Modeling Savings from Prophylactic REACT Antioxidant Use Among a Cohort Initially Aged 50-55 Years: A Canadian Perspective

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Abstract

Context: Cataract surgery is the most frequent elective surgical procedure, exceeding in number the sum of the next 5 most commonly performed surgical procedures, costing 12% ($3.4 billion) of the USA Medicare budget. Although the Age Related Eye Disease Study (AREDS) has shown no nutritional efficacy in cataract risk reduction, the REACT study, using a more sensitive endpoint, found significant reduction in cataract progression using an antioxidant cocktail of vitamins E, C, and β-carotene. Incidence data for cataract, broken down by age and sex for the entire population of the province of Ontario, Canada, were obtained from the Ontario Health Insurance Plan (OHIP).

Objectives: to estimate the potential economic consequences to Ontario of the REACT antioxidant cocktail consisting of β-carotene, vitamin E and vitamin C, for reduction of risk of cataract in a cohort of all people initially aged 50-54 years in 2001.

Methods: Using extrapolated values for risk reductions, potential savings were calculated as the incremental cost difference between the estimated medical costs for the untreated cohort and the same cohort if treated with the REACT cocktail. Different scenarios were explored for cost savings.

Results: For the Ontario cohort of ca. 788,000, for the REACT cocktail treatment, costs were $101 million: savings of $37 million or $364 per cataract operation averted were calculated.

Conclusion: REACT antioxidant supplementation appears to be a dominant strategy for reducing risk of cataract. Applied to the whole Canadian population, the potential medical cost savings for cataract are $1.46 billion direct costs. These values would be tenfold higher for the USA, because of the population size and currency difference. Averting the need for some cataract operations would reduce the need for scarce operating rooms: an estimate would be freeing up approximately 20 operating rooms for Canada, the equivalent to the operating rooms of several large hospitals. Optometrists could use REACT medication to decrease the need for surgeries.

Key words: Cataract, risk reduction, present value, cost savings, economic effects, vitamins E, C, and β-carotene, REACT, oxidative stress

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Introduction

Vitamin E is a lipid-soluble vitamin. Although anti-oxidant properties are perceived to be of most importance, vitamin E has many other effects.[1] An accumulating medical literature attests to the benefits of vitamin E in diseases where oxidative damage plays an important pathophysiological role, including the formation of cataract,[2-5] the development of macular degeneration[6] and acute coronary syndromes.[7,8]

Recently a cocktail of antioxidants (vitamins E and C and β-carotene) used in the Roche European-American Cataract Trial (REACT) has shown efficacy in reducing risk of cataract progression by a similar factor to that reported for vitamin E.[3,9] Classification and regression tree (CART) analysis indicated that the

vitamin E in the cocktail appeared to be the agent involved in reduction of risk of cataract progression.[4] Although a similar antioxidant cocktail used in the Age-Related Eye Disease Study (AREDS) did not show any reduction of cataract risk,[10] the end point used was not as sensitive to small cataractous changes as that used in the REACT study.[9]

Cataract is the most frequently chosen elective surgery procedure, exceeding in the USA the number of the total of the next five most frequently performed procedures. Although risk of AMD progression to the wet form has been decreased by an antioxidant supplement (AREDS),[11] no effect in reducing cataract risk was shown by this group. This has been attributed to the less sensitive end point chosen to measure cataract progression.[12]

With the aging North American population, the number of cataract operations is likely to increase. Based on the population projections by Statistics Canada, the number of cataract operations in Canada is predicted to increase to 190% of the 2001 number by 2026.[13] In the USA the rate is expected to rise to approximately 150% of the 1994 number by 2016.[14] An increasing incidence would result in substantial economic consequences. At present cataract surgery represents a large portion of all health care expenditures; 0.7 % of all hospital and physicians' costs for all Ontario residents through the Ontario Health Insurance Plan (OHIP), and 2.9 % for those over 65 years.[15] Similarly, cataracts represent a major proportion (12%) of the U.S.A. Medicare budget for all U.S.A. residents age 65 and older.[16]

Preventive strategies, such as vitamin E supplementation (VES)[17] or treatment with an antioxidant cocktail described in the REACT study,[3] with the potential to reduce the risk of cataract formation in the aging population, would be important advances. Benefits might be realized not only by the individual, including better eyesight and the avoidance of surgery, but also to society where scarce health care dollars, through avoidance of surgery, could be directed elsewhere.

Because the REACT study was a double blind randomized prospective clinical study which showed significant risk reduction for cataract progression of early cataracts, we sought to develop a cost-effectiveness model, extrapolating the risk reduction to long-term effects of REACT antioxidant supplements[3] in a hypothetical cohort of middle-aged Ontarians.

In Canada, cataract operations have been identified as one of five medical procedures for which wait times must be decreased by government. For this reason, preventive measures such as the REACT cocktail of beta carotene, vitamin C and vitamin E would be important in decreasing the risk of progression of cataracts.

Because optometrists perform the majority of eye examinations in the U.S.A. and Canada, they are thus most likely to observe early cataracts such as those studied in the REACT study. This model study suggests that, if the REACT treatment of cataracts can decrease the incidence of cataract operations, then, by prescribing it, optometrists could substantially contribute to decreasing the wait time as well as the amount of operating room time required for fewer cataract operations.

Materials and Methods

Analyses were undertaken for a hypothetical cohort composed of all persons aged 50-55 years in the Province of Ontario, Canada,[13] during 2001. Population projections to the year 2026, prepared by Statistics Canada, were used to predict the numbers of men and women at risk for cataract. Death rates are incorporated into the population projections eliminating the need to correct separately for this. Cataract operation frequency broken down by age and sex were provided by the Ontario Health Insurance Plan, which pays for all

operations in the province as part of the socialized medicine plan in Ontario.

For REACT, risk reduction projections for the progression data from the REACT study[3] was extrapolated to obtain a predicted reduced risk of incidence of cataract operations over a 25-year period. The model hypothesizes that five years after REACT supplement treatment begins, the expected benefits begin for a cohort of persons initially aged 50-55 years in 2001 and followed for a period of 25 years after treatment began. For REACT supplements, a second model was used in which treatment began for a cohort aged 60-65 instead of age 50-55, because the members of REACT study group were initially slightly older than 60 years old.

Perspective

For the primary analyses we have taken the perspective of a third party payer, in this case the Ontario Ministry of Health, the insurer of medical and hospital care. Our model estimates the costs and benefits of REACT multiple antioxidant[3,12] risk reduction of cataract formation (costs to Ontario Ministry of Health, OMOH).

General Outline of the Model

The population at risk is considered under two situations with the net benefit calculated as the incremental difference between the two. First, it is assumed that the members of the cohort with early cataract are treated with REACT antioxidant cocktail for 25 years and that compliance is complete, reducing risk of cataract progression by the factor found in the REACT study. The first five years outcomes are not reduced, as suggested by previous studies.[2] REACT antioxidant cocktail is then continued for 20 additional years and reductions in the risk of adverse outcomes are modeled. The cohort sizes for each five year period in the population projections[13] are used to estimate the costs for each five year period. Second, in the control situation without REACT, costs and outcome events are estimated assuming usual medical care. A cost-benefit analysis was performed where the formula for present value (PV) of the net benefit is of the form:

Net benefit (PV)=cost savings realized (PV)-cost of supplementation (PV)

All costs and benefits were corrected to the present using a 3% discount rate, and costs were corrected to 2001 using the Canadian Consumer Price Index (CPI).

Model Tested

Medical Direct Costs

Reduction of cataract costs. The first scenario considers that the risk of cataract formation and the subsequent need for cataract surgery are reduced by REACT supplementation. Estimates of direct costs (including costs of hospitals, physicians, and secondary cataract formation) are included in **Table 1,** p.215.

Outcomes and Risk Reduction

Cataract, an opacity of the eye lens which interferes with vision, is treated surgically by excision of the lens with replacement with a plastic intraocular lens (IOL). Approximately 50% of patients will require laser capsulotomy to treat secondary cataract within two years of IOL implantation.[18] The incidence of cataract was taken from three different sources: (1) the published figures from the Framingham Eye Study[19,20] and (2) the actual number of cataract operations, by age and sex, for the year 1992-3 for the province of Ontario,[15] divided by the number of persons of the same age and sex for 1992-3 obtained from tables published by Statistics Canada[13] and (3) the calculated cataract operation incidence from the REACT study, extrapolated to give the risk reduction for cataract incidence at 5 year intervals over a 25 year period (for the cohort aged 50-55 initially) or a

Table 1. Costs of cateracts for Ontario.

Cataract Surgery Costs For Ontario (1996)		
Code Or Description	**Inpatient**	**Day Surgery**
E140	380.60	380.60
E140c 2 Units Anesthesia	136.60	136.60
E950 Capsulotomy $148.85 X 50%	74.43	74.43
Ontario Cost Control Project	1658.00	1086.00
A234 After Care Costs (2 Visits)	47.80	47.80
Occp + Foldable Iol	235.00	235.00
Totals	2532.43	1960.43
Weighted Average 90% Day Surgery	2017.63	
Cpi Correction 1996 (135.6) to 1998(139.15) to 2001	2070.45	

Table 2. Ontario cataract operation incidence.

Ontario '93 Population			**Total Number Cataract Excisions**		**Percentage**				**5 Year Percentage**	
AGE	M	F	F	M	M	%OP*	F	%OP*	M	F
50-54	261	266.6	458	687	0.263	82.7	0.172	85.4	1.316	0.86
55-59	226.0	235.3	1068	1092	0.483	91.6	0.454	92.1	2.42	2.27
60-64	219.4	231.6	2137	1988	0.906	90.5	0.923	89.6	4.53	4.61
65-69	190.0	222.6	4107	3220	1.695	90.3	1.845	87.5	8.47	9.23
70-74	145.6	190.4	5600	4088	2.81	88.3	2.94	84.6	14.0	14.7
75-79	91.9	137.0	6731	3881	4.22	91.5	4.91	85.2	21.1	24.5
80-84	54.0	97.1	5336	3185	5.89	85.0	5.50	75.4	29.5	27.5
85+	33.1	86.2	3140	1162	3.51	80.4	3.64	48.5	17.6	18.2

* Percent Outpatient

15 year period (for the cohort aged 60-65 years initially). (See **Table 2,** p.215)

Estimated Treatment Effects

The REACT treatment effect, along with the 95% confidence intervals reported by the Roche European American Cataract Trial[3] is a reduction cataract risk of 49% (Confidence interval 20% -80%), similar to the risk reduction we reported for vitamin E.[21,22]

Cataract

In a double blind randomized trial, vitamin E[4] was shown to result in similar risk reduction of cataract progression to that shown in our case control study,[2] as did the complete antioxidant cocktail with additional vitamin C and β-carotene, in reducing risk of cataract severe enough to necessitate a cataract operation. The risk reduction values for cataract are supported by 4 of 5 additional separate population studies showing similar risk reduction associated with increased vitamin E intake or blood levels.[17] A preliminary meta-analysis of these papers and our results suggested approximately 56% risk reduction for cataract.[17] The lack of effect found by the VECAT vitamin E supplementation cataract study and the AREDS cataract study 10 have been ascribed to the use of less sensitive end points for cataract measurement and more advanced age and initial cataract stage in these studies.[23] By comparison the REACT trial used a more precise measurement of cataract progression,[23] and is supported by a large number of case-control studies[17] which showed significant treatment effects by meta analysis.

Estimated Costs and Savings

All costs, unless specified, are in 2001 Canadian dollars. The yearly cost of REACT supplements was $150. Costs of cataract are detailed in **Table 3, p.217.** Ontario Health Insurance Plan (OHIP) values were used for the costs of hospitalization,[15] physician services, and diagnostic tests. In economic analysis it is appropriate to calculate the "present value" (PV) of both future costs and benefits using a discount rate reflecting the actual time preference. A discount rate of 3% has been used,[24] and comparisons to 5% discount rate are included in several tables for comparison (See **Table 4**, p. 217).

Sensitivity Analyses

The following variables were explored in sensitivity analyses: discount rate (0-20%), the cost of REACT supplementation($150-$300/yr), cost of initial cataract surgery ($0-$10,000), compliance, and the estimated treatment effects for reducing risk of cataract (0-100%).

Results

Direct Medical Costs: Cataract Risk Reduction by REACT supplementation:

For the cohort aged 50-55 initially, the estimated cost(PV) of cataract operations is $301 million, while for the treated cohort the estimated cost of cataract operations is $163 million. The total cost of REACT supplementation is $101 million, resulting in cataract treatment savings of $137 million for the model (**Table 4**), and a net savings of $36.9 million after REACT cost was deducted.

The savings per cataract averted were $364. For supplementation from a cohort aged 65 initially, the cost of supplementation was $83 million. The savings were $10 million, or $141 per cataract averted. The savings per initial member of the cohort were $14 per person.

Sensitivity Analyses, Mortality, and Compliance: Economic analyses of the costs to the Ontario Ministry of Health of cataract were not sensitive to the cost of REACT supplements up to $200, slightly more than the (current) cost of $150/year. The data also supported a robust relationship for savings

Table 3. Cost analysis of REACT for incident cataract alone.

Years	Age	Population Size (thousands)		Cost of REACT ($millions)		Surgery Costs Net Savings ($millions)						Overall net Savings
						Untreated		Treated		$millions		
		M	F	M	F	M	F	M	F	M	F	
2001-2005	50-54	389.6	398.8	3.86	2.57	11.4	7.7	11.4	7.7	--	--	(6.43)
2006-2010	55-59	380.9	397.3	5.54	5.81	16.5	17.3	8.5	8.8	8.0	8.5	5.2
2011-2015	60-64	368.3	392.3	9.23	10.02	27.5	29.8	14.0	15.2	13.5	14.6	8.82
2016-2020	65-69	347.1	379.7	13.98	16.64	41.6	49.5	21.2	25.2	20.4	24.3	14.03
2021-2025	70-74	313.2	356.6	17.95	15.42	53.4	45.9	27.2	23.4	26.2	22.5	15.29
Total				50.56	50.5	150.4	150.1	82.3	80.3	68.1	69.8	36.93
Totals (M+F)				**101**		**301**		**163**		**137.9**		**36.9**

Table 4. Worst case scenario analyses at 3% and 5% discount rates.

	Discount rate (%)	REACT Cost ($)	Net Savings: Cataract less REACT ($)
	3%	(101×10^6)	(45×10^6)
	5%	(384×10^6)	(35×10^6)
Cost / person	3%	(128)	(57)
	5%	(97)	(44)

–Numbers in parentheses indicate that there is a net excess cost.
–These estimates assume a 3 or 5% discount rate and a 20% relative risk reduction

by varying up to threefold the discount rate, cost of cataract surgery, and risk reduction for cataract. Reduced compliance simply reduced the savings by the percent of the cohort failing to comply.

Worst Case Scenarios

In order to investigate whether the scenarios would continue to be economically attractive, we included the lower limits of the 95% confidence intervals in our model. Reduction in cataract medical direct costs resulted in a net loss of $44.7 million using a 3% discount rate, and a net loss of $34.9 million for a 5% discount rate.

Discussion

The main result of this economic analysis is that modest reductions in the risk of common, and expensive, outcomes from a low-cost intervention can lead to profound economic and personal gains. If the benefits of REACT supplements modeled in this analysis are substantiated by ongoing trials, at a cost of only $150 per year, respectively, REACT antioxidant supplements will be a bargain for the Ontario Ministry of Health as well as a bargain for Ontario society at large.

Possible Mechanisms of Action of VE, VC and Antioxidant Supplements

Vitamin E is the major dietary lipid antioxidant used in most cells.[25,26] Its mechanism of action is primarily due to scavenging free radicals, thus preventing the formation of lipid peroxides and oxidized by-products which initiate the pathogenic processes. Recently it has been reported that some of the antioxidant effects may be mediated by elements controlling gene expression.[27-29] In cataract of the lens outer layer (cortex) these antioxidant properties prevent damage to the lens cell membrane.[22,30] Vitamin C has been shown to regenerate oxidized vitamin E, which in turn has a high probability of regenerating oxidized β-carotene.[31]

Cost Implications: A "Dominant Strategy?"

The possibility of net cost savings as a result of REACT antioxidant supplementation is somewhat surprising, since this does not occur very frequently in public health interventions or medicine. This is referred to as a "dominant strategy," that is one which produces more health at less cost. A current example is the folic acid supplementation of pregnant women to avoid spinal cord abnormalities in the fetus. According to Laupacis[32] a medical treatment costing up to $20,000 per Quality Adjusted Life Year (QALY) is strongly supported for adoption, one costing $20,000 - $100,000 is moderately supportable, while one costing more than $100,000/QALY is only weakly supportable.

If cataract incidence is decreased, our proposed model of REACT supplementation shows a net savings and is therefore clearly dominant. This scenario is competitive per cataract averted at a savings of $364, less than the cost of surgical treatment ($2,232) clear evidence that this is a dominant strategy.

Worst Case Scenario

One way to view the model is to examine the impact of REACT in the 'worst case' scenarios, that is, estimating the minimum treatment effect using the lower confidence intervals of the risk reductions reported in the literature and reduced compliance rates by physicians and patients. These correspond to relative risk reductions of 20% for cataract. This risk reduction resulted in a cost per cataract averted of $1079, still less than the cost of a cataract operation ($2,232).

Study Limitations

For cataract the benefit has been estimated from the randomized REACT trial[3] as well as case-control studies, and population studies.[21,22] They may not

be stable and more accurate estimates await the results of trials in progress or planned. Notwithstanding, our 'worst case scenario', and sensitivity analyses suggest that a modest effect, say a 10% relative risk reduction, would still have profound and favourable economic consequences. Moreover, such a small effect is certainly possible given the current state of knowledge.

Conclusions

REACT antioxidant supplementation appears to be a dominant strategy providing additional health benefit for little (cataract only). If benefits from REACT supplementation are substantiated in ongoing clinical trials, their use perhaps in combination with other antioxidants would be a bargain both to society and the individual. Subsidizing their cost would be a cost-effective strategy for OHIP to introduce.

Averting the need for some cataract operations would also reduce the need for scarce operating rooms: an estimate would be freeing up approximately 20 operating rooms for Canada, the equivalent to the operating rooms of several large hospitals.

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