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BRIEF REPORT

Staple Food Fortification with Folic Acid and Iron and Gastrointestinal Cancers: Critical Appraisal of Long-Term National Fortification

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ABSTRACT

The co-occurrence of wheat flour fortification with folic acid and iron and gastrointestinal cancer incidences were critically assessed in the East Azerbaijan province in Northwest of Iran. In an ecological design, overall gastrointestinal cancer rate ratios and their 95% confidence intervals (95% CI) were calculated as primary outcome before (2004–2006) and after (2007–2015) the introduction of fortification. No consistent changes were observed in esophageal and gastric cancer, but the rate ratios of colorectal cancer increased significantly after fortification in the 35–54 years age group (women: 2.07, 95% CI: 1.79–2.49; men: 1.59, 95% CI: 1.33–1.89) and the 55–74 years age group (women 1.50, 95% CI: 1.27–1.76; men: 2.51, 95% CI: 2.13–2.95). The increased incidence of colorectal cancer was contemporary with long-term fortification; further investigation is required to establish the associations.

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Introduction

Folic acid and iron levels play a crucial role in maternal and child health (1,2). Currently, 81 countries have mandatory rules for fortifying staple food (mainly wheat flour) with folic acid or a combination of folic acid and iron in order to ensure sufficient daily intakes of these micronutrients among people (3). However, studies reveal the probable adverse effect of long-term effects of folic acid and iron supplementation on the risk of gastrointestinal cancer (4–6). Conversely, a recent study highlights the safety of folic acid supplementation without any upper limit for folic acid intake (7). Despite controversial findings on probable non-favorable effect of iron and folic acid supplementation on gastrointestinal cancers, there are limited studies assessing the effect of long-term folic acid and iron fortification on gastrointestinal cancers.

We aimed to study the co-occurrence of folic acid and iron fortification and the incidence of common gastrointestinal cancers. In this study, the incidence of these cancers before and after implementation of fortification programs was compared, in order to provide insights into possible impacts of long-term food fortification on gastrointestinal cancers.

Materials and Methods

We compared the cumulative rates of gastrointestinal cancers from 2004 to 2006 (before) with 2013 to 2015 (after) the induction of folate and iron fortification. The study was done in the East Azerbaijan province of northwest Iran among homogenous Azeri ethnic people with similar lifestyles and with higher rates of gastrointestinal cancers (8–10).

We used national censuses of each every 5 years. The national fortification law was legislated since 2005 and implemented nationally in 2007. Approximately 88% of the consumed flour has been fortified in Iran since March 2006 (11). The fortification premix consists of 1.5 and 30 parts per million of folic acid and ferrous sulfate, respectively (1,11). The data regarding fortification were gathered from provincial food administrations and the ministry of health.

The incidence of gastrointestinal cancer, defined according to the International Classification of

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Table 1. Age-adjusted standard rates for gastrointestinal tract cancers before and after mandatory flour fortification with folic acid and iron, in East Azerbaijan, Iran.

		Before fortification			After fortification								
Esophageal Ca (ICD 15)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Age 35–54 years	F	12.03	43.07	36.92	52.96	23.95	12.05	15.03	35.97	23.6	18.78	18.14	20.41
	M	11.41	34.7	21.99	19.08	17.22	15.69	15.62	13.62	14.83	13.41	9.62	13.57
Age 55–74 years	F	133.76	217.6	186.52	290.18	238.37	69.62	225.7	167.32	117.55	145.6	140.11	203.51
	M	68.84	27.02	80.92	98.93	85.76	90.86	81.65	88.71	47.57	47.46	61.37	52.16
Gastric Ca (ICD 16–17)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Age 35–54 years	F	21.49	19.43	17.55	20.60	14.76	30.2	7.73	10.21	18.89	23.43	10.49	20.72
	M	12.23	44.08	37.79	53.92	23.83	12.23	15.48	36.61	24.08	28.9	18.03	19.87
Age 55–74 years	F	151.59	77.41	69.14	94.22	76.94	225.3	73.30	51.22	47.35	122.74	55.97	105.26
	M	130.97	205.15	175.85	268.16	217.66	71.23	232.97	172.74	121.7	147.19	143.79	208.58
CRC (ICD 18–21)		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Age 35–54 years	F	15.05	14.57	19.41	25.51	32.83	24.56	19.45	28.28	18.18	23.69	23.92	26.75
	M	15.53	20.78	22.21	33.17	26.39	24.95	16.04	20.16	25.17	24.01	25.52	32.13
Age 55–74 years	F	35.54	50.24	44.56	60.51	44.05	52.44	87.32	64.39	49.07	63.87	65.45	84.43
	M	36.16	40.72	50.73	83.04	90.37	66.47	95.12	76.31	65.33	91.27	87.04	114.08

The age-adjusted standard rates are reported per 100,000 inhabitants.
Abbreviations: Ca: cancer; CRC: colorectal cancer; F: female: ICD: international classification disease; M: male.

Disease, using codes 15 for esophageal cancer, 16 for gastric cancer, and 18–21 for colorectal cancer, as reported in the cancer registry based on data obtained from local pathology centers. Completeness of the coverage was measured as the number of reported cases of cancer per year divided by the number of gastrointestinal cancers in Iran estimated by the WHO. The incident cases were classified by sex at 1-year intervals from 2004 to 2015 and by age group (35–49 years and 55–74 years) at 5-year intervals. The crude incidence rates of cancers were calculated per 100,000 people by age and sex. We then calculated the age-adjusted rates using the province's annual population and the world standard population (12) and adjusted the estimated rates for each year with the calculated coverage of the provincial cancer registry for the same year. The rate ratio and 95% confidence intervals (CI) between two periods were calculated using accumulated age-adjusted incident cases for each age group before and after fortification (13).

We next calculated the trends in the age-adjusted rates for gastrointestinal cancers for the whole 12-year period (2004–2015). The age-adjusted rate calculation and trend analysis were performed using the Joint Point Regression Program, Version 4.4.0.0 (https://surveillance.cancer.gov/joinpoint/). The Joint Point regression model was used to identify changes in cancer trend by describing the continuous changes (14). The entire trend was analyzed for each type of cancer by sex (male and female) and age category (35–54 years and 55–74 years), and the average annual percentage of change in trend for each cancer was calculated for the entire period (2004–2015). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Project identification code: TBZMED.REC.1394.1193).

Results

The mean cohort size during the study period was 3,753,666, accounting for 4.6% of the total population in Iran. Overall, 49% of the cohort was female, 69% lived in urban areas, 37% were aged 30–60 years, and most were of Azeri ethnic background. The age-adjusted standard rates for gastrointestinal cancers before and after mandatory flour fortification and trends analysis and cumulative rate differences for gastrointestinal cancers from before to after fortification are depicted in Tables 1 and 2. The rate ratios of esophageal cancer were significantly lower after the fortification period in all men (0.60, 95% CI: 0.48–0.75 for age 35–54 years and 0.79, 95% CI: 0.66–0.93 for age 55–74 years) and for gastric cancer, in all women (0.44, 95% CI: 0.36–0.56 for age 35–54 years; 0.76, 95% CI: 0.68–0.86 for age 55–74 years). The rate ratios of colorectal cancer were significantly higher after the fortification period for those aged 35–54 years with odds ratio (OR) of 2.07, (95% CI: 1.79–2.49) for women; and OR of 1.59, (95% CI: 1.33–1.89) for men, and for those aged 55–74 years (OR 1.50, 95% CI: 1.27–1.76 for women; and OR 2.51, 2.13–2.95 for men) as well. There were no significant or consistent trends for the gastrointestinal cancers by sex or age group. However, a significant decreasing trend was detected for esophageal cancer in men, with average decreases of −7.2% (95% CI: −11.7 to −2.1) in the 35–54 years age group and −5.9 (95% CI: −9.9

Table 2. Trends analysis and cumulative rate differences for gastrointestinal tract cancers from before and after mandatory flour fortification with folic acid and iron in East Azerbaijan, Iran.

Cancer site sex		AAPC[a]	95% CI for trend	P for trend	Rate ratio[b]	95% CI for rate ratio
Esophageal Ca (ICD 15)						
Age 35–54 years	F	−7.0	−15.1 to 1.9	0.1	0.71	0.59 to 0.85
	M	−7.2	−11.7 to −2.1	0.0	0.60	0.48 to 0.75
Age 55–74 years	F	−3.0	−11.5 to 1.2	0.5	1.1	1.00 to 1.24
	M	−5.9	−9.9 to −1.7	0.0	0.79	0.66 to 0.93
Gastric Ca (ICD 16–17)						
Age 35–54 years	F	−4.8	−13.7 to 5.0	0.3	0.44	0.36 to 0.56
	M	−7.3	−15.3 to 6.1	0.1	0.57	0.47 to 0.68
Age 55–74 years	F	−2.9	−11.9 to 7.0	0.5	0.76	0.68 to 0.86
	M	−8.1	−10.1 to 7.3	0.7	1.00	0.98 to 1.22
CRC (ICD 18–21)						
Age 35–54 years	F	8.1	−4.8 to 8.8	0.6	2.07	1.79 to 2.49
	M	1.7	−3.7 to 7.1	0.5	1.59	1.33 to 1.89
Age 55–74 years	F	5.1	1.0 to 9.4	0.0	1.50	1.27 to 1.76
	M	11.6	0.1 to 24.5	0.0	2.51	2.13 to 2.95

[a]Average annual parentage of change in cancer rates.
[b]$P < 0.05$ is regarded as significant. Before fortification = 2004–2006. After fortification = 2013–2015.
Abbreviations: AAPC: average annual parentage of change; Ca: cancer; CRC: colorectal cancer; F: female: ICD: international classification disease; M: male.

to −1.7) in the 55–74 years age group. For colorectal cancer, there were average increasing trends of 5.1% (95% CI: 1.0–9.4) for men and 11.6% (95% CI: 0.1–24.5) for women in the 55–74 year age groups. No other significant trends were detected.

Discussion

In this study, changes in the rates of esophageal and gastric cancer were not consistent among men and women in each age group. However, the accumulated age-adjusted incidence rates for colorectal cancer were significantly higher after fortification compared with before fortification in both sexes and both age groups.

Colorectal cancer rates were significantly higher at years 7–9 after fortification was introduced in all sex and age groups. Given that the rates were adjusted for the reported coverage of the corresponding year, the observed increases were not significantly affected by increased coverage of the cancer registry system over time. The increase in colorectal cancer occurred with the reported increase in mean serum folate in women 2 years after folic acid fortification (15). Our findings are also consistent with those of other ecological studies in the USA, Canada, and Chile that were performed at shorter intervals after introducing fortification (16,17). However, the short follow-up times in these studies meant that the association of folic acid fortification and increased colorectal cancer rates could not be reported with confidence.

Based on a systematic review and meta-analysis of 44 controlled studies (18), we previously reported that there were conflicting results in studies of the role of folate intake and folic acid supplementation on colorectal cancer risk. Specifically, no beneficial effect on colorectal cancer was shown for folic acid intake. Given the crucial role of folic acid in methylation, the excess folate may even induce carcinogenesis through pre-cancerous cellular replication, tumor genesis activation, and natural cell killer inhibition (19). Colorectal epithelial cells have high replication rates and higher folate absorption because the colorectal microbiome produces an excess of folate, highlighting the potential for adverse effects of excessive folic acid intake in colorectal cancer. Along with folic acid, iron fortification might also contribute to increased rates of colorectal cancer. Findings from a cohort study indicated that there was an association between iron intake and increased colon cancer risk (20), meanwhile, findings from an in vitro study showed that folic acid affected iron metabolism within colorectal cells, enhancing the iron-induced peroxidation process (21). Although fortification with both folic acid and iron appears to increase the rate of colorectal cancer by 7–9 years, further research is still required to reach any definitive conclusions.

There were inconsistent changes in terms of sex and age in esophagus and gastric cancer rates, however, in a meta-analysis by Zhao et al., the risk of esophageal cancer was shown to be reduced by 30% at higher serum folate levels (22). Tio et al. and Larsson et al. also demonstrated the beneficial effects of folate intake on esophageal cancer (23,24). In these studies, though, the effect of total folate status on esophageal cancer was assessed, which might have been different from that of synthetic folic acid. Findings from this study provide evidence that national folic acid fortification combined with iron was accompanied by inconsistent changes in rates of esophageal or gastric cancer. Despite the evidences indicating iron

supplementation can have an undesired effect on gastrointestinal cancer (5,25), there was no increase in rates of any of these cancers after 9 years of flour fortification with iron.

Findings from this study provide evidence that national folic acid fortification combined with iron was accompanied with increased colorectal cancer rates. That said, further investigations are required to establish the effects of folic acid and iron fortification on colorectal cancer risk.

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Author Contributions

Conceptualization, S.M. and S.D.; Methodology, S.M.; Software, S.M., R.D.; Validation, R.D., S.D., and S.M.; Formal Analysis, S.M.; Investigation, S.M.; Resources, S.D., R.D.; Data Curation, R.D.; Writing – Original Draft Preparation, S.M.; Writing – Review and Editing, G.B., B.Z.A.; Visualization and Supervision, G.B., BZA.; Project Administration, S.D.; Funding Acquisition, S.D. All authors have read and approved the final manuscript.

Disclosure Statement

The authors declare no conflict of interest.

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