Cost Effectiveness of Whole Population BRCA Genetic Screening for Cancer Prevention in Israel

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ABSTRACT

With the growing technical ease and reduction in genetic screening costs, whole population *BRCA* screening may be a feasible option. Our objective was to investigate the cost effectiveness of whole population screening for *BRCA* mutations in Israel, for varying degrees of *BRCA* carrier state. Lifetime costs of whole female population screening for *BRCA* mutation carrier state versus nonscreening were compared using a Markovian process decision analysis model. Model parameters including ovarian and breast cancer risks were obtained from previously published data. Screening and other treatment-related costs were received from the Israeli Ministry of Health pricing list according to specified codes. Quality-adjusted life years were used for cost-effectiveness analysis. Sensitivity analysis was conducted to evaluate model uncertainties, specifically varying degrees of *BRCA* prevalence. Results show that whole population *BRCA* screening in Israel is cost effective across a wide range of *BRCA* prevalence rates with an incremental cost-effectiveness ratio of 81,493 new Israeli Shekels for a *BRCA* prevalence of 2.5%, increasing to 250,000 new Israeli Shekels for a 0.75% prevalence rate, per quality-adjusted life year gained. Discount rate and population *BRCA* prevalence and rate of risk reduction salpingo-oophorectomy are the most influential parameters in the model. Whole population screening for *BRCA* mutations should be offered as part of general health screening strategies by national medical insurance providers, even for non-Ashkenazi Jews. Our algorithm can be applied for other countries, adjusting local costs of screening and treatment.

Prevention Relevance: Whole population *BRCA* mutation screening in Israel is cost effective across a wide prevalence rate and should be offered as part of general health screening strategies by national medical insurance providers for cancer prevention.

Introduction

Current recommendations for *BRCA* testing in Israel, as in most countries, are clinical and based upon personal or family history of breast or ovarian cancer. Using this clinical, family-history based screening strategy has the potential of missing most carriers (1, 2). With the advances in next-generation genetic sequencing and the reduction in genetic testing costs, whole population screening has become a feasible option (3). Previous studies have shown that population-based *BRCA* screening among Ashkenazi Jewish women which have a high prevalence of *BRCA* carriers is cost effective in the United States and the United Kingdom (4), also for varying degrees of Ashkenazi Jewish ancestry (5). In fact, when all four grandparents are Ashkenazi, whole population screening was found to be cost saving (4). Among Jews of Sephardic ancestry, where *BRCA* prevalence is lower, population-based *BRCA* testing was also found to be highly cost effective compared with clinical criteria approach (6). Due to several generations of mixed Ashkenazi and Sephardic marriages, the exact prevalence of *BRCA* carrier state in Israel is still unknown but reaches as much as 2.5% of Jews of Ashkenazi ancestry and at least 0.7% of the pure Sephardic population (7–9) perhaps making whole population screening particularly effective. The aim of our study was to investigate the cost effectiveness of whole population *BRCA* screening in Israel, for varying degrees of *BRCA* prevalence.

Materials and Methods

Lifetime costs of whole female population screening for *BRCA* mutation carrier state starting at the age of 30 versus nonscreening were compared using a Markovian process decision analysis model (**Fig. 1**). The model assumed that all women in the screening arm would have genetic screening. Women found positive for *BRCA* would be offered risk reduction salpingo-oophorectomy (RRSO) at age 40 for ovarian cancer prevention and breast screening with yearly breast

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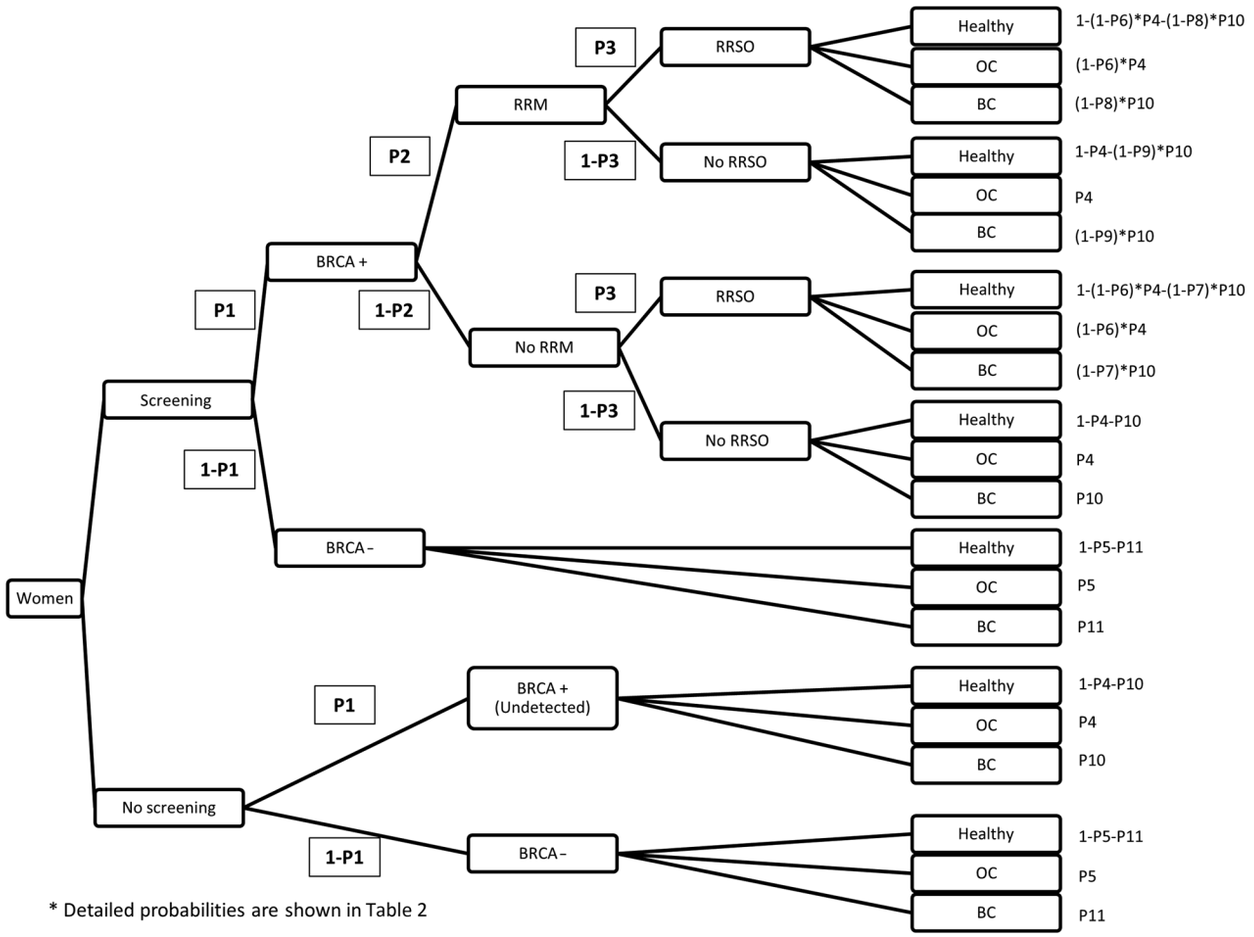

Figure 1.
Markovian decision analysis model, probabilities are shown in **Table 2**.

MRI/ultrasound and or risk reduction mastectomy (RRM) for breast cancer prevention. Costs were discounted at 3%. Quality-adjusted life years (QALY), which reflect both quality and quantity of life lived and incremental cost-effectiveness ratios (ICER), were used for cost-effectiveness analysis. One-way sensitivity analysis was conducted with all variables to evaluate model uncertainty. In addition, we conducted a probabilistic sensitivity analysis (Monte Carlo simulation) using 100 trials, with each including 10,000 subjects.

BRCA screening

BRCA screening in the model was done by using a 14-mutation panel most commonly used for *BRCA* genetic testing in Israel. This panel includes the three most common BRCA founder mutations [*BRCA1 185delAG NM_007294.4:c.66_67AG* (*p.Glu23fs*), *BRCA1 5382insC NM_007294.4:c.5266dup* (*p.Gln1756fs*), and *BRCA2 6174delT NM_000059.4:c.5946del* (*p.Ser1982fs*)] that account for the vast majority of inherited cancer risk due to *BRCA1* and *BRCA2* in Israel (8).

Model costs

Screening and other treatment-related costs were received from the Israeli Ministry of Health's 2020 pricing list according to specified codes with conservative assumptions of health resources utilities (**Table 1**). Elaborate costs used in the model are shown in Supplementary Tables S1 to S3 for ovarian cancer treatment, breast cancer treatment, and *BRCA*-positive patients' follow-up, respectively.

Probabilities

Model probabilities are presented in **Table 2**. The probability of being at the end of each arm of the model constructed was calculated by multiplying the probabilities of events along the arm path. Mean age used in the model for developing sporadic ovarian cancer was 55 years (10) and 62 years for breast cancer (11). Among *BRCA* carriers, average ages used were 45 and 50 for ovarian and breast cancer, respectively (12, 13). The mortality rates of subjects who developed breast cancer or ovarian cancer were based on stage distribution and Kaplan–Meier survival curves for each stage, based on the Surveillance,

Table 1. Total costs used in model.

	IMH[a] code	Cost (Israeli shekels)	Remark
BRCA founder mutation	J1311	632	IMH pricing list
Risk reduction salpingo-oophorectomy	G0231	16,034	IMH pricing list
RRM	G0045	29,510	IMH pricing list
Ovarian cancer diagnosis and treatment		495,353	Calculated (Supplementary Table S1)
Breast cancer diagnosis and treatment		174,438	Calculated (Supplementary Table S2)
Yearly ovarian cancer + breast cancer screening for BRCA carriers		2,651	Calculated (Supplementary Table S3)
Yearly breast cancer screening for BRCA carriers after RRSO (including hormone replacement therapy)		2,753	Calculated (Supplementary Table S3)

[a]IMH: Israeli Ministry of Health (Ministry of Health pricing list, 2020, https://www.health.gov.il/Subjects/Finance/Taarifon/Pages/PriceList.aspx).

Epidemiology and End Results program database. Survival curves were extrapolated by fitting Weibull distribution using the Nelder–Mead Algorithm.

BRCA prevalence

As the true prevalence of *BRCA* mutation carriers in Israel is not yet known due to several generations of mixed Ashkenazi and Sephardic marriages, sensitivity analysis was done to account for varying degrees of *BRCA* prevalence.

QALYs and ICER

Values of health benefits for each strategy (screening vs. nonscreening), from payer prospective, were calculated using QALYs. QALYs are calculated by multiplying the utility value associated with a given state of health by the number of years lived in that state, where QALY of one reflects 1 year lived in perfect health and QALY of zero represents death state. The ICER was then calculated by using the formula: (average cost screening – average cost nonscreening)/(average QALY screening – average QALY nonscreening). The ICER calculated enabled to determine whether whole population screening is cost effective or not, compared with willingness to pay threshold. An intervention was defined as cost effective if the ICER per QALY is between 1 and 3 times per capita GNP [GNP in Israel is estimated at 42,160 USD, equivalent to 142,500 new Israeli Shekels (NIS), estimated during October 2020]. Interventions below 1 GNP per capita are considered very cost effective (14, 15).

Institutional Review Board

As this work is a theoretical, mathematical/financial model, not involving any human or animal subjects in any form, after consultation with our local Institutional Review Board (IRB), it was exempt from the need of IRB approval.

Results

For a *BRCA* prevalence of 2.5%, the known *BRCA* prevalence among Jews of Ashkenazi ancestry (7, 8), whole population screening is very cost effective, with an ICER of 81,493 NIS, per QALY gained (24,110 USD), data are shown in **Table 3**.

One-way sensitivity analysis was conducted for all variables. Results are presented on a tornado diagram (Supplementary Fig. S1). The diagram presents how model parameters influence the ICER calculated. *BRCA* population prevalence and discount rate (set at 3% in our model) and RRSO acceptance rate are the most important variables affecting the ICER. As shown in **Fig. 2**, as the prevalence of *BRCA* carrier state decreases, the ICER increases. For a theoretical prevalence of 1%, the ICER is 176,395 NIS per QALY gained (52,187 USD).

Table 2. Probabilities used in model.

Probability	Description	Analysis 1 Value	Range assumed	Reference
P1	Population prevalence of BRCA	0.0245	0.001–0.3	(2, 4, 7)
P2	Probability that BRCA carrier will undergo RRM	0.278	0.1–0.3	(29)
P3	Probability that carrier will undergo RRSO	0.65	0.3–0.75	(22, 23)
P4	Probability that BRCA carrier without RRSO will get OC	0.2987	0.24–0.35	(37)
P5	Probability that a noncarrier will experience OC	0.0128	0.0005–0.0989	(10)
P6	Reduction in risk of ovarian cancer from RRSO	0.8	0.8–0.96	(33, 38)
P7	Reduction in risk of breast cancer from RRSO	0	0.37–0.65	(33)
P8	Reduction in risk of breast cancer from RRM with RRSO	0.91	0.78–0.99	(34, 35, 39)
P9	Reduction in breast cancer risk from RRM without RRSO	0.91	0.62–0.98	(39)
P10	Probability that a BRCA carrier without RRM will experience breast cancer	0.53	0.44–0.62	(4, 5, 37)
P11	Probability that a noncarrier will experience breast cancer	0.13	0.11–0.14	(11)

Abbreviations: BC, breast cancer; OC, ovarian cancer.

Table 3. Cost-effectiveness analysis of whole population BRCA screening versus nonscreening for BRCA prevalence of 2.5%.

Strategy	Cost (NIS)	Incremental cost	QALY	Incremental QALY	ICER (NIS)
3% Discount rate					
No screening	19,799		24.84645157		
BRCA screening	23,231	3,432	24.888561	0.042109433	81,493
Not discounted (0% discount rate)					
No screening	34,197		49.56087		
BRCA screening	39,745	5,548	49.68924	0.12827	43,223

For a *BRCA* prevalence of 0.75%, which is the estimated *BRCA* prevalence among Sephardic Jews (9), the ICER is 250,000 NIS (73,964 USD). Whole population screening strategy compared with no screening equates to 15.4 and 6.1 days in life expectancy gain for prevalence of 2.5% and 1%, respectively, at a 3% discount rate.

Figure 3 displays the acceptability curve. The acceptability curve is a visual aid for communicating the results of probabilistic sensitivity analysis in cost-effectiveness models. Acceptability curve presents the relative cost effectiveness as a function of the ICER threshold (WTP). For each WTP value, the graph uses net benefits to determine the percentage of simulation iterations in probabilistic sensitivity analysis that favor each strategy. In our study, we found that at a willingness to pay threshold of 340,000 NIS (which are equivalent to 100,000 USD), about 90% of simulation iterations in the whole population *BRCA* screening would be cost effective (**Fig. 3**).

Discussion

Each year around 360 new cases of ovarian cancer and 4,850 new cases of invasive breast cancer are diagnosed in Israel, posing a tremendous medical and economic burden on the Israeli health system. As *BRCA* is an actionable gene that enables very effective prevention measures, identification of carriers may have far-reaching implications. With the improving ease in the technical aspect of genetic testing and the reduction in testing costs, whole population screening is becoming ever more feasible and must be taken into account from both the medical and the economic aspects. For any screening program, event prevalence has a huge impact on screening effectiveness, and as the true prevalence of *BRCA* in Israel, as in most countries, is unknown, we conducted a sensitivity analysis to control for this uncertainty. Our data show that screening for *BRCA* mutations in Israel would be cost effective across a wide range of *BRCA* prevalence values, starting at the highest probable prevalence of 2.5% among Jews of pure Ashkenazi origin, where screening is very cost effective, through to a theoretical prevalence of 0.75% of population, where screening was still found to be cost effective compared with per capita GNP in Israel.

Our data are comparable with data from previous reports from other countries. Manchanda and colleagues reported that population-based screening among Ashkenazi Jewish women is cost saving with a baseline-discounted ICER of -2,079£ per QALY in the United Kingdom (4). Further analysis revealed

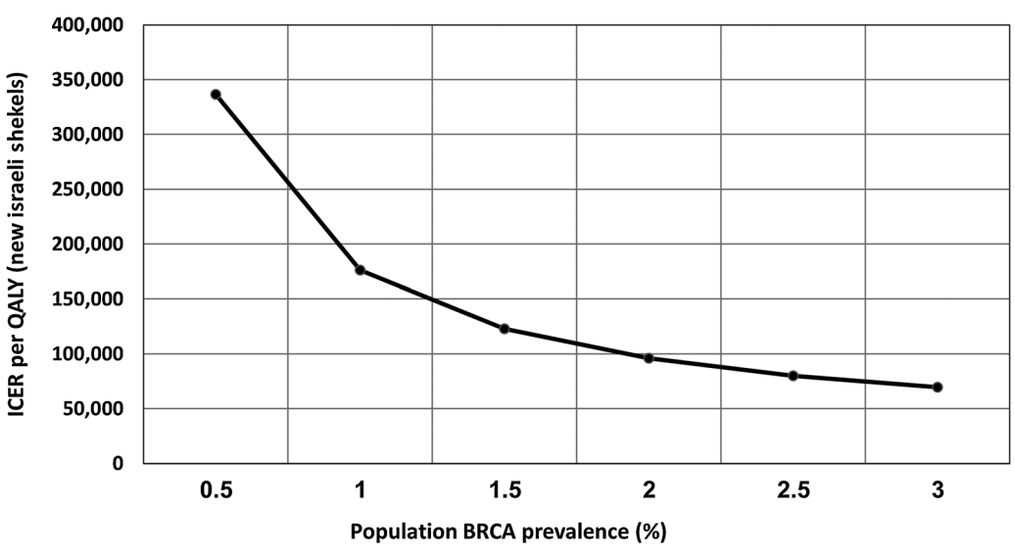

Figure 2.
ICER for varying BRCA population prevalence rates.

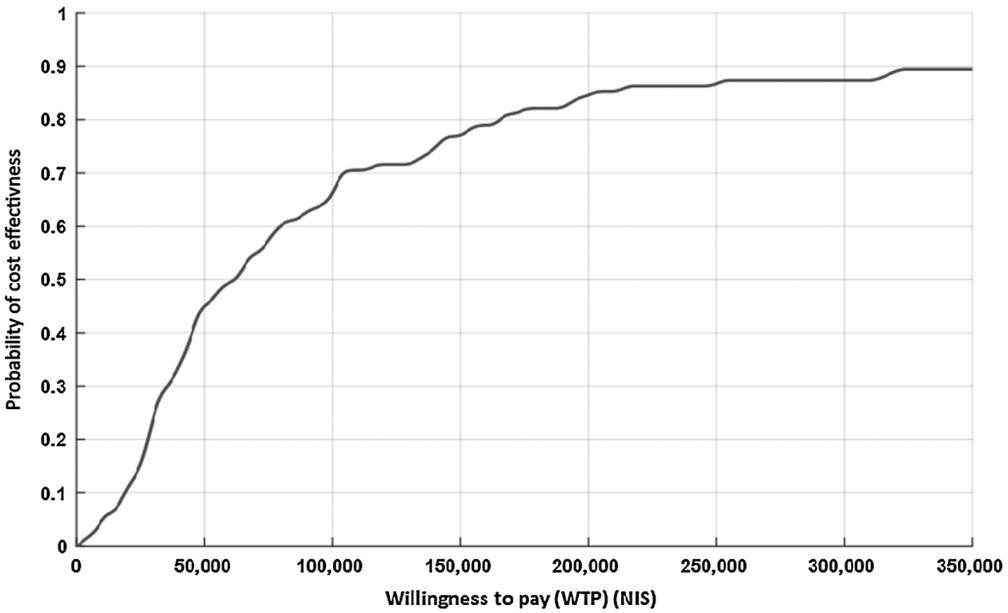

Figure 3.
Acceptability curve for population-based BRCA screening in Israel.

that population-based screening is cost effective also for varying levels of Ashkenazi Jewish ancestry, in the United Kingdom and the United States (5). Even among Jews of Sephardic ancestry, who usually carry one of the three most common *BRCA1* mutation, with a prevalence of 0.5% to 1% in the United Kingdom and in the United States, population-based screening was found to be cost effective (6).

The current strategy of family history–based screening lacks the sensitivity required as a screening tool and has the potential of missing over 50% of carriers at risk (1, 16, 17) and with the growing ease of genetic screening may soon be an unacceptable alternative from both medical and legal standpoint. After diagnosis, the reported uptake of RRSO among *BRCA* carriers varies geographically and culturally, but may reach as high as 98% at designated centers (18–21). Consultation with a gynecologic oncologist seems to play an important role in the uptake of risk reduction surgery among effected patients (21). The reported uptake of RRSO in Israel varies between 49% and 78% (22, 23). Raising the rate of RRSO uptake would improve further the cost effectiveness of screening.

Even though surgical menopause has a direct negative effect on quality of life measures such as vasomotor symptoms, sexual function, bone health as well as cardiovascular health, it is important to note that after surgery, hormone therapy is not contraindicated and even encouraged and that available literature shows that breast cancer risk following RRSO in premenopausal *BRCA* carriers would not change with hormone replacement therapy (HRT) use (24, 25). Moreover, quality of life does not seem to differ between carriers who underwent RRSO to carriers who opt for periodic gynecologic screening and even the general population. RRSO is associated with significantly fewer breast and ovarian cancer worries and more favorable cancer risk perception (26–28). Uptake of RRM is generally lower than that RRSO among *BRCA* carriers (22, 23, 28), yet those who choose to have RRM show high degree of satisfaction mainly due to the reduction in fear of cancer (29).

The main strength of our work is the sensitivity analysis conducted. This analysis enabled us to estimate cost effectiveness of screening with varying degrees of *BRCA* prevalence values, thus overcoming the uncertainty of the true *BRCA* prevalence in the general Israeli population, including subpopulations with lower estimated *BRCA* prevalence. This model may be used in other countries where *BRCA* prevalence has yet been elucidated. Other strengths of our work include the inclusion of newest, highly costly drugs such as bevacizumab and PARP inhibitors in the treatment algorithm of breast and ovarian cancer. PARP inhibitors were only recently approved for the first-line treatment of patients with *BRCA*-positive ovarian cancer in Israel and add considerably to the costs involved with treatment of these patients. Our algorithm also used the most up-to-date probability estimates of ovarian cancer risk reduction after RRSO, 80% in our model, and not the 96% reduction previously reported (30). Moreover, even though it seems biologically plausible that RRSO may also influence the pathophysiology of breast cancer development, the protective effect of RRSO on breast cancer, which was previously estimated at 50% (30–33), is now under debate. Several newer publications that used RRSO as a time-dependent covariate did not conquer any protective effect of RRSO on breast cancer incidence (34–36). Thus, in our model, we assumed zero effect of RRSO on breast cancer. Had we used

50% as the estimated protective effect of RRSO on breast cancer incidence, the ICER calculated would be even more cost effective than the one reported (50,494 NIS per QALY gained for a *BRCA* prevalence of 2.5%).

Our work has several shortcomings. Our model compared whole population screening with no screening and not to family history–based screening as is currently offered. We believe that family-based screening, although recommended, is highly opportunistic, inconsistent, and greatly depends on the awareness of the primary care physician at the time cancer diagnosis and its implementation are extremely difficult to assess. In our model, we used a very conservative estimation of costs involved with breast and ovarian cancer treatment that took into account only the basic treatment needs of the "ideal" breast/ovarian cancer patient and omitted many complications involved with the surgical and medical treatment of these patients. Even with these conservative estimations, we found screening to be cost effective. Finally, implementing a population-based genetic screening strategy, although cost effective, would raise many challenges that would need to be overcome, starting from the logistics involved in screening whole population, through the challenges of handling positive tests, down to solving ethical dilemmas that would rise once this delicate, personal genetic information is known.

In conclusion, with the progress in genetic testing technologies and decreasing costs, population-based screening for *BRCA* mutations, as well as for other actionable genetic mutations, may become a feasible option, displacing more obsolete recommendations such as family history–based screening.

Authors' Disclosures

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Authors' Contributions

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