Association Between Aspirin and Cancer Risk: A Mendelian Randomization Analysis

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Introduction

- Previous researches have reported on the protective effect of aspirin on different types of cancers. However, evidence from observational studies can be biased by multiple confounding factors. Also, it remains unclear whether aspirin use is casually related to a decreased cancer risk.

Objectives

- Consequently, we conducted Mendelian randomization analyses, using single nucleotide polymorphisms (SNPs) as instrumental variables to investigate the casual effect of aspirin on different types of cancers.

Methods

- Mendelian randomization analyses were conducted using pooled statistics from corresponding researches and several large-scale consortia. Inverse-variance weighted, MR-Egger and weighted median methods were utilized to evaluate the possible causal relationship between aspirin and the observed reduction in cancer risk. Results were shown by odds ratios (OR) and their corresponding 95% CIs. Analyses were conducted using the package "TwoSampleMR" in R.

Result

- A total of 19 cancers corresponding to 344,392 cases and 5,424,758 controls were included in the final analysis.

- In contrast to the lower risk for various cancer types reported in conventional observational studies, our MR results only showed a decreased risk in lung cancer [odds ratio (OR) 0.0418; 95% confidence interval (CI) 0.0031-0.5638; P=0.0168] and squamous cell lung cancer [OR=0.002; 95% CI 1.2145×10^{-5}-0.3009; P=0.0153].

- Insignificant results were observed in other types of cancers including lung adenocarcinoma, breast cancer, ovarian cancer, colon cancer, kidney cancer, liver cancer, esophageal cancer, oral cancer, pancreas cancer, rectal cancer, malignant melanoma, non-melanoma skin cancer, Hodgkin's lymphoma as well as non-Hodgkin's lymphoma.

Number of cancer cases and controls in Mendelian randomization analyses

Trait	Consortium	Number of cases	Number of controls	Population	Sex
Lung cancer	ILCCO	11,348	15,861	European	Males and females
Lung adenocarcinoma	ILCCO	3442	14,894	European	Males and females
Squamous cell lung cancer	ILCCO	3275	15,038	European	Males and females
Breast cancer	BCAC	122,977	105,974	European	Females
ER+ breast cancer	BCAC	69,501	105,974	European	Females
ER− breast cancer	BCAC	21,468	105,974	European	Females
Ovarian cancer	OCAC	25,509	40,941	European	Females
Skin cancer					
Malignant melanoma	Neale Lab	2677	334,482	European	Males and females
Non-melanoma skin cancer	MRC-IEU	672	462,261	European	Males and females
Colon cancer	MRC-IEU	1494	461,439	European	Males and females
Kidney cancer	MRC-IEU	1114	461,896	European	Males and females
Liver cancer	MRC-IEU	169	462,764	European	Males and females
Esophageal cancer	MRC-IEU	201	462,732	European	Males and females
Oral cancer	MRC-IEU	103	462,830	European	Males and females
Lymphoma					
Hodgkin's lymphoma	MRC-IEU	440	462,493	European	Males and females
Non-Hodgkin's lymphoma	MRC-IEU	293	462,717	European	Males and females
Pancreas cancer	MRC-IEU	233	462,777	European	Males and females
Prostate cancer	PRACTICAL	79148	61,106	European	Males
Rectal cancer	MRC-IEU	328	462,605	European	Males and females

Mendelian randomization estimates of the associations between aspirin use and risks of different types of cancers

Cancer Type	Inverse variance weighted		Weighted median		MR Egger	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Lung cancer						
Lung cancer overall	**0.0418 (0.0031, 0.5638)**	**0.017**	**0.0129 (0.0006, 0.3007)**	**0.007**	**0.0001 (0.0000, 0.1027)**	**0.047**
Lung adenocarcinoma	0.0538 (0.0002, 11.6075)	0.287	**0.0058 (0.0000, 0.7525)**	**0.038**	0.0002 (0.0000, 984.7818)	0.329
Squamous cell lung cancer	**0.0019 (0.0000, 0.3009)**	**0.015**	**0.0025 (0.0000, 0.5832)**	**0.031**	0.0001 (0.0000, 452.2191)	0.297
Breast cancer						
Breast cancer overall	0.2944 (0.0527, 1.6437)	0.163	0.9271 (0.2091, 4.1096)	0.9201	3.2437 (0.0224, 470.1204)	0.663
ER+ breast cancer	0.2133 (0.0281, 1.6166)	0.135	0.9753 (0.1700, 5.5942)	0.978	6.3429 (0.0238, 1688.6930)	0.545
ER− breast cancer	0.2777 (0.0513, 1.5032)	0.137	0.4337 (0.0568, 3.3120)	0.421	0.3425 (0.0016, 74.3467)	0.712
Ovarian cancer	0.4994 (0.0749, 3.3281)	0.473	1.9494 (0.1727, 22.0039)	0.589	37.5909 (0.2377, 5945.6460)	0.219
Skin cancer						
Malignant melanoma	1.0206 (0.9912, 1.0508)	0.172	1.0281 (0.9878, 1.0700)	0.175	0.9955 (0.9128, 1.0857)	0.923
Non-melanoma skin cancer	1.0074 (0.9971, 1.0178)	0.161	1.0068 (0.9933, 1.0205)	0.324	1.0045 (0.9750, 1.0349)	0.780
Colon cancer	1.0058 (0.9871, 1.0249)	0.543	0.9996 (0.9784, 1.0212)	0.968	1.0380 (0.9875, 1.0910)	0.203
Kidney cancer	1.0043 (0.9828, 1.0263)	0.697	1.0113 (0.9910, 1.0320)	0.278	1.0341 (0.9730, 1.0991)	0.330
Liver cancer	0.9976 (0.9924, 1.0027)	0.352	1.0002 (0.9935, 1.0069)	0.960	1.0072 (0.9927, 1.0219)	0.378
Esophageal cancer	0.9986 (0.9924, 1.0049)	0.662	0.9962 (0.9888, 1.0037)	0.319	0.9886 (0.9721, 1.0053)	0.237
Oral cancer	0.9974 (0.9934, 1.0014)	0.207	0.9977 (0.9926, 1.0027)	0.361	1.0019 (0.9906, 1.0134)	0.752
Lymphoma						
Hodgkin's lymphoma	0.9918 (0.9808, 1.0030)	0.151	0.9926 (0.9810, 1.0043)	0.212	0.9919 (0.9584, 1.0267)	0.664
Non-Hodgkin's lymphoma	0.9975 (0.9908, 1.0043)	0.474	0.9947 (0.9858, 1.0037)	0.249	0.9950 (0.9762, 1.0143)	0.633
Pancreas cancer	1.0006 (0.9945, 1.0067)	0.848	1.0045 (0.9967, 1.0124)	0.257	1.0023 (0.9853, 1.0195)	0.807
Prostate cancer	2.1355 (0.2307, 19.7642)	0.504	1.9590 (0.4446, 8.6323)	0.374	520.1727 (4.4692, 60542.9500)	0.050
Rectal cancer	1.0038 (0.9965, 1.0110)	0.310	0.9986 (0.9896, 1.0077)	0.763	1.0138 (0.9935, 1.0345)	0.243

Conclusions

- The potential effect of aspirin in cancer prevention still needs to be interpreted with cautions and aspirin is still too early to be recommended as a universal chemoprotective agent for primary cancer prevention. Further randomized controlled trials with a more rigorous design are warranted in the future.