MyLynch Assumptions and References

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Cancer Penetrance Estimation

All cancer penetrances were determined by a rigorously curated literature review in which cancer penetrances could be extracted and stratified by the lynch gene with a pathogenic mutation, sex, and age (Braun, Yang, Griffin, Parmigiani, & Hughes, 2018). The impacts of the interventions on cancer risk were estimated by taking these baseline cancer penetrances, conditional on the gene, sex, and age, and applying an odds ratio, hazard rate, or relative risk from a peer-reviewed study on the impact of the respective interventions on respective cancer risk.

Assumptions

The assumptions and references in this document are for the intervention options in the app only (colonoscopies, aspirin, weight loss, hysterectomies, and oophorectomies). For all other assumptions and references regarding cancer penetrances refer to Braun et al., 2018.

Colonoscopy Intervention

The relative risk estimate of colorectal cancer (CRC) for individuals with a MLH1 or MSH2 mutation who receive colonoscopies every three years compared to those who do not is 0.44 (Jarvinen, et al., 2000). The application assumes that the relative risk of 0.44 is the same for all Lynch genes.

It is further assumed that the data which the carrier risk estimates were based on was drawn from a mix of individuals who received colonoscopies every three years or less and those who did not. The estimated proportion of those receiving colonoscopies every three years or less is 0.821. This proportion was interpolated from two- and five-year colonoscopy rates of a sample of individuals with Lynch drawn from the CRC Family Registry (Kim, et al., 2016). Two additional relative risks were calculated using the proportion and then applied to the data for the purpose of relating the mixed data to individuals receiving colonoscopies every three years or less and to those who do not.

The CRC risk estimates for EPCAM carriers and male MSH2 carriers who do not follow their prescribed colonoscopy schedules are quite high. Calculating CRC risks for younger individuals with high penetrance Lynch genes using the method spelled out in the above paragraph results in risk estimates at older ages to reach 100%. These risks were censored down to 90% to become more in-line with maximum lifetime risk estimates published by other studies. Risk estimates for CRC in Lynch patients are assumed to be biased low due to the proliferation of colonoscopies and therefore these very high estimates, although alarming, may be possible for those who do not receive colonoscopies (Watson & Lynch, 2001). There are studies that suggest the theoretical lifetime maximum CRC risk for a lynch patient can exceed 90% and approach 100% (Vasen, et al., 1996) (Aarnio, et al., 1999). Considering the great benefit colonoscopies provide in preventing cancer (Jarvinen, et al., 2000) and that the vast majority of patients get regular colonoscopies (Kim, et al., 2016), the curves showing risk with regular colonoscopies provide a more reasonable risk estimates.

Aspirin Regimen Intervention

The hazard rate estimates for CRC in individuals with a MLH1, MSH2, or MSH6 mutation taking 600mg of aspirin per day compared with those not taking aspirin is 0.56 two years or greater from the start of the intervention (Burn, et al., 2020), 0.63 at 5 years (Burn, et al., 2011), and 0.65 at 10 years (Burn, et al., 2020). It is assumed that this hazard rate can be extended to PMS2 and EPCAM carriers. The application applies smoothing of the hazard rate from year 1 to year 10. Additionally, it is assumed the baseline penetrance data consisted of an insignificant number of individuals on a 600MG aspirin dosage and therefore the baseline risks were not adjusted for lack of aspirin use.

Weight Loss Intervention

Research indicates each single point increase in BMI increases the hazard rate of CRC by 7% for individuals with a MLH1 mutation (Movahedi, et al., 2015). This application further assumes the opposite is true; there is a 7% decrease in the hazard rate for each single point decrease in BMI. The hazard rate decrease begins after 5 years to align with the study referenced in Movahedi, et al., 2015. Smoothing is then applied to the hazard rate from years 1 to 5.

Research also indicates for each 5kg weight gain, the odds ratio of women developing endometrial cancer increases by 20% (Trentham-Dietz, Nichols, Hampton, & Newcomb, 2006). This application assumes the opposite is true; there is a 20% decrease in the odds ratio for every 5kg of weight lost. It is also assumed that the benefit of weight loss is the same for the sub-population of individuals with Lynch.

It is assumed that the data which the carrier risk estimates were based on was drawn from a sample of individuals of varying BMIs and that the average BMI of this sample was 27.7 for men and 28.2 for women (Fryar, Kruszon-Moran, Gu, & Ogden, 2018). The original risk estimates are modified to match the current BMI of the user, as well as the BMI which corresponds to the user's selected weight loss option.

If the user's height and weight correspond to a BMI above the normal range (≥25), then the user is shown the weight loss intervention options and the weight loss hazard rate for CRC and/or the weight loss odds ratio for endometrial cancer are applied to the risk estimates. If the user meets the criteria be shown the weight loss intervention options, then the user is provided with a range of weight loss options from 0 pounds of weight loss up to a maximum number of pounds to lose. The maximum number of pounds to lose is the lesser of either the number of pounds that corresponds to a 5-point BMI decrease or the number of pounds that would bring the user just inside the normal BMI range.

Surgical Interventions

Hysterectomies and bi-lateral oophorectomies are assumed to reduce endometrial and ovarian cancer risk down to 0%. These surgeries are assumed to be prophylactic in nature. All references to oophorectomies in the app are assumed to be bi-lateral (removal of both ovaries).

Intervention Interactions

It is assumed that all interventions for the same cancer are additive.

References

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