Should we destroy all communication satellites because regulation of their application is necessary to protect privacy? Should we destroy all forms of social media because a powerful few can restrict its use for pornography, pedophilia or hate crimes?

If the risk of undesirable outcomes were enough to stop a technology from going forward, we would see little innovation, as most new technologies come with risks (Glover, 2006). Recall that even libertarians such as Nozick are willing to cede some autonomy in exchange for a rights-based regulation system (Glover, 1984). As there are appropriate, rights-based regulations in place for satellite or internet use, there must be some appropriate version of regulation available for PGD. I propose that regulations should be considered, but only in 2 ways: 1) as an equalizing force, and 2) to prevent rights abuse. In the first case, regulation would not favour one outcome or another but may flip flop in its trajectory depending on the ratio between two outcomes, the perfect example being the sex ratio equalizing regulation proposed by Nozick (Glover, 1984). In the second case, our decisions could mimic existing rights-based legislature for other technologies. In addition, it could include Glover's suggestion that centralized bodies exist only to enforce regulations, and to act as veto in otherwise public decisions about the legislature (Glover, 1984). This democratic implementation of PGD regulations would both reflect the public's current pessimistic intuitions about human virtue and provide flexibility for gradual changes in our intuitions (Glover, 1984).

Luckily, in the case of PGD, there are several biological laws that will regulate the progression of PGD in a cautious and gradual way. To start, allowing parents to select embryos with the intent of enhancing their children will not produce unbridled enhancement of children born through PGD, nor will it produce an extreme phenotypical enhancement in one generation. There are two forces behind this. First, PGD does not create genetic material *de novo*, and is thus limited by the available genetic material. A woman has a limited number of eggs. As genes are added to the list of desired phenotypes, the probability that any one embryo will contain them all decreases exponentially. Second, an embryo that was selected because it has a gene linked to increased height will not produce a 7-foot person. Mendelian traits, phenotypes that are linked to only one gene, are rare (Abraham, 2012). The majority of our traits are the products of several genes interacting with each other and with the environment in complex ways, and so the effect that GE using PGD will have on the immediate progeny will likely be limited to Mendelian genotypes (Abraham, 2012).

In summary, a combination of Glover's principles and biological limitations provides a very practical way forward from the transhumanist-bioconservative impasse. GE using PGD is morally indistinguishable from GT using PGD. Limiting its use is illogical, especially while we simultaneously use GT for the benefit of humanity. GE implementation need not produce inequality, whether socioeconomic, gender-based or rights-based. Despite the absence of rights-abuse, change in human intuitions may come slowly, but I believe that taking a libertarian but cautious approach in the application of GE using PGD would facilitate that adjustment process and provide us with concrete experiences on which to critically evaluate our intuitions. Based on historical examples of novel ideas about technology and human social structures, a shift in our moral compass and an acceptance of its benefits seems entirely possible if we employ appropriate regulation and implement GE gradually.

Notes

[1] Once fertilized embryos have undergone early cell division to form a morula (a ball of genetically identical cells), some cells can be removed without compromising the embryo's development. The DNA from these cells can be screened to identify which type of allele exists at a certain gene locus. In other words, laboratory tests decode the

DNA at the known location of a gene, and in doing so can sometimes determine if it is a gene that will cause disease or disorder.

[2] Genes for diseases such as Huntington's Tay-Sachs and cystic fibrosis are some such undesirable alleles negatively selected using PGD (Purdy, 1996; Abraham, 2012).

[3] Sex selection is a common example of PS done today (Abraham, 2012)

[4] Such anti-abortionists being those who believe that an embryo is significantly less of a person than a fetus (Purdy 1996). PGD to execute NS, which terminates life at the embryo stage, could thus be morally permissible, since a non-person does not have a right to life (Tooley, 1972).

[5] According to Thompson, embryos – even if they are persons – have no right to impose upon the autonomy of the parents (especially the mother) in deciding if and when to undergo a pregnancy (Thompson, 1971).

[6] The utilitarian view always aims to take overall benefit or happiness (utility) into consideration when calculating the morality of a given action (Singer, 1974).

[7] This philosophy that holds the view that it is permissible and even desirable to push the limits of humanity using technologies. (Roache and Clarke, 2009).

[8] Parents are currently using Canadian IVF clinics to eliminate several disease genes using PGD (Abraham 2012). The number of fertile parents seeking PGD is also increasing, although its most common use is still NS for unhealthy embryos in women with low fertility (Abraham 2012). Perhaps the most striking trend is the increasing desire of PS and the willingness of those parents who cannot obtain screening for the traits they want in Canada to go to Mexico, where IVF clinics will even allow sex selection during PGD (Abraham, 2012).

[9] The Supreme Court of Canada prohibits PS of sex, and most Canadian PGD practitioners strictly refuse any form of PS (Abraham 2012). Dr. Nisker, a pioneer in PGD and the founder of the second largest Canadian IVF clinic, shut down PGD altogether when he realized that the majority of his patients were requesting PS (Abraham, 2012).

[10] In IVF, several embryos are implanted to increase the probability of success of the pregnancy, The outcome is that several health embryos are discarded during every OVF treatment. An anti-abortionist philosophy would see this as an act of killing unjustly – making IVF an immoral practice.

[11] An interesting implication of allowing GE as a function of parent's reproductive anatomy is that some parents may consider selecting for a disability such as deafness, especially if they possess the disability themselves (Chadwick & Levitt, 1998). Is such a decision morally equal to other forms of GE? In the framework of this argument, one would have to agree that it is. Moreover, children with elected disabilities such as deafness serve as a further distinctive quality between GE and Nazi-style eugenics scenarios, for in the first they are valued as members of society and in the second they are killed.

[12] For further ethical dilemmas surrounding perpetuation of immoral practices versus minimizing their casualties, see MSF paper by Sheather and Shah (2011).

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Role of Estrogen Receptors in Male Reproductive Physiology

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Résumé :

(traduction)

Les récepteurs des œstrogènes canoniques (ER α/β) ont un mécanisme d'action génomique, fonctionnant comme des facteurs de transcription nucléaires pour les gènes œstrogéno-dépendantes. Les récepteurs œstrogéniques sont bien établis au sein de l'appareil reproducteur mâle où l'œstrogène joue un rôle essentiel au niveau de la fertilité masculine.

La caractérisation récente du nouveau récepteur œstrogénique couplé à une protéine G GPR30 (également connue sous GPER1), reposant sur la capacité des voies de signalisation intracellulaires non génomiques de transduire des signaux œstrogéniques, nécessite un réexamen du rôle des récepteurs des œstrogènes au niveau de la reproduction masculine. En outre, l'affinité des œstrogènes environnementaux (xéno-œstrogènes) pour les sous-types de récepteurs œstrogéniques pourra fournir de renseignements supplémentaires concernant les effets reproductifs de ces produits chimiques sur la fertilité des hommes.

Nous examinons ici la structure et les fonctions de chaque récepteur œstrogène dans le cadre de la reproduction masculine, en portant une attention particulière aux conséquences reproductives de l'exposition aux xéno-œstrogènes.

Mots-clés : GPR30, GPER1, xeno-œstrogène, signalisation, reproduction mâle

Abstract:

Canonical estrogen receptors (ER α/β) have a genomic mechanism of action, functioning as nuclear transcription factors for estrogen-dependent genes. Estrogen receptors are well established within the male reproductive tract with estrogen playing an essential role for male fertility.

The recent characterization of novel G-protein coupled estrogen receptor GPR30 (alternatively known as GPER1), depending on non-genomic intracellular signaling pathways to transduce estrogenic signals, requires a re-examination of the roles of estrogen receptors in male reproduction. Further, the affinity of environmental estrogens (xenoestrogens) for estrogen receptor subtypes may provide additional understanding of the reproductive effects of these chemicals on male fertility.

Here we review the structure and functions of each estrogen receptor within the context of male reproduction, with special consideration of the reproductive implications of xenoestrogen exposure.

Keywords: GPR30, GPER1, male reproduction, signalling, xenoestrogen

Traditional Estrogen Receptors

Traditionally, estrogen receptors are known as ligand-dependent transcription factors which have been found to be located within the confines of the cell's membrane and bind the steroidal hormone estrogen (Hess et al., 1997). These conventional nuclear steroidal receptors have been identified as ERα and Estrogen Receptor-β (ERβ), where ERβ was discovered less than 20 years ago in 1996. These receptors are produced by two separate and distinct genes found on separate chromosomes and are also not isoforms of each other (O'Donnell, Robertson, Jones, & Simpson, 2001).

A main difference between these two receptors involves their individual expression within specific tissues. ERα is the major species expressed in the uterus, liver, adipose tissue, skeletal muscle, pituitary, and hypothalamus. Conversely, ERβ is the dominant form in ovary and prostate tissues, and regions of the brain such as the limbic system, cerebellum, and cerebral cortex (O'Donnell et al., 2001; Shughrue & Mechenthaler, 2000).

The structure of both receptors involves six functional domains denoted A-F (O'Donnell et al., 2001). Among these domains, the A/B domain is the least homologous between the two, and contains the activation function 1 (AF-1) region—one of the two areas critical for the transactivation function, or increased rate of gene expression, of the members of the ligand-activated nuclear receptor family. The C domain of these estrogen receptors is the most highly conserved region, implicating its importance in functional value, and it contains the DNA binding domain with zinc-finger motifs (O'Donnell et al., 2001). Ligands bind specifically within the E domain, which is moderately conserved, and although each receptor (ERα and ERβ) binds estradiol (17β -estradiol or E2) with similar affinity, the relative binding affinity of other ligands displays discrepancies (Kuiper, Carlsson, Grandien, Enmark, Häggblad, Nilsson, et al., 1997). Within the C'-terminus of the E domain lays the other critical area for transactivation function (AF-2), and this place is denoted as the F domain (O'Donnell et al., 2001).

The signal transduction of ERα involves the action of AF-1 and the E2-dependent AF-2. AF-2 has been demonstrated in several studies to be controlled by ligand binding activity, specifically E2. In contrast, AF-1 possesses three major phosphorlyation sites at serines 104 and/or 106, serine 118, and serine 167; and since mutations of these sites reduces transactivation by ERα, it is suggested that phosphorylation plays an important role in regulating AF-1 activity (Chen et al., 2002; Lannigan, 2003). Serine 118 (S118) appears to be a target for phosphorylation by cyclin-dependent kinase 7 (Cdk7) in response to estrogen and in a ligand-independent manner by the ERK1/2 mitogen activated protein kinases (MAPK) signal transduction pathway in response to cell surface signals. This means that S118 becomes phosphorylated in the presence of E2 binding, yet the experimental induction of MAPK activity leads to increased S118 phophorylation, ultimately resulting in ligand -independent transactivation by ERα (Chen et al., 2002). Moreover and thinking in the endogenous context without experimental intervention, perhaps an estrogen transactivation response (as a result of S118 phosphorylation) can occur via initiation of a MAPK pathway through the means of a now known cell surface estrogen receptor. This process would not involve E2 binding directly to the Erα protein but rather a surface receptor which then relays secondary messages via a MAPK cascade—meaning that G-Protein Estrogen Receptor-30 (GPR-30), a surface membrane estrogen receptor, may indeed be a candidate in this described signal transduction where ERα does not need to depend on interaction with E2 for transcriptional activation.

In general however, the initiation of these activation function domains, whether through ligand-dependent or independent pathways, leads to increased association with co-activators and to secondary messages translocating ERα/ERβ to the nucleus—if it is not there already but rather in the cytosol. This results in the receptor-complex binding to the estrogen response element within the promoter region of the DNA via the zinc finger motifs of the C domain allowing gene expression to occur (Lannigan, 2003). With the investigation of ligand-independent pathways providing cross-talk routes of action in conjunction with growth factor signalling pathways, the exact molecular mechanisms of estrogen action are now known to be more complex than originally thought (O'Donnell et al., 2001).

Estrogen and G-Protein Coupled Receptors

In recent years a unique estrogen receptor located on the cell membrane has been identified. This transmembrane G protein-coupled receptor (GPCR) has been named GPR30 or alternatively G protein-coupled estrogen receptor 1 (GPER1). The role of GPR30 in estrogen signaling is still

controversial, however proposed suggestions implicate that it is a functional estrogen receptor involved in non-genomic estrogen signaling, meaning that it can induce a rapid effect within the cell independent of nuclear receptors for estrogen (Olde & Leeb-Lundberg, 2009). The traditional estrogen receptor transcriptional modification mechanisms require 45 minutes for new protein synthesis and it is estimated to be much longer for the alteration of cellular physiology. In contrast, it has been found that 17β-estradiol can alter neuronal firing within seconds and since this discovery, the ideology of a rapid, non-genomic capability of E2 has been applied and investigated in the context of different cellular mechanisms across different tissues (Kelly & Wagner, 1999).

A GPCR is a seven transmembrane domain cell surface receptor associated with a G protein, which carries the ability to bind the guanine nucleotides GDP and GTP. The associated G protein is a heterotrimeric protein composed of three different subunits: α, β, and γ. Upon ligand binding, an allosteric change occurs in the alpha subunit of the G protein (Gα), giving it the ability to now bind GTP in exchange for GDP, and further activating Gα which dissociates it from its other subunits. This Gα is now able to move on to activate effector enzymes and relay a secondary messaging cascade. These second messengers most commonly involve cyclic nucleotides, inositol triphosphate (IP3) and diacylglycerol (DAG), and calcium ions Ca^{2+}.

An early speculation of the relationship between estrogen and GPCRs involves the regulation and modulation of membrane receptors by the intracellular estrogen receptors. This viewpoint suggests estrogen receptors are able to activate adenylate cyclase production or couple to phospholipase C (PLC) beta through G-protein modification and activation, and have been demonstrated to lead to rapid increases in intracellular Ca^{2+} concentration as well as the formation of inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) (Simoncini & Genazzani, 2003). Some findings also suggest that ERα and ERβ can associate with the plasma membrane and even couple with G proteins to activate many of the cellular cascades dependent on GPCRs (Kelly & Wagner, 1999; Razandi, Pedram, Greene, & Levin, 1999). This characterization of signal transduction activation proposes that estrogen can rapidly regulate multiple cellular functions through the recruitment of G protein pathways but also modulate longer-term processes such as gene expression, protein or DNA synthesis through nuclear-destined activated estrogen receptors (Simoncini & Genazzani, 2003; Razandi, et al., 1999).

Another characterization regarding the interaction between estrogen and GPCRs involves the action of GPER1, which only in 2005 was classified by the International Union of Pharmacology (IUPHAR) as a membrane estrogen receptor (Olde & Leeb-Lundberg, 2009). The rapid activation of mitogen-activated protein kinases, Erk-1 and Erk-2, by E2 were able to be shown in MCF-7 cells, which express ERα and ERβ, as well as in SKBR3 breast cancer cells, which lack both ERα and ERβ. Thus, the estrogen-induced activation of this pathway is not necessarily dependent upon the traditional estrogen receptors alone. Furthermore, MDA-MB-231 breast cancer cells, cells that lack GPER1, are insensitive to ERK-1/-2 activation via E2 (Filardo, Quinn, Bland, & Frackelton, 2000).

GPER1: Signal Transduction

It has been reported that GPER1 has the ability to signal via Gαs proteins, and through a pertussis toxin-sensitive G-protein (Gβγ)—pertussis toxin sensitivity is a common method to discriminate whether a signaling pathway is following the Gα subunit or the Gβγ complex since they are both able to promote Erk-1/-2 activation, yet the Gβγ complex is indicated as pertussis toxin-sensitive (Olde & Leeb-Lundberg, 2009; Filardo et al., 2000). Activation of the Gαs protein in turn activates adenylyl cyclase, increasing the cytosolic concentration of the second messenger cyclic adenosine monophosphate (cAMP), and triggering further events such as the activation of protein kinase A (PKA) leading to increased expression of cAMP-inducible genes (Olde & Leeb-Lundberg, 2009).

The activation of the pertussis toxin-sensitive G-protein ultimately results in transactivation of the epidermal growth factor (EGF) receptor via cleavage of membrane-tethered heparin-bound EGF, intracellular Ca^{2+} mobilization, ERK1/2 activation, and Src related tyrosine kinase activity—Src proteins are adapter proteins with domains that carry the ability to phosphorylate tyrosine residues (tyrosine kinases), an additional step of regulation for this form of cell growth (Filardo et al., 2000; Prossnitz et al., 2008). EGF receptor transactivation leads to multiple downstream events such as the activation of PLC, MAPKs, and phosphatidylinositol 3-kinases (PI3K). PLC activation generates second messengers IP3 and DAG, and the MAPKs and PI3Ks initiate numerous pathways regulating transcription factors (Prossnitz et al., 2008). Thus, the initiation of Gαs proteins and Gβγ complexes outlines the

beginning of the two suggested pathways of signal transduction for GPER1—leading to transcriptional activation as well as rapid signaling via the activated EGF receptor. Again, multiple routes of action may indicate developed cross-talk mechanisms for evolutionary-important pathways.

GPER1: Areas of Debate

One area of controversy around GPER1 involves whether or not E2 acts independently of GPER1 or actually binds to it, as several laboratories have been unable to demonstrate estradiol binding or estradiol-activated signal transduction in GPER1 expressing cells (Otto et al., 2009; Otto et al., 2008). In order to establish the role of GPER1, the selective receptor agonist G-1 was developed with a higher affiity over both Erα and ERβ (Olde & Leeb-Lundberg, 2009). Otto *et al.* (2008) attempted *in vivo* experiments with estradiol and G-1 in uterus and mammary gland tissues, organs that are targets for estrogen, yet were not able to show any estrogenic effects with G-1. They continue to conclude that GPER1 is still an orphan receptor, meaning it has a similar structure to known receptors but the exact endogenous ligand has yet to be identified.

Another basis for dispute is the sub-cellular localization of GPER1. In both cells transfected and endogenously expressing GPER1, Otto *et al.* (2008) confirmed the receptor localized to the endoplasmic reticulum. In contrast, Filardo *et al.* demonstrate detectable expression of GPER1 on the surface of transfected HEK-293 cells using fluorescence-activated cell sorting, and confirming with confocal microscopy using lectin concanavalin A as a plasma membrane marker (Filardo et al., 2007). Furthermore, it has been shown by some that membrane-impermeable conjugates of E2 to bovine serum albumin (E2-BSA) have the ability to stimulate GPR30-dependent elevation of intracellular cAMP concentrations (Kelly & Wagner, 1999; Filardo et al., 2007). Fractionation studies as well are in support of the plasma membrane as the site of GPR30 action with specific E2 binding and G protein activation (Filardo et al., 2007).

However, another proposition suggests that GPER1 is localized to the plasma membrane, yet after treatment with E2, followed by the resulting elevation of intracellular Ca^{2+} concentration, translocation occurs of GPER1 from the plasma membrane to the cytoplasm within one hour (Funakoshi, Yanai, Shinoda, Kawano, & Mizukami, 2006). Altogether, the present knowledge of the novel GPER1 and its associated mechanisms of transduction, as well as the actual sub-cellular location, are in their juvenile stages, and more investigations are warranted.

GPER1: Male Reproductive Tissue

Although the actions and physiology of GPER1 within the male reproductive tissues is not well defined, the presence of GPER1 and its mRNA has been found in the mouse spermatogonial cell line GC-1 (Olde & Leeb-Lundberg, 2009; Chimento, et al., 2010). Here the physiological role of GPER1 is suspected to work in conjunction with Erα through cross-talk pathways allowing estrogen the ability to mediate transcriptional responses in the regulation of testicular function (Chimento et al., 2010). It was within this cell line that Chimento *et al.*(2010) demonstrated that E2 and G-1 activate the EGFR/ERK pathway (the same pathway as previously described) leading to downstream stimulation resulting in GC-1 cell growth. These findings of proliferative activity have suggested that a high level of GPR30 expression levels may predispose cells to estrogen sensitivity, altered responsiveness, and tumour proliferation (Prossnitz & Maggioloini, 2009).

The same EGFR/ERK pathway as a result of GPER1 activation has been described within immature rat Sertoli cells. In these cells, E2 and GPER1 interaction may regulate gene expression involved with apoptosis. Thus, Lucas *et al.* have proposed that GPER1 may mediate actions important for Sertoli cell function and maintenance of normal testis development and homeostasis (Lucas, Royer, Siu, Lazari, & Porto, 2010).

Implications

The implications of having multiple routes of estrogen activation, with both functional genomic and non-genomic receptors, may predispose cells to be easily responsive to estrogen-mimicking compounds from the environment. In turn, this may lead to the recent phenomenon known as endocrine disruption, referring to the ability of exogenous chemicals to interfere with hormonal systems and having the potential to negatively affect human health (Swedenborg, Rüegg, Mäkelä, & Pongratz, 2009).

With the increase in abundance of chemicals present in today's modern industrial society, environmental exposures to estrogen have become an area of investigation for many researchers. An example of one of these exogenous estrogenic compounds, known as xenoestrogens, is bisphenol A (BPA). BPA is used in its polymeric form as lining of food and beverage containers, baby bottles, medical tubing, and dental fillings (Swedenborg et al., 2009). This lipophilic compound leaks out of plastics when heated—a significant route of exposure—and has been shown to accumulate in human adipose tissue, plasma, urine, and breast milk (Swedenborg et al., 2009; Howdeshell et al., 2003).

Moreover, it has been shown that GPER1, like traditional estrogen receptors, are bound and activated by several endocrine-disrupting chemicals (EDCs) (Swedenborg et al., 2009). These environmental estrogens have been demonstrated to activate alternative estrogen signaling pathways to traditional ER-binding as they have been able to invoke estrogenic responses in the HEK293 ER-negative cell line stably transfected with the GPER1 receptor. The binding affinities of these xenoestrogens, including BPA, for GPER1 are similar to their affinities for ERs (a relative binding affinity of 2-3% to that of E2). Thus, it has been indicated that non-traditional estrogenic actions via GPER1 have the characteristics and potential for endocrine disruption by a variety of xenoestrogens (Thomas & Dong, 2006). Therefore, due to estrogen's essential role in male reproductive health and normal fertility, the regulation of the use and exposure of these xenoestrogens is a valid avenue of policy to begin to critique; especially since the newly understood effects and mechanisms are still in their early stages where more research is warranted to precisely define them.

Conclusions

Altogether, our understanding of the physiological mechanisms of estrogen receptors has evolved to become a complex domain, especially when considering the recent findings of non-genomic signalling. Estrogenic effects have been demonstrated to be activated through both traditional ERs and the novel GPR30 membrane receptor. Signal mediation through GPR30 has been found to involve rapid cellular signalling pathways via secondary messengers, resulting in the release and transactivation of epidermal growth factor receptors (Prossnitz et al., 2008). The variety of proposed and demonstrated pathways may suggest crosstalk mechanisms, as well as specificity to tissues.

Within the tissues of the male reproductive system, estrogen's importance in development as well as in maintaining normal fertility is well recognized (Hess, 2003; Hess et al., 1997). Taking into account the various means by which estrogen has been shown and proposed to activate responses within cells, the fact that modern industrial society is continuing to allow exposure of populations to xenoestrogens on a daily basis should lead to grounds for concern. The environmental presence of exogenous estrogenic -mimicking chemicals and their ability to interact with our bodies is a recent area of research, yet has already had profound political effects such as the restrictions on BPA inclusion in the production of certain products. To further supplement these policy changes, future directions should involve delineating the specific pathways, interactions, and characteristics of endocrine disruption with regards to the estrogen receptors—novel and traditional. The transcriptional activities of GPR30 versus ERs must be clarified, and their individual contributions toward physiological effects need to be more clearly defined (Prossnitz et al., 2008). Determining the precise roles in the rapid signalling effects of estrogen and the ability of steroid receptors to exert responses via non-transcriptional mechanisms may even open new avenues of pharmacological possibilities (Simoncini & Genazzani, 2003).

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Concours de présentation par affiche en épidémiologie 2012

École Interdisciplinaire des sciences de la santé — Université d'Ottawa, Canada

Chaque année, les étudiants de premier cycle de troisième et quatrième années suivant le cours d'épidémiologie à l'École des sciences de la santé de l'Université d'Ottawa, participent à un concours qui récompense les meilleurs projets de recherche en épidémiologie.

Les fruits de leurs travail — un article de recherche et une affiche présentée au grand public — sont de bons exemples de ce que produisent les étudiants de premier cycle à la fin de leur baccalauréat. Nous souhaitons vous présenter les lauréats du concours de 2012 et leur offrir nos félicitations pour leur contribution à la recherche épidémiologique.

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PCA3 Gene Testing: A Promising Method for Determining Prostate Cancer | Le test PCA3 : Une Méthode Prometteuse pour la Détection du Cancer de la Prostate

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Résumé

Objectif: Évaluer l'utilité du test PCA3 dans la définition du risque de cancer de la prostate (CaP) et la prévision de résultats des biopsies tumorales.

Contexte: Le PCA3 est un ARN non codant spécifique de la prostate qui est surexprimé de façon significative chez les patients atteints d'un CaP. L'utilisation du test PCA3 présente de nombreux avantages, notamment la réduction du nombre de biopsies inutiles, la réduction des risques liés à la biopsie et le recours à une procédure multivariable aux côtés de PSA, l'analyse du sérum etc., pour indiquer un risque de cancer de la prostate.

Méthodes: Une revue de littérature des études examinées par des pairs et publiées en anglais entre 2008-2012 portant principalement sur «le gène 3 spécifique du cancer de la prostate» et «l'évaluation des risques».

Conclusion: Trois tendances se sont dégagées de la revue de littérature sur le test PCA3 : i) Le gène PCA3 a le potentiel de signaler le risque d'un CaP et de prédire les résultats futurs d'une biopsie. ii) Le test PCA3 pourrait être utilisé avec d'autres méthodes pour permettre aux cliniciens de mieux comprendre la progression de la maladie. iii) Il sera nécessaire d'effectuer encore plus de tests de confirmation.

Abstract

Objective: To evaluate the usefulness of the PCA3 gene test in determining risk of PCa (prostate cancer) and predicting tumour biopsy results.

Background: PCA3 is a prostate specific, non-protein coding RNA that is significantly over expressed in prostate cancer patients. The use of PCA3 gene testing has many potential benefits including the reduction of unnecessary biopsies, the reduction of harmful biopsy symptoms, and the use of a multivariable procedure alongside PSA, serum testing, etc. to indicate risk of prostate cancer.

Methods: Literature review of English peer-reviewed studies published between 2008-2012 predominantly on the topics of "prostate cancer antigen 3" and "risk assessment".

Conclusion: Three trends emerged from the literature review on PCA3 gene testing: i) The PCA3 gene has potential to indicate risk of PCa and predict future biopsy outcomes. ii) PCA3 gene testing could be used with other methods to give clinicians further insight on disease progression. iii) More confirmatory testing needs to be done.

Is Race a Prognostic Factor for Ovarian Cancer Survival? The Answer is not just Black and White: A Systematic Review and Meta-Analysis | La Race Joue-t-elle un Rôle Pronostic de Survie chez les Femmes Atteintes du Cancer de l'Ovaire ? Il Ne S'agit Pas là d'une Réponse Noir sur Blanc : Revue Systématique et Méta-Analyse

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Résumé

Contexte: Parmi les malignités gynécologiques aux États-Unis, le cancer épithélial de l'ovaire a le taux de mortalité le plus élevé, dépassant le cancer de l'endomètre et le cancer du col de l'utérus combinés. En dépit des progrès réalisés dans les domaines des techniques chirurgicales et la chimiothérapie qui ont permis d'accroître le nombre d'options de traitements pour les femmes atteintes de cette maladie, la mortalité demeure élevée, avec 15 460 femmes qui mourront du cancer de l'ovaire en 2011. Ces résultats reflètent bien le fait qu'il n'existe aucun outil de dépistage efficace pour le cancer de l'ovaire. Par conséquent, la majorité des cas sont diagnostiqués à un stade avancé et le pronostic n'est souvent guère encourageant. Il a été postulé à travers plusieurs études que la race joue un rôle pronostic de survie chez les femmes atteintes du cancer de l'ovaire. Des études épidémiologiques menées sur une large échelle ont réussi à démontrer une incidence et un taux de mortalité plus faible du cancer épithélial de l'ovaire chez les Afro-américaines que chez les femmes blanches; toutefois, le taux de survie relatif chez les Afro-américaines semble être considérablement plus faible.

Objectif : Déterminer s'il existe des disparités dans les taux de survie chez les Afro-américaines et les femmes blanches qui cherchent à obtenir un traitement pour le cancer de l'ovaire.

Méthodes : Une revue de littérature des études examinées par des pairs et publiées en anglais. La recherche a été effectuée à l'aide de bases de données PubMed, Scopus et Toxline en utilisant les mots-clés MeSH suivants : «cancer de l'ovaire» OU «carcinome», «inégalités raciales» OU «différences», «taux de mortalité» OU «mortalité», ET «race» OU «ethnie». Les critères d'inclusion étaient le pays d'origine (États-Unis), langue anglaise seulement et l'utilisation de femmes tant Afro-américaines que blanches comme sujets de recherche. Les articles choisis ont été analysés en utilisant les proportions de risque, les graphiques en forêt, les courbes d'estimation de survie de Kaplan-Meier, et les taux de survie à 5 ans.

Résultats : Cette revue systématique confirme le fait que la race est un facteur déterminant des résultats de survie du cancer de l'ovaire. Les femmes d'origine afro-américaine sont 1,126 fois plus à risque d'éprouver des résultats de survie plus faibles que les femmes blanches. Parallèlement à la littérature précédente, cette recherche confirme que les Afro-américaines ont continuellement des taux de survie à 5 ans considérablement plus faibles que les femmes. L'analyse du graphique en forêt et du graphique en entonnoir met en évidence la présence d'un biais de publication relativement faible et l'existence d'une homogénéité dans le cadre de cette méta-analyse.

Conclusion : Des preuves statistiquement significatives montrant que les Afro-américaines éprouvent des résultats de survie du cancer de l'ovaire plus faibles que les femmes blanches. Malgré cette constatation, il serait hâtif de conclure que la race est le seul facteur pronostic. La race est un déterminant social qui influence d'autres variables affectant le traitement et la survie du cancer de l'ovaire, comme l'éducation, l'emploi, le statut socio-économique et l'accès aux services de santé. Par conséquent, d'autres études sont nécessaires pour mieux évaluer la relation entre les résultats de survie et la race.

Abstract

Background: Among gynecologic malignancies in the United States, epithelial ovarian cancer has the highest mortality rate, surpassing uterine and cervical cancer combined. Despite advances in surgical techniques and chemotherapy that have provided an increasing number of treatment options for women with this disease, mortality remains high, with 15, 460 women expected to die from ovarian cancer in 2011. These outcomes reflect the fact that there is no effective screening tool for ovarian cancer. Therefore the majority of cases are diagnosed in advanced stages and prognosis is usually poor. Race has been postulated to be a prognostic factor of survival in women with ovarian cancer in a number of studies. Large epidemiological studies have demonstrated a lower incidence and death rate of epithelial ovarian cancer for African-America women compared to White-American women; however, relative survival for African-American women appears to be significantly poorer[1].

Objective: To determine if there are disparities in survival outcomes in African American and White-American women who seek treatment for ovarian cancer.

Methods: Literature review of English peer-reviewed articles. The search was conducted in Pubmed, Scopus and Toxline databases using MeSH terms: “ovarian cancer” OR “carcinoma”, “racial disparities” OR “differences”, “survival outcomes” OR “mortality” AND “race” OR “ethnicity”. Inclusion criteria were country of origin (United States), English language only and the use of both African-American and White-American women as research subjects. Selected articles were analyzed using hazard ratios, forest plots, Kaplan-Meier survival plots and five-year survival rates.

Results: This systematic review confirms that race is a determinant of ovarian cancer survival outcomes. Women of African-American origin have a 1.126 greater risk of experiencing worse survival outcomes than White-American women. Concurrent with previous literature, this research confirms that AA women consistently have significantly lower 5 year survival than WA women. Analysis of the forest plot and funnel plot demonstrate relatively low publication bias and systematic homogeneity in this meta-analysis.

Conclusion: Statistically significant evidence demonstrating that African-American women experience worse survival outcomes in ovarian cancer than White-American women. Despite this finding, it would be premature to conclude that race is the only prognostic factor. Race is a social determinant that influences other variables that affect treatment and survival of ovarian cancer such as education, occupation, socioeconomic status and access to health care. Therefore, future studies are required to further assess the relationship between survival outcomes and race.

Risky Business: A “Quasi” Systematic Review Comparing Characteristics of Agricultural Injury Between Adults and Children | Une Activité Risquée : Une Revue ‘Quasi’ Systématique Comparant les Caractéristiques des Blessures en Milieu Agricole Entre les Adultes et les Enfants

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Résumé

Contexte : L’agriculture est la quatrième industrie la plus dangereuse au Canada. Contrairement à d’autres industries, le secteur agricole présente un risque unique de blessure chez les enfants. Les coûts des soins de santé associés aux blessures en milieu agricole se situent entre 200 et 300 millions de dollars par année.

But et objectifs : Le but de cette étude est d’évaluer les différences dans les taux, les mécanismes et les facteurs de risque entre les adultes et les enfants par rapport aux blessures graves liées à l’agriculture en Ontario.

Méthodes : Une revue quasi-systématique a été réalisée à l’aide de plusieurs bases de données académiques, y compris PubMed, Scopus et Google Scholar. Les mots-clés utilisés dans les recherches sont les suivants : «blessures agricoles», «blessures à la ferme», «adultes», «enfants», «facteurs de risque», «mécanismes», «taux», «Ontario» et «Canada». Les rapports les plus récents du Programme canadien de surveillance des blessures en milieu agricole (PCSBMA) ont également été utilisés.

Résultats : De 1990 à 2004, on dénombre 453 cas d’accidents mortels en milieu agricole en Ontario et, parmi ceux-là, 15.4% sont survenus chez les jeunes âgés de 0 à 15 ans. Au cours de cette même période, 3679 personnes ont subi des blessures agricoles nécessitant une hospitalisation, et les jeunes de 0 à 15 ans représentent 15.2% de ces hospitalisations. Chez les adultes (de 16 à 64 ans), les trois principaux mécanismes de blessures mortelles sont les renversements (28%), les enchevêtrements (12%) et les écrasements (12%). Chez les enfants (de 0 à 15 ans), ceux-ci sont les écrasements (51%), la noyade (16%) et les renversements (13%). Les facteurs de risque communs tant aux adultes qu’aux enfants incluent l’âge, le sexe, la saison, le rang de l’exploitant, le type de bétail et l’utilisation abusive des machines. Les facteurs de risque spécifiques aux enfants incluent : être un spectateur descendu de la machinerie et être passager à bord d’une machinerie agricole. Les facteurs de risque spécifiques aux adultes sont des médicaments, des conditions médicales, et le travail isolé.

Conclusion : Les enfants et les adultes ont des taux, des mécanismes, et des facteurs de risque particuliers par rapport aux blessures en milieu agricole. Les politiques et les stratégies de prévention devraient tenir compte de ces différences.

Abstract

Background: Agriculture is the 4th most hazardous industry in Canada. Unlike other industries, agriculture poses a unique risk of injury to children. Healthcare costs for agriculture injuries range between 200 and 300 million dollars per annum.

Purpose and objective: The study aim is to evaluate differences in rates, mechanisms, and risk factors between adults and children in relation to acute agriculture-related injuries in Ontario.

Methods: A quasi-systematic review was performed using academic databases including: PubMed, Scopus and Google Scholar. Key words searched included: “Agricultural Injuries”, “ Farm Injuries”, “Adults”, “Children”, “ “Risk Factors”, “ Mechanisms”, “Rates”, “Ontario” and “Canada”. The most recent reports from the Canadian Agricultural Injuries Surveillance Program (CAIR) were also utilized.

Results: From 1990-2004, there were 453 cases of fatal agricultural injuries in Ontario; 15.4% of those occurred in youth ages 0-15. During the same period, there were 3679 hospitalizations due to agricultural injuries and 15.2% were youth ages 0-15. For Adults (16-64), the top three mechanisms of fatal injuries are rollover (28%), entanglement (12%), and run-over (12%). For children (0-15) they are run-over (51%), drowning (16%) and rollover (13%). Risk factors common to both adults and children include age, gender, season, operator rank, type of livestock and misuse of machinery. Risk factors specific to children include being a bystander to machinery use and riding as a passenger on farm equipment. Risk factors specific to adults are medications, medical conditions and working alone. Conclusion: Children and adults have unique rates, mechanisms and risk factors of agricultural injury. Policy and prevention strategies should reflect these differences.

Conclusion: Children and adults have unique rates, mechanisms and risk factors of agricultural injury. Policy and prevention strategies should reflect these differences.

APPEL À CONTRIBUTIONS

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