Nutrients and diet quality in gastrointestinal cancers

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Chapter

3

Staple food fortification with folic acid and Iron and gastrointestinal cancers: critical appraisal of long-term national fortification

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Chapter 3

Abstract

The co-occurrence of flour fortification with folic acid and iron and gastrointestinal cancers incidences were critically assessed in the East Azerbaijan province of northwest Iran. In an ecological design, overall gastrointestinal cancers rate ratios and their 95% confidence intervals (95%CI) were calculated as a 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 y age group (women: 2.07, 95%CI: 1.79–2.49; men: 1.59, 95%CI: 1.33–1.89) and the 55–74 y 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 investigations are required to establish the associations.

Key Messages

Long term national folic acid fortification combined with iron was not accompanied by consistent changes in esophageal or gastric cancer rates; nonetheless, the observed significant increase in colorectal cancer rates after fortification requires further investigation.

Introduction

Folic acid and iron levels play a crucial role in maternal and child health. [1,2].
Over 53 countries mandate fortifying wheat flour with iron and folic acid to ensure sufficient daily intakes of these micronutrients among people [2-4]. However, there are evidence on long-term folic acid and iron supplementation, leading to increased risk of gastrointestinal cancer [4-6]. Despite the findings on the probable non-favorable effect of iron and folic acid supplementation on gastrointestinal cancers, limited studies are 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 the present study, the incidences of these cancers before and after implementation of fortification programs were compared to provide insights on possible impacts of long term food fortification on gastrointestinal cancers.

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 [7-9].
We used national censuses of each every five 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 [10]. The fortification premix consists of 1.5 and 30 parts per million of folic acid and ferrous sulfate, respectively [1,10]. 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 Disease, using codes 15 for esophageal cancer, 16 for gastric cancer, and 18–21 for colorectal cancer, as reported in cancer registry-based on data obtained from local pathology centers. Completeness of 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 [11]. The incident cases were classified by sex at 1-year intervals from 2004 to 2015 and by age group (35–49 years and 70–74 years) at 5-years 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% 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/join-point/). 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 y and 55–74 years), and the average annual percentage of change in trend for each cancer was calculated for the entire period (2004–2015).

Results

The mean cohort size during the study period was 1,143,597, accounting for 1.5% of the total population in Iran. Overall, 49% of the cohort was female, 69% lived in urban areas, 37% were aged 30–60 y, and most were of Azeri ethnic background. The Crude numbers and age-adjusted standard rates for GI tract cancers before and after mandatory flour fortification are depicted in **Table 1** & **Table 2**. 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 y age group and -5.9 (95%CI: -9.9 to -1.7) in the 55–74 y 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 y age groups. No other significant trends were detected (**Table 3**).

Table 1. Crude number of incident gastrointestinal cancers cases adjusted for cancer registry coverage, stratified for gender and age, East Azerbaijan population, 2004-2015

		Before Fortification			After Fortification								
Esophageal Ca (ICD 15)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	31.67	61.67	38.57	34.28	45.71	20.00	44.00	30.67	23.75	15.29	32.94	27.06
	M	20.00	35.00	66.67	41.67	43.33	43.33	55.00	76.67	40.00	36.67	46.67	50.00
Age 55–74 y	F	126.67	155.00	112.86	91.43	118.57	121.43	113.33	74.67	85.00	75.29	69.41	88.24
	M	100.00	181.67	120	122.87	135.71	142.67	122.67	109.33	83.75	83.54	88.24	94.12
Gastric Ca (ICD 16–17)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	56.67	61.67	32.86	50.00	24.29	24.00	37.33	22.67	21.25	21.18	32.94	47.07
	M	23.33	78.33	62.86	98.57	91.43	76.00	88.00	82.67	65.00	56.47	55.29	89.41
Age 55–74 y	F	176.67	155.00	102.86	127.14	110.00	108.00	124.00	84	78.75	71.76	96.47	169.41
	M	29.00	217.00	183.00	262.00	184.00	231.00	245.00	201.00	148.00	145.00	184.00	296.00
CRC (ICD 18–21)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	23.32	58.33	42.86	58.57	84.29	76.00	89.33	89.33	53.75	63.53	80.00	96.47
	M	21.67	83.33	55.71	94.29	70.00	72.00	106.67	61.33	75.00	64.71	81.18	103.34
Age 55–74 y	F	45.00	83.33	77.14	90.00	80.00	96	157.33	105.33	87.55	116.47	134.12	163.53
	M	26.67	80.00	97.14	124.29	121.43	108	156.00	109.33	102.50	137.65	177.65	203.56
Mean Population		**Years 2004 to 2015**											
Age 35–54 y	F	397,249											
	M	405,933											
Age 55–74 y	F	168,561											
	M	171,854											

Abbreviations: Ca, cancer; ICD, international classification disease; CRC, colorectal cancer.

Table 2. Age-adjusted standard rates for gastrointestinal tract cancers before and after mandatory flour fortification with folic acid and iron, in East Azerbaijan population, 2004-2015.

		Before Fortification					After Fortification					
Esophageal Ca (ICD 15)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	12.03	43.07	36.92	52.96	23.95	12.05	15.03	35.97	23.6	8.78	18.14	20.41
	M	6.88	12.77	19.47	12.31	13.12	9.24	12.01	16.4	7.92	6.98	7.3	7.96
Age 55–74 y	F	90.68	113.51	81.69	65.43	86.13	75.44	70.73	46.02	51.8	47.25	38.39	49.44
	M	65.93	119.67	79	82.4	88.23	88.63	75.98	69.3	54.37	53.58	50.83	53.46
Gastric Ca (ICD 16–17)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	18.99	20.78	11.45	16.57	7.46	6.23	9.74	5.88	5.61	5.36	7.36	10.68
	M	7.67	27.87	21.4	33.26	31.3	20.52	23.86	22.62	17.69	15.23	12.47	20.12
Age 55–74 y	F	127.35	113.51	75.01	92.15	80.72	66.28	76.04	51.87	48.19	44.73	54.25	94.4
	M	33.23	240.13	169.79	248.24	172.39	190.5	202.83	169.08	115.47	108.37	124.41	200.55
CRC (ICD 18–21)		**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Age 35–54 y	F	7.05	23.57	19.41	25.51	32.83	24.56	1.45	28.28	18.18	23.69	23.92	26.75
	M	7.53	28.78	22.21	33.17	26.39	24.95	16.04	20.16	25.17	24.01	25.52	32.13
Age 55–74 y	F	32.06	60.78	56.53	66.65	59.16	60.03	98.55	65.81	54.61	72.91	74.78	91.36
	M	18.17	54.26	64.44	84.52	80.52	67.16	100.41	69.3	65.07	90.31	101.37	117.25

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

Table 3. Trends analysis and cumulative rate differences for gastrointestinal tract cancers from before to after fortification in East Azerbaijan population, 2004-2015.

Cancer site		AAPC[1]	95%CI for trend	P for trend	Rate Ratio[2]	95%CI for rate ratio
Esophageal Ca (ICD 15)						
Age 35–54 y	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 y	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 y	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 y	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 y	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 y	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 o 2.95

1 Annual parentage of change in cancer rates,
2 P value < 0.05 is regarded as significant. Before fortification = 2004–2006. After fortification = 2013–2015.
Abbreviations: Ca, cancer; ICD, international classification disease; CRC, colorectal cancer

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 aggregated 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 seven to nine 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 two years after folic acid fortification [3]. 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 [15,16]. 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 [17], 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 [17]. 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 killers inhibition [18]. Colorectal epithelial cells have high replication rates and higher folate absorption because the colorectal microbiome produces an excess of folate [19], 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 5–7 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 were accompanied by inconsistent changes in rates of esophageal

or gastric cancer. Despite the evidence 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 nine 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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