Modifiable risk factors and cancer in Ireland; methodology annex

Cancer incidence data

Cancer incidence data for 2016 was obtained for Irish adults from the National Cancer Registry Ireland (NCRI) which records all incident cancers in Ireland. All age groups were included in this analysis. Results were calculated for males, females and persons.

Determining cancer outcomes

Incident cancer cases for all cancers excluding non-melanoma skin cancer was the primary cancer outcome in the model. Cancer type was included if classified by the International Agency for Research on Cancer (IARC) or World Cancer Research Fund (WCRF) as having "sufficient" (IARC) or "convincing" (WCRF) evidence of a causal association with a specific risk factor (1). Cancer sites included are as follows: Oral cavity (C00-C06), Nasopharynx (C11), Pharynx and oropharynx (C09, C10, C12-C14), Oesophagus (C15), Stomach (C16), Bowel (C18-C20), Anus (C21), Liver (C22), Pancreas (C25), Gallbladder (C23), Sino-nasal (C30-C31), Larynx (C32), Lung (C33-C34), Bone (C40-41), Melanoma (C43), Kaposi sarcoma (C46), Breast (C50), Vulva (C51), Vagina (C52), Cervix (C53), Uterus (C54-C55), Ovary (C56), Penis (C60), Bladder (C67), Kidney (C64-C66, C68), Eye (C69), Brain and CNS (C70-C72), Thyroid (C73), Myeloma (C90), Hodgkin lymphoma (C81), Non-Hodgkin lymphoma (NHL) (C82-C85, C96), Leukaemia (C91-C95).

Determining modifiable factors

The modifiable risk factors included in the model were determined as mentioned above; a factor was included if classified by IARC or WCRF as having "sufficient" (IARC) or "convincing" (WCRF) evidence of a causal association with a cancer outcome. Modifiable factors included are smoking status, alcohol consumption, overweight and obesity, physical activity level, processed meat intakes, ultraviolet-B (UVB) exposure (reported as sunburn history and sunbed use), radiation exposure, air pollution, post-menopausal hormones, oral contraceptives and exposure to infection.

Determining exposure to modifiable risk factors among Irish population

For each potential modifiable risk factor examined, literature was reviewed to identify most suitable Irish-based population prevalence data where possible- preferably nationally representative surveys. Ideally, age- and sex- specific prevalence estimates were obtained so as to calculate the population attributable fractions (PAFs) for cancer by age and sex (where evidence of causality was specific to those attributes). Many of the potential risk factors carry an increased burden with increased exposure, for example smoking and alcohol consumption (2). For some risk factors, including physical activity, increased cancer risk is associated with lower exposure and therefore needed to be calculated as a deficit against recommended levels (2).

When calculating PAFs, the amount of time between exposure to risk factor and cancer outcome (time lag) was considered. This can be difficult to determine as the amount of time varies depending on the risk factor and the cancer site, however based on methodology used by similar studies we have used 10 years as the

time lag (1). When exposure of the Irish population to risk factors was not available for 2006, data from the closest possible timeframe was selected.

The “Survey of Lifestyle, Attitudes and Nutrition in Ireland (SLAN) 2007” dataset was obtained to determine exposure to several lifestyle risk factors in the Irish population (3). This survey involved 10,364 respondents across Ireland aged over 18 years and was representative of the Irish population when compared with Census 2006 figures. Data was obtained on smoking behaviour, body mass index (BMI) and physical activity levels. BMI was self-reported but was also independently measured in a sub-sample of respondents (n= 967 aged 18-44 years and n= 1,207 aged over 45 years). The data reported from the independently measured sample was used in this analysis. Processed meat and alcohol intakes were extracted from the National Adult Nutrition Survey (NANS) (2008-10). Information on prevalence of exposure to the majority of infection types are reported by the Health Protection Surveillance Centre (HPSC). See table 1 for full list of risk factor exposure data sources.

Table 1. List of data sources for Irish exposure to risk factors

Modifiable risk factors	Source of Irish exposure data (year of data collection)
Smoking status	Irish Social Science Data Archive (ISSDA) SLAN (2007) (3)
Overweight & obesity	ISSDA SLAN (2007) (3)
Physical activity level	ISSDA SLAN (2007) (3)
Alcohol intakes	NANS (2008-2010) (4)
Processed meat intakes	NANS (2008-2010) (4)
UVB exposure	Sunburn; Boyle et al. (2008, Northern Ireland) (5)
	Sunbed; Irish Cancer Society survey (2007) (unpublished)
Radiation exposure	Radiological Protection Institute Ireland (various) (6)
Air pollution	Environmental Protection Agency (2006) (7)
HRT	Primary Care Reimbursement Service (PCRS) Data (2006) (unpublished)
Oral contraceptives	PCRS Data (2006) (unpublished)
Exposure to infection	HPSC (2006) (8–10) (exc H. Pylori; Murray et al. (11) 1997, Northern Ireland)

Identifying relative risks for each cancer outcome and modifiable risk factor

Recently published relative risks (RRs) as a result of systematic searching by Brown et al. were obtained (1). Brown et al. determined that meta-analysis should be the preferred source of RRs, followed by cohort studies and case control/other studies selected when no other source available (1). Recent literature was systematically reviewed to determine if there were any more recent meta-analyses available. See appendix 1 for table of search terms for systematic searching. It was preferable that the data should also be consistent with the available exposure and outcome data in relation to the categories of exposure or the units of measurement used and the outcome measured where possible. The effects of different risk factors on cancer incidence can vary depending on sex, age etc. and so differences in the risks of cancer among various sub-populations also needed to be considered. Appendix 2 lists RRs used in analysis.

Calculating population attributable fractions (PAFs)

The PAF is interpreted as the proportion of cases that would be prevented if exposure to a causal factor in the entire population was reduced to the level of the reference category (i.e. ideal exposure).
For the majority of risk factors, the PAF was calculated using the standard formula (1):

$$\frac{(p_1 \times ERR_1) + (p_2 \times ERR_2) + (p_3 \times ERR_3) \ldots + (p_n \times ERR_n)}{1 + [(p_1 \times ERR_1) + (p_2 \times ERR_2) + (p_3 \times ERR_3) \ldots + (p_n \times ERR_n)]}$$

where p_1 is the proportion of the population in exposure level 1 (and so on) and ERR_1 is the excess relative risk (relative risk -1) at exposure level 1 (and so on). This formula was applied to categorical variables. Some of our exposures were calculated differently; processed meat intakes, exposure to air pollution and radiation were calculated as continuous exposures. For example, in the case of processed meat intakes the data incorporated is the average exposure (rather than the percentage of consumers) and the RR is reported as per 50g intake increment and so the following formula is used:

$$\frac{\exp[\ln(RRunit) \times \bar{x}] - 1}{\exp[\ln(Rrunit) \times \bar{x}]}$$

where RR_{unit} = relative risk for each unit increment in the exposure and $\bar{x}$= average exposure.
Due to lack of suitable data in relation to either the relative risk for or population exposure to Epstein-Barr virus, Human Papillomavirus, Kaposi Sarcoma Herpesvirus and diagnostic radiation, pre-calculated PAFs were identified in the literature rather than being calculated within this project (1). PAFs were calculated and different PAF types were combined in Stata and are expressed in this report as percentages. Using this approach, the number of cancers at each site that could be attributed to each risk factor was estimated and applied to the NCRI cancer incidence data. PAFs for all risk factors combined, for each cancer type and for all

cancers combined, were obtained by first applying the first relevant PAF in the sequence to the total number of observed cases, to obtain the number of cases attributable to that factor only. Each subsequent PAF in the sequence was applied only to the number of observed cases not yet explained by the risk factors earlier in the sequence, as described by Parkin et al. (12).

Additional information

UVB exposure

The estimated population attributable risk for exposure to natural and artificial sources of UVB in this research will be underestimated as only sunbed usage and sunburn history are accounted for. Everyday sun exposure is not included in this analysis. The PAF and attributable cases of non-melanoma skin cancer (NMSC) as a result of exposure to sunbeds and occurrence of sunburn were also calculated. The results of this separate analysis are included in the report but it is important to note that these figures were not incorporated into the overall analysis i.e. total cancer cases. The RRs are therefore not included in appendix 2. As per Koster et al. 2018 (13), the middle risk estimates reported in the IARC monograph for sunburn was used in this analysis (1.3 (1.1-1.5) for squamous cell carcinoma and 1.6 (1.2-2.0) for basal cell carcinoma). The RR for sunbed usage was 1.67 (1.29-2.17) for squamous cell carcinoma and 1.29 (1.08-1.53) for basal cell carcinoma (14).

Alcohol intake

Alcohol intakes were acquired from the NANS dataset and units were calculated from the question that participants were asked in relation to how often they drank alcohol per week. In order for data to be consistent with the published RRs, data was then categorized into four groups according to the percentage of people consuming a median ethanol/g; these groupings included non-alcohol consumers and those with intakes of either ≤ 12.5g/d, 12.5-50g/d or >50g/d.

Physical Activity

The RR for physical activity was reported as RR for those with <600 or between 600 and 3999 MET mins/week. However SLAN reported physical activity as “low”, “moderate” or “high” using International Physical Activity Questionnaire methodology (IPAQ) scoring protocol (3). IPAQ defines moderate as at least 600 MET mins/week and high as at least 1500 MET mins/week. Therefore SLAN data was re-categorized as “low” vs “moderate and high” to be consistent with RR data.

Air pollution

The RR for air pollution is reported in units of particulate matter $(PM)_{2.5}$ per µg m^3. This information was only collected at one location in Ireland in 2006; Old Station Road Cork, and therefore might not be representative of the whole country.

Oral contraception

In the case of oral contraception, the PAF for current usage was calculated. We had two potential sources of data on exposure; PCRS data (2006) or data from the Irish Contraception and Crisis Pregnancy (ICCP) Study 2004 (15). PCRS data was included in this analysis as the timeframe was more appropriate, however a sensitivity analysis was carried out in which the PAFs were also calculated using ICCP data. While oral contraceptives are a risk factor for certain cancer types, it is also important to note that usage decreases the risk of other cancer types and therefore the effect of usage on overall cancer risk is likely to be very small.

Infection exposure

Where available, reports by the HPSC provided infection prevalence data for infections included in this analysis. In the case of hepatitis C, data was obtained from a presentation on "Estimating the incidence and prevalence of chronic hepatitis C in Ireland" by Niamh Murphy and Lelia Thornton, HPSC (16). There was no *H. pylori* infection prevalence data available for the Republic of Ireland and therefore data from Northern Ireland was used (11). This data was collected in the 1980s and there has been European based research showing decreases in prevalence between 1990 and 2014, therefore we applied a 3.1% mean annual decrease from 1990 to 2006 to estimate H. *pylori* infection prevalence (17). Pre-calculated PAFs were used for HPV and EBV as per Parkin et al. (1).

Radiation Exposure

The Radiological Protection Institute of Ireland published a report in 2008 on "Radiation doses received by the Irish population" with information on both radon and background radiation exposure (6). The report states that the principal source of data on radon in Ireland is the National Radon Survey which took place between 1992 and 1997. The total annual per caput dose in Ireland from radon was calculated as 2.23 mSv, however the RR for radon exposure is reported in Bq/m^3. The Environmental Protection Agency assumes a home reference level of 200 Bq/m^3 is equivalent to a 5 mSv dosage and therefore the estimated annual dose is 89.2 Bq/m^3. The background radiation figure of 0.9 Sv was calculated by adding the figures reported for cosmic radiation, gamma radiation from soils and radioactivity in food (various years).

Sensitivity Analysis

Parkin et al. conducted sensitivity analysis using the upper and lower confidence intervals of the RR data therefore we repeated this for the updated/additional RRs in this project. We also conducted similar sensitivity analysis using risk exposure data for several risk factors where data were available. As per Parkin et al. and other similar studies, the results of the sensitivity analysis were not reported as they may be misleading; the ranges do not take into account all the possible biases of the PAF calculations (1).

Projections of cancer incidence

Models to project all cancer cases (excluding NMSC) that are attributable to major risk factors, smoking, BMI and alcohol consumption, are needed to help inform policy-makers where public policy actions can drive improvements in lifestyle which may have the greatest impact on reducing cancer burden in Ireland.

Irish demographic cancer incidence projections have been produced by applying the average age specific incidence rates for each age group (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-85 and 85+) for the years 2011-2015 to the estimated population up to 2035. This methodology has previously been reported (18).

In order to project the cancer cases attributable to each risk factor up to 2035, we multiplied the projected incidence by the PAF calculated using 2006 exposure data for males and females. This assumes that exposure to the risk factors do not change over time.

In relation to smoking, a target scenario was then modelled which assumed that the percentage of current smokers will fall to 5% by 2025 based on “Tobacco Free Ireland 2025” goals (19). In this scenario, the proportion of the population that were no longer categorised as current smokers were now categorised as ex-smokers.

In the case of BMI, we applied two scenarios; these were based on either an absolute 5% reduction or a 5% increase in the prevalence of both overweight and obesity, i.e. the percentage of people in the normal weight group increases or decreases by 10%.

For alcohol, we also applied a scenario in which the following changes were made;

1) Non-drinkers increased by 5%.
2) Light drinkers increased by 5% for men, and unchanged for women.
3) Moderate drinkers decreased by 5%.
4) Heavy drinkers decreased by 5% for men, and unchanged for women.

The reason for the different treatment for men and women was due to there being only 0.5% of women in the heavy drinker category, hence a 5% reduction would give little insight.

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Appendix 1; systematic search terms for relative risk literature (adapted from Brown et al.)

Combinations of cancer type and risk factor search strings were made using AND. Searches were made in PubMed with the addition of “meta-analysis” and filtered by custom dates of 1/4/17 (end date of Parkin et al. literature search) and 25/01/19.

Cancer type	**Search string**
Melanoma skin cancer	melanoma OR skin AND (cancer OR tumour)
Oral cavity cancer	(oral OR mouth) AND (cancer OR tumour)
Nasopharyngeal cancer	(nasopharynx OR nasopharyngeal) AND (cancer OR tumour)
Pharyngeal cancer	(oropharynx OR oropharyngeal OR pharynx OR pharyngeal) AND (cancer OR tumour)
Oesophageal cancer	(oesophagus OR oesophageal) AND (cancer OR adenocarcinoma OR squamous cell AND (cancer OR tumour)
Stomach cancer	(stomach OR gastric OR cardia) AND (cancer OR adenocarcinoma OR tumour)
Bowel cancer	(colorectum OR colorectal OR colon OR rectum OR rectal OR bowel) AND (cancer OR tumour)
Anal cancer	(anus OR anal) AND (cancer OR tumour)
Liver cancer	(liver OR hepatic OR hepatocellular) AND (cancer OR carcinoma OR tumour)
Pancreatic cancer	(pancreas OR pancreatic) AND (cancer OR adenocarcinoma OR tumour)
Gallbladder cancer	Gallbladder AND (cancer OR tumour)
Laryngeal cancer	(larynx OR laryngeal) AND (cancer OR tumour)
Lung cancer	lung AND (cancer OR adenocarcinoma OR squamous cell carcinoma OR tumour)
Kaposi sarcoma	kaposi sarcoma
Breast cancer	breast AND (cancer OR carcinoma OR tumour)
Vulval cancer	(vulva OR vulval) AND (cancer OR tumour)

Vaginal cancer	(vagina OR vaginal) AND (cancer OR tumour)
Cervical cancer	(cervix OR cervical) AND (cancer OR tumour)
Uterine cancer	(uterus OR uterine OR endometrium OR endometrial) AND (cancer OR carcinoma OR tumour)
Ovarian cancer	(ovary OR ovarian) AND (cancer OR carcinoma OR tumour)
Penile cancer	(penis OR penile) AND (cancer OR carcinoma OR tumour)
Prostate cancer	(prostate OR prostatic) AND (cancer OR carcinoma OR tumour)
Bladder cancer	(bladder OR urothelium OR urothelial) AND (cancer OR carcinoma OR tumour)
Kidney cancer	(kidney OR renal OR renal cell) AND (cancer OR carcinoma OR tumour)
Thyroid cancer	thyroid (cancer OR tumour)
Myeloma	myeloma
Hodgkin lymphoma	Hodgkin lymphoma OR Hodgkin's disease
Non-Hodgkin lymphoma	non-Hodgkin lymphoma
Leukaemia	leukaemia OR leukemia
Brain and other central nervous system tumours	(brain OR nervous system OR spinal cord OR glioma OR meningioma) AND (cancer OR tumour)
Sino-nasal	(Sino-nasal OR sinonasal) AND (cancer OR tumour)

Risk factor	**Search string**
Tobacco	tobacco OR cigarette OR smoking OR environmental tobacco smoke OR secondhand smoke
Overweight and obesity	weight OR BMI OR body mass index OR obesity OR obese OR overweight OR adiposity OR body size
Sunburn and sunbed	sunburn OR sunbed OR indoor tanning
Infections	hepatitis B virus OR HBV

	hepatitis C virus OR HCV human papillomavirus OR HPV human immunodeficiency virus OR HIV OR acquired immune deficiency syndrome OR AIDS Helicobacter pylori OR H. pylori Epstein Barr virus OR EBV Kaposi sarcoma herpesvirus OR KSHV OR human herpesvirus 8 OR HHV8
Alcohol	alcohol OR alcoholic OR ethanol
Radiation - ionising	radon x-ray nuclear medicine OR radio-isotopes therapy radiotherapy
Processed meat	Meat OR bacon OR ham OR sausages OR jerky OR salami OR cured OR salted
Air pollution	(air OR environment OR outdoor) AND pollution
Insufficient physical activity	physical OR activity OR exercise OR physically active OR sedentary
Post-menopausal hormones	hormone replacement therapy OR ((menopausal OR menopause) AND hormone therapy) OR
Oral contraceptives	(oral AND (contraceptive OR contraception)) OR birth control pill

Appendix 2: Relative risk figures used (adapted from Brown et al. 2018)

Risk factor[a]	Cancer type																								
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin	Melanoma	Other cancer types[h]
Tobacco (cigarette) smoking [i] [ii] [iii] [iv] [v] [vi] [vii] [viii] [ix] [x] [xi] [xii] [xiii] [xiv] [xv]																									
Current vs never																									
	8.96	1.91	1.95	3.43	2.32	4.21	1.62	1.61	2.2	1.11	1.44	7.01			3.44	1.35	1.47								
	8.96	1.91	1.95	3.43	2.32	4.21	1.2	1.86	2.2	1.11	1.44	7.01	1.83	1.49	3.56	1.35	1.47								
Former vs never																									
Males	3.85	1	1.39	1	1.62	2.18	1.34	1.47	1.17	1.15	1.11	2.37			1.92	1.22	1								
Females	3.85	1	1.39	1	1.62	2.18	1	1	1.17	1.15	1.11	2.37	1.26	1	2.04	1.22	1								
Passive smoking exposed vs unexposed																									
Males	1.23																								
Females	1.37																								
Overweight and obesity [xvi] [xvii] [xviii] [xix] [xx] [xxi] [xxii] [xxiii] [xxiv] [xxv] [xxvi] [xxvii] [xxviii]																									
Overweight vs healthy weight (BMI 25<30 vs BMI 18.5<25)																									
Males					1.87		1.22	1.18	1.15	1.17	1.17					1.22				1	1	1.1	1.17		
Females					1.87		1.22	1.18	1.12	1.07	1.07			1.08		1.38		1.13	1.34	1.22	1	1.1	1.12		
Obese vs healthy weight (BMI 30+ vs BMI 18.5<25)																									
Males					2.73		1.61	1.83	1.2	1.38	1.38					1.63				1.54	1	1.27	1.23		
Females					2.73		1.61	1.83	1.15	1.17	1.17			1.11		1.95		1.2	2.54	1.75	1.6	1.27	1.15		

Risk factor[a]	Cancer type																								
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin	Melanoma	Other cancer types[h]
Infections																									
Helicobacter pylori (H. pylori) [xxix]																									
Persons							5.9																	6.3		
Hep B [xxx]																									
Persons								20.3																		
Hep C 38 [xxxi]																									
Persons								23.8																2.03		
HIV [xxxii] [xxxiii]																									
Persons																								10.6		8.06
Alcohol [xxxiv]																									
Light (median daily ≤12.5g ethanol) vs never																									
Persons		1		1		1.34		1		1	1	1						1.04							
Moderate (median daily 12.5-50g ethanol) vs never																									
Persons		1.81		1.81		2.56		1		1.17	1.17	1.49						1.23							
Heavy (median daily 50g+ ethanol) vs never																									
Persons		5.07		5.07		5.45		2.16		1.33	1.33	2.39						1.6							
Ionising radiation																									
Background radiation (cosmic, gamma, internal, per Sv) [xxxv]																									
Persons	1.02	1.03			1.02		1.01			1.02	1				1.02	1	<1.2	1.02			1.02	1.02				1.03
Radon (per 100 Bq/m3) [xxxvi]																									
Persons	1.16																								

Risk factor[a]	Cancer type																								
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin	Melanoma	Other cancer types[h]
Processed meat (per 50g per day) [xxxvii]																									
Males										1.13	1.13														
Females										1.13	1.13														
Air pollution [xxxviii]																									
Anthropogenic $PM_{2.5}$, per 10µg m^3																									
Persons	1.09																								
Anthropogenic PM_{10}, per µg m^3																									
Persons	1																								
Physical activity (600-3999 vs <600 MET-minutes per week) [xxxix]																									
Persons										0.9															
Post-menopausal hormones [xl] [xli] *(Current vs never-users)*																									
Females														1.43				1.66							
Oral contraceptives (current- vs never-users) [xlii] [xliii]																									
Females													1.9					1.21							
Sunbed usage (ever vs never use) [xliv]																									
Persons																								1.20	
Sunburn history (ever vs never) [xlv]																									

Risk factor[a]	Cancer type																								
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin	Melanoma	Other cancer types[h]
Persons																								1.92	

Key to superscript notes

a Relative risks obtained only for cancer type-risk factor combinations classified by IARC as 'sufficient' or WCRF as 'convincing'; blank cells indicate no RR was sought as the combination is not classified as above. RR = 1 if cancer type-risk factor association is not significant in the source evidence chosen.

b Mucinous ovarian cancer only for tobacco (cigarette) smoking

c Acute myeloid leukaemia only for tobacco (cigarette) smoking, all leukaemia excluding chronic lymphocytic for ionising radiation (RR varies with age, dose, sex, age at and time since exposure so RR given is upper bound)

d Postmenopausal breast cancer only for overweight and obesity, female breast cancer only for alcohol

e Gastric cardia cancer only for overweight and obesity, non-cardia only for H. pylori

f Meningioma only for overweight and obesity; brain, other central nervous system and intracranial tumours (malignant, benign and uncertain or unknown behaviour) for ionising radiation

g Mucosa-associated lymphoid tissue (MALT) lymphoma only for H. pylori

h Conjunctiva for HIV; bone and 'all other solid cancers' for ionising radiation (background radiation)

i Salivary gland for ionising radiation (background radiation)

Appendix 2 references

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