

Epidemiology of pancreatic cancer

- setting the scene

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Introduction

- Descriptive epidemiology
 - incidence, mortality - worldwide and in Ireland
 - treatment and survival in Ireland
- Aetiology of pancreatic cancer
 - established risk factors
 - recent hypotheses
- PanCAM study
 - All-Ireland case-control study of pancreatic cancer

Pancreatic cancer worldwide

Incidence

- ~232,000 new cases diagnosed worldwide each year
- 61% occur in developed countries
- ranks 13th in terms of most common cancers

Mortality

- ~227,000 deaths from pancreatic cancer worldwide each year
- ranks 8th in terms of most common causes of cancer death
- Mortality/incidence ratio (M/I) = 98%

Incidence in Ireland



Pancreatic cancer incidence in Ireland

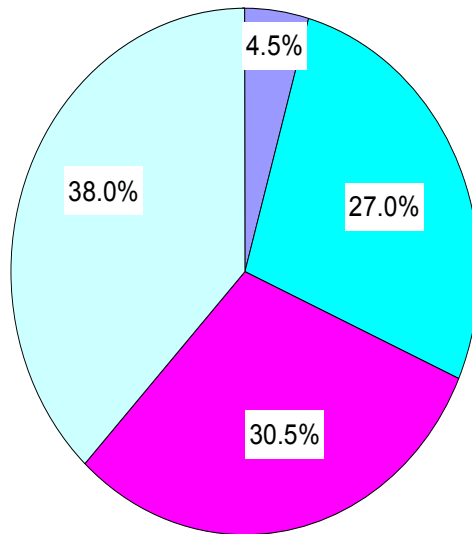
- 360 new cases diagnosed each year (1994-2005)
- 179 in males; 181 in females
- accounts for 2.5% of cancers in males, 2.7% in females*
- 10th most common cause of cancer in both sexes*

** excluding non-melanoma skin cancer*

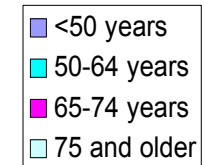
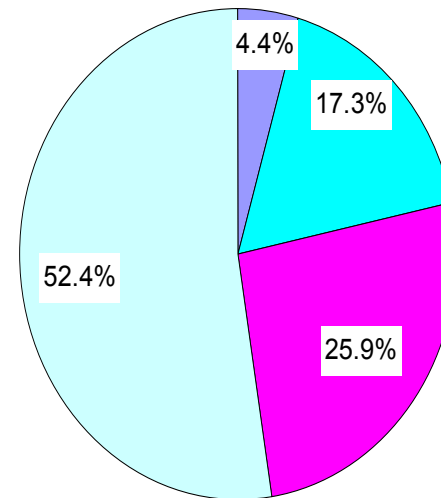
Source: National Cancer Registry, 2007

Age composition of pancreatic cancer cases at diagnosis, by sex, Ireland 2003-2005

Males



Females

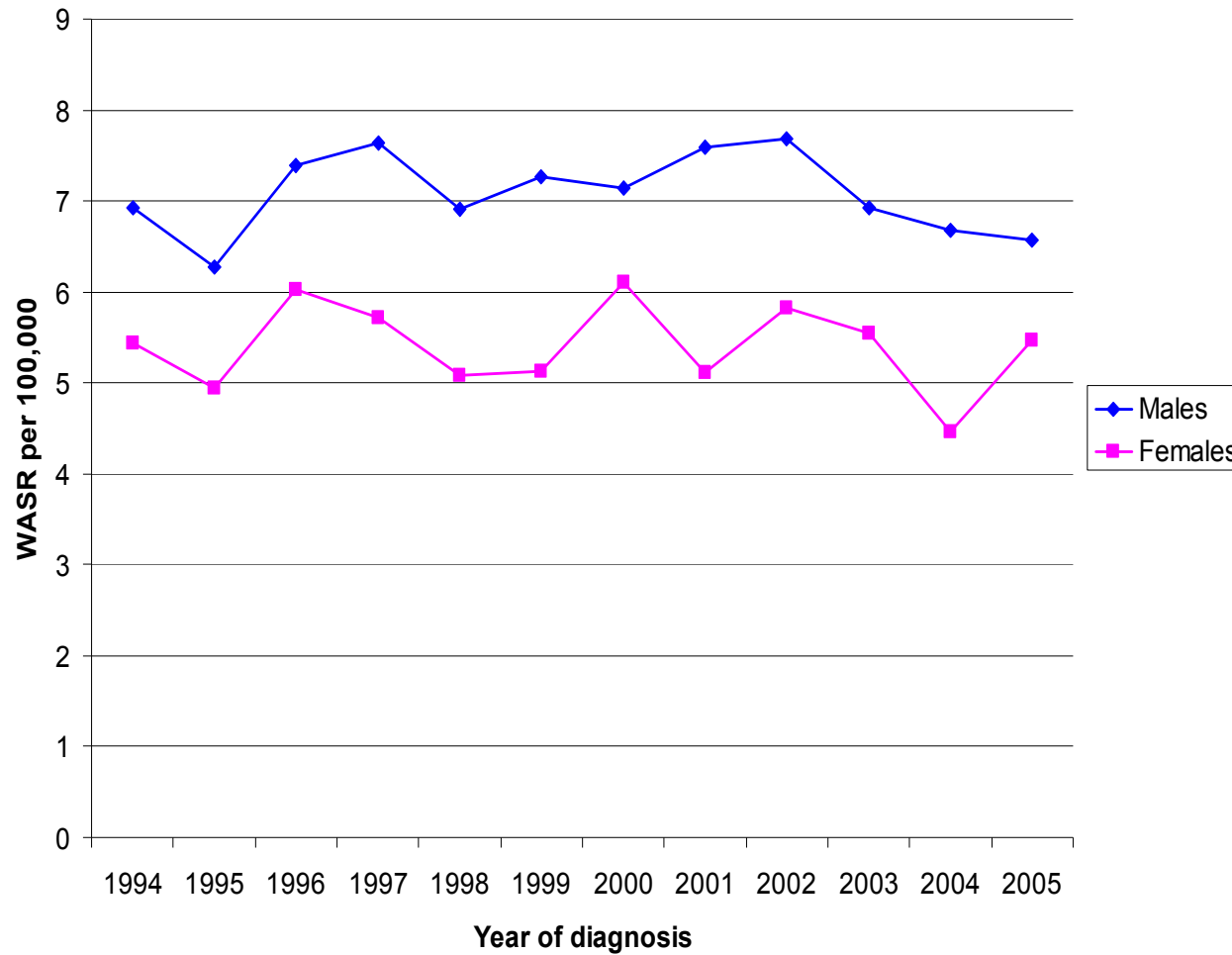


Rising numbers of cases over time, Ireland

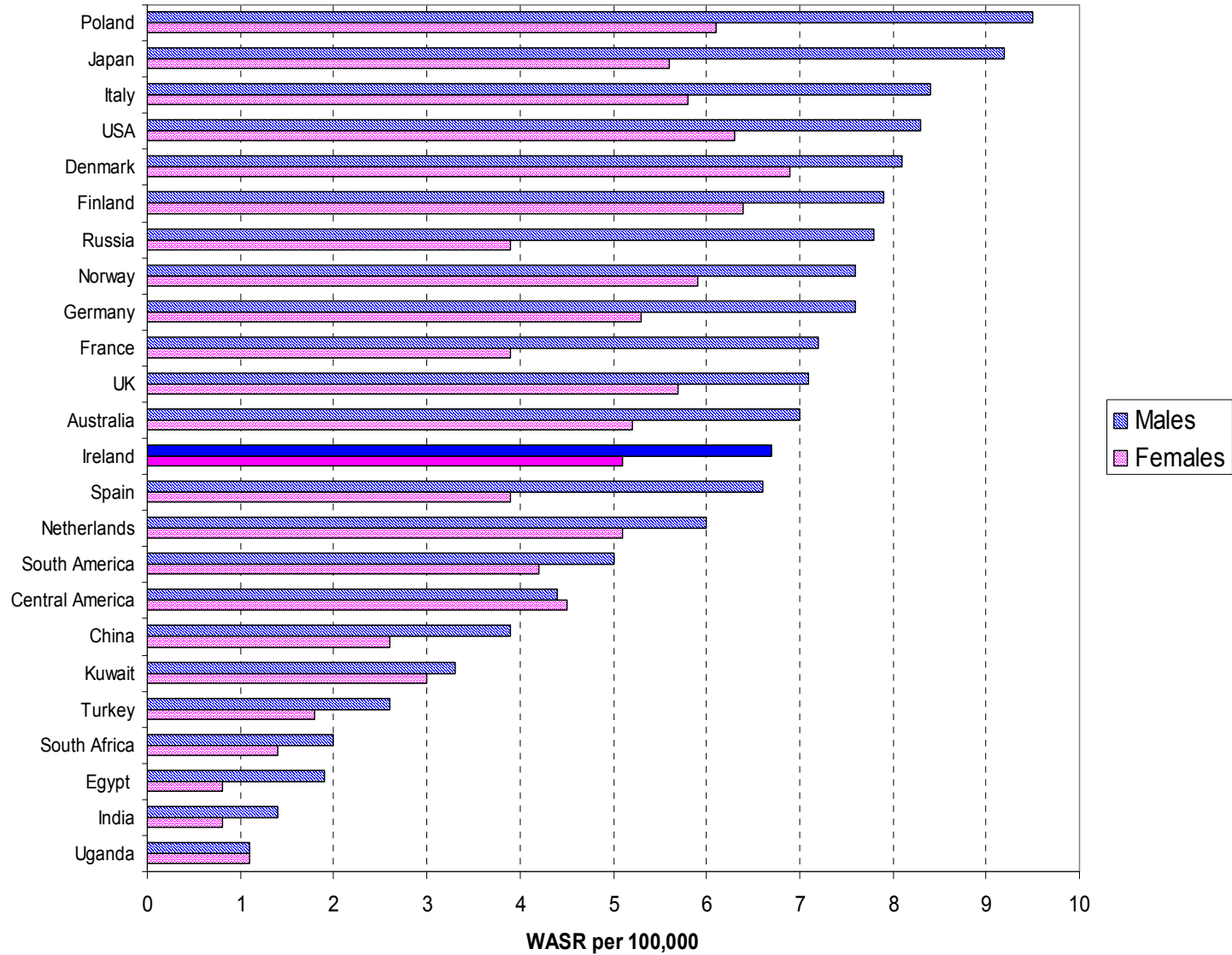
| Average annual numbers of cases by period of diagnosis | Males | Females |
|---|--------------|----------------|
| 1994-1996 | 162 | 170 |
| 2003-2005 | 185 | 189 |
| | | |
| % change over time | +14% | +12% |

- Increase mainly due to demographic changes

Age-standardised incidence rates of pancreatic by year of diagnosis and sex, Ireland, 1994-2005



Age-standardised incidence of pancreatic cancer, by country/region, 2002



Future incidence in Ireland

- Incidence projected to rise in future years

| Average annual numbers of cases by period of diagnosis | Males | Females |
|---|--------------|----------------|
| 1994-1996 | 162 | 170 |
| 2003-2005 | 185 | 189 |
| 2020 | 388 | 324 |
| | | |
| % change between 2003-05 and 2020 | +110% | +71% |

Mortality in Ireland



Pancreatic cancer mortality in Ireland

- 367 deaths each year (1994-2004)
- 185 in males; 182 in females
- Accounts for 4.6% of cancer deaths in males, 5.2% in females
- 8th most common cause of cancer death in males, 6th in females

Age-standardised mortality rates of pancreatic by year and sex, Ireland, 1950-2004



Treatment and survival

Treatment received, Ireland, 1994-2003

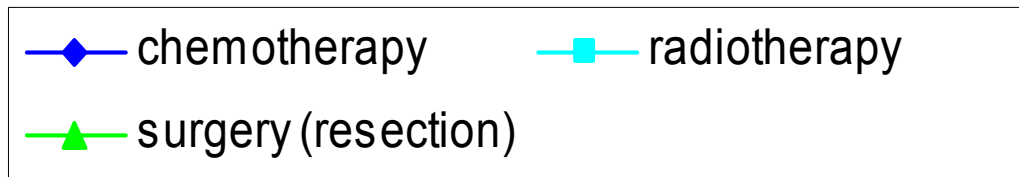
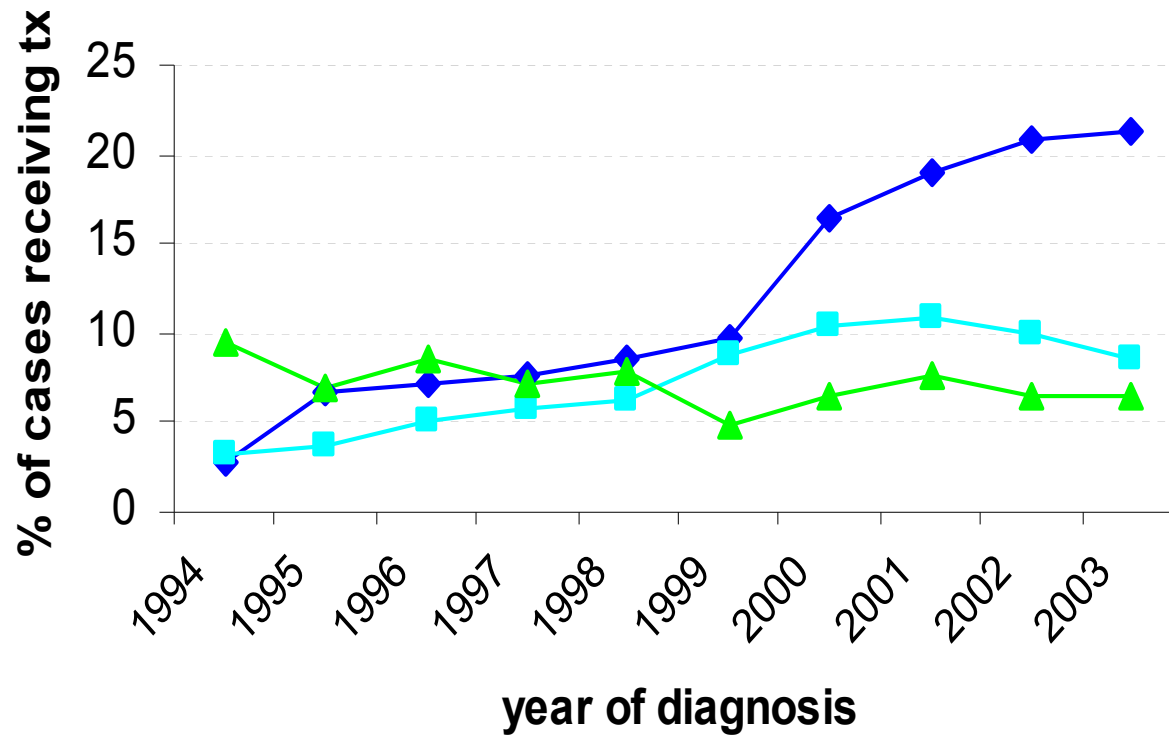
| Treatment received within 1-year of diagnosis* | No. | % |
|--|-------|-------|
| Cancer-directed surgery** | 229 | 7.2% |
| Chemotherapy | 389 | 12.3% |
| Radiotherapy | 232 | 7.4% |
| Other surgical treatment*** | 1,447 | 45.7% |
| No treatment | 1,327 | 41.9% |

* categories not exclusive

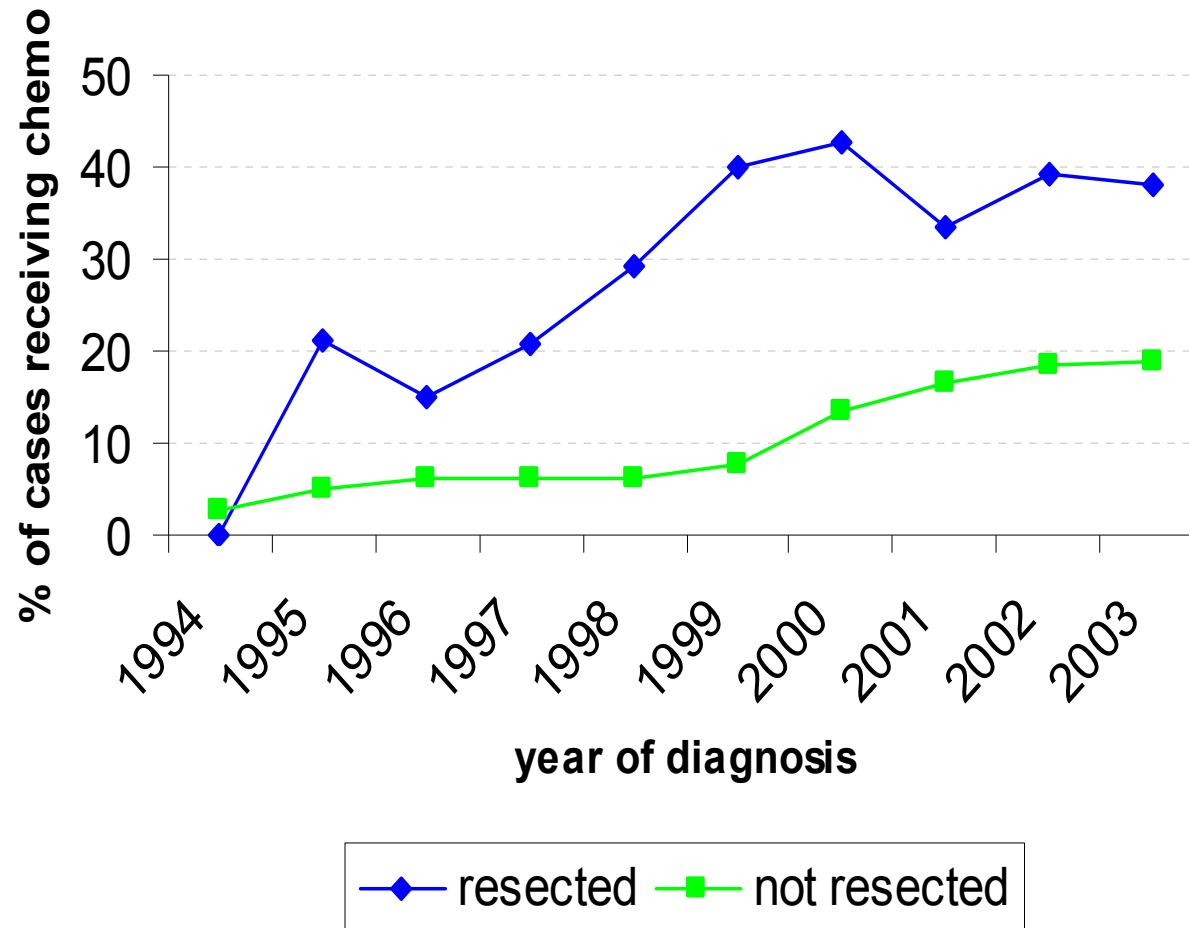
** resection: radical pancreaticoduodenectomy, partial or total pancreatectomy

*** stents, biliary bypass, etc

Treatment received: Ireland, all patients



Chemotherapy receipt: by resection



Survival, Ireland, 1994-2003

- median FU = 2.7 months
- 1-year (crude) survival = 13.7%
 - 49.6% in surgically treated patients
 - 10.9% in non-surgical patients

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- Improvement in survival over time

| 1-year survival | diagnosed 1994-98 | diagnosed 1999-03 |
|------------------------|--------------------------|--------------------------|
| all patients | 12.5% | 14.7% |
| surgically treated | 39.5% | 61.5% |
| non-surgical | 10.3% | 11.5% |

Aetiology – pancreatic cancer risk factors

Aetiology

- Relatively little known about risk factors
- Relatively few studies
 - difficult to conduct
 - poor patient prognosis
 - low participation rates
 - proxy interviews – inaccurate data
- Growing interest in recent years
 - several new studies starting
 - consortia forming of (high quality) existing studies and new studies

Medical history

Chronic pancreatitis (CP)

- CP patients have ~18-fold higher risk of pancreatic cancer than general population (Lowenfels et al., 1999; Talamini et al., 1999; Malka et al., 2002)
- prolonged inflammation may initiate or promote development of cancer

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Diabetes

- positive association between prior diabetes and pancreatic cancer

| Reference | No. of patients/studies | Diabetes | Pooled Relative Risk (RR) with 95% CI |
|----------------------|--------------------------|-----------------------|---------------------------------------|
| Huxley et al., 2005 | 9200 | Type II | 1.5 (1.3-1.8) |
| Stevens et al., 2007 | 3 cohort; 6 case-control | Type I or young onset | 2.0 (1.37-3.01) |

Allergies

History of atopy-related allergies

- Associated with reduced risk of pancreatic cancer (Gandini et al., 2005)
 - respiratory allergy (excl asthma): pooled RR=0.63 (0.52-0.76)
 - dermal allergy: pooled RR=0.66 (0.49-08.89)

History of asthma

- Unrelated to pancreatic cancer risk: pooled RR=1.01 (0.77-1.31)

History of food or drug allergies

- Unrelated to pancreatic cancer risk: pooled RR=1.08 (0.70-1.58)

Postulated mechanism

- hyperactive immune system leading to increased immune surveillance

Dental health

- Possible positive association with tooth loss and/or periodontal disease

| Reference | Study design, etc | Comparison | RR with 95% CI |
|----------------------------------|--|--|-------------------|
| Stolzenberg-Solomon et al., 2003 | cohort; male smokers; Finland | Toothless vs lost 0-10 teeth | 1.63 (1.09-2.46) |
| Michaud et al., 2007 | cohort; male health professionals; USA | History of periodontal disease vs none | 1.64 (1.19-2.26) |

Possible mechanism: inflammation

Smoking

“Cancer of the pancreas is causally associated with cigarette smoking “

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- Smokers vs non-smokers: RR = 1.5-3.0
- Risk increases with
 - duration of smoking
 - number of cigarettes smoked daily
- Risk decreases with increasing time since quitting smoking
- Stronger risks with smoking in more recent years – smoking plays role in later stages of pancreatic carcinogenesis ?

Body mass index

There is convincing evidence that greater body fatness is a
cause of pancreatic cancer

(WCRF/AICR, 2007)

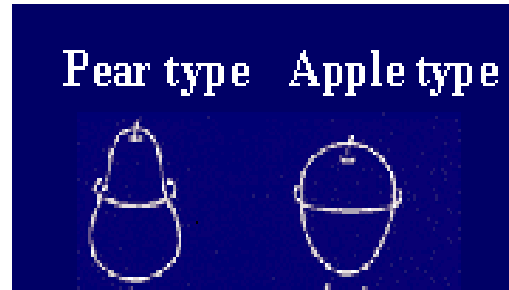
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- 13 of 23 cohort studies found increased risk with increased body fatness/BMI
 - pooled RR = 1.14 (1.07-1.22) per increase of 5 kg/m²
 - dose-response relationship (↑ risk with ↑ BMI)
- Possible mechanisms
 - inflammation
 - effects on steroid hormones and growth factors

Body fat distribution/central adiposity



- Apple-type fat distribution (central adiposity/abdominal fatness) is a probable cause of pancreatic cancer (WCRF/AICR, 2007)

| Measure | No. of cohort studies | Findings |
|----------------------------------|-----------------------|-----------------------------|
| Waist circumference | 3 | ↑ risk with ↑ circumference |
| Waist-hip ratio | 2 | ↑ risk with ↑ ratio |
| Tendency for central weight gain | 1 | ↑ risk |

Physical activity

There is limited evidence that greater physical activity protects
against pancreatic cancer

(WCRF/AICR, 2007)

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Studies reporting ↓ risk with ↑ activity

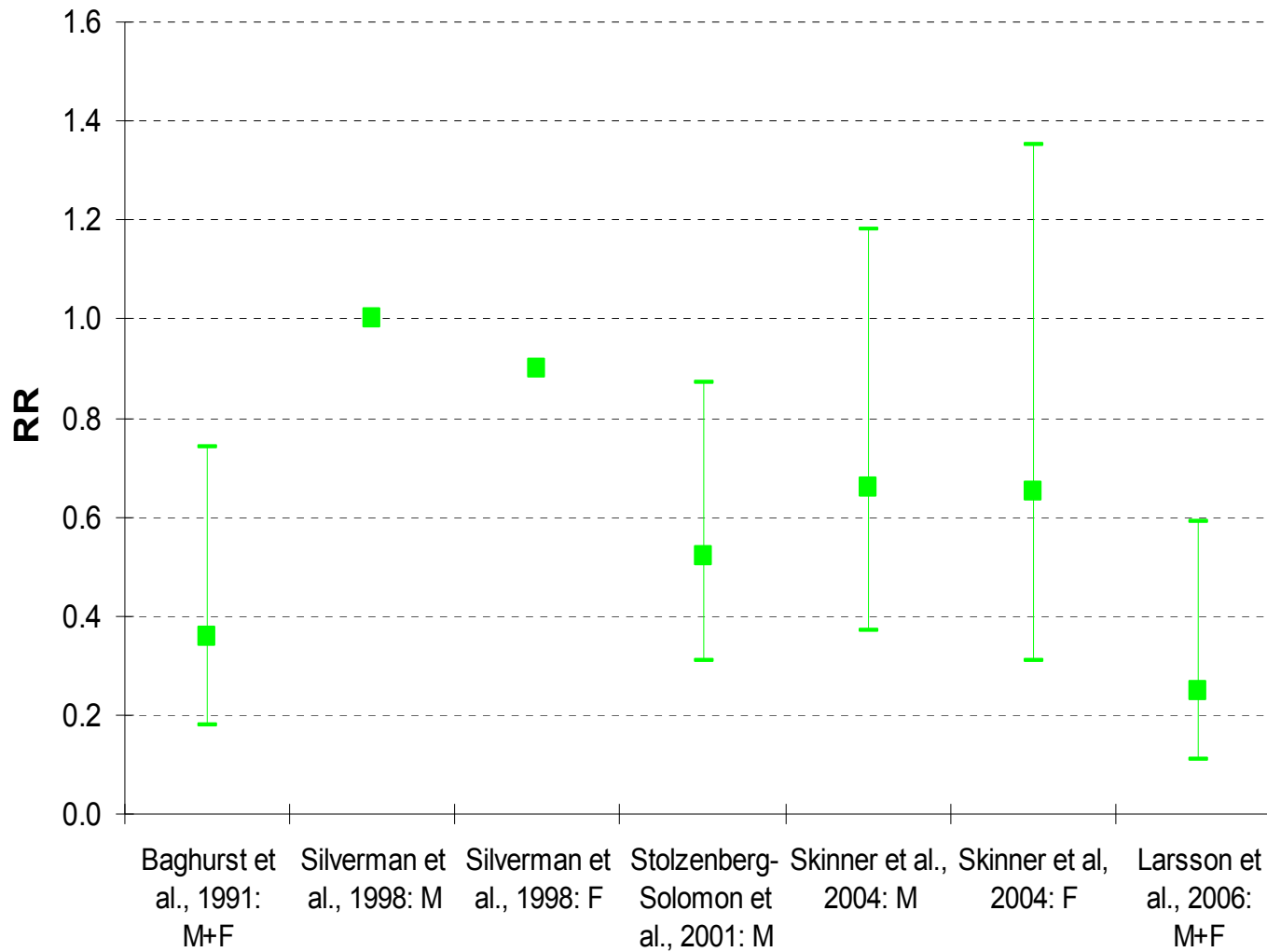
| Measure | No. of positive studies |
|-----------------------|------------------------------|
| Total activity | 2/3 cohort; 1/1 case-control |
| Occupational activity | 1/1 cohort; 2/2 case-control |
| Recreational activity | 5/9 cohort; 3/3 case-control |
| Walking | 3/4 cohort |
| Vigorous activity | 3/5 cohort; 1/1 case-control |

Folate

- B vitamin
- natural sources – green leafy vegetables, liver, yeast, meat, milk, tea
- synthetic form – folic acid
- key role in DNA methylation and DNA synthesis and repair
- folate/folic acid may be involved in a range of diseases including cancers



Relative risk (RR), with 95% CI, for highest vs lowest folate intake



Other dietary risk factors

Fruit

- Possible inverse association (WCRF/AICR, 2007)

| Study type | No. of studies | Relative risk (RR) per 100/g day |
|--------------|----------------|----------------------------------|
| cohort | 3 | 0.92 (95% CI 0.81-1.04) |
| case-control | 8 | 0.89 (95% CI 0.95-0.98) |

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Red meat

- Possible positive association (WCRF/AICR, 2007)
- 4 / 7 cohort studies found increased risk in highest vs lowest intake groups
- RRs in range 1.5-2.8

Genetic contribution to pancreatic cancer

- 5-10% of pancreatic cancers caused by an inherited disorder (Lynch et al., 1996)
 - hereditary pancreatitis
 - familial breast cancer (BRCA2)
 - HNPCC, FAP
 - familial atypical multiple mole melanoma (FAMMM)
- Evidence for genetic contribution to pancreatic cancer over and above what can be explained by familial syndromes
 - 3-5-fold higher risk of pancreatic cancer in those with a close relative with the disease (Michaud, 2004).
 - not explained by familial clustering of environmental or lifestyle factors

What other genes could be involved?

Low penetrance, polymorphic genes acting together with other genes, or environmental or lifestyle exposure(s), to affect risk of pancreatic cancer



gene-gene or gene-environment interaction

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gene-gene or gene-environment interaction

Examples

MTHFR, MTR, TS

related to folate

CYP1A2

tobacco

NAT1, NAT2

tobacco, red meat

XRCC1, XPC

DNA repair capacity

(Wang et al., 2005; Jiao et al., 2006; Li et al., 2006; Wang et al., 2006)

the **PanCAM** STUDY

**Pancreatic Conditions Aetiology and
Management:
an all-Ireland case-control study**

Aim

To establish a data and specimen bank for studies into aetiology, early diagnosis, and survival of pancreatic cancer in Ireland

Objectives

- To investigate
 - risk factors for pancreatic cancer
 - diet, lifestyle, medical history, medication use, occupational exposures, etc
 - patterns of referral, treatment, patient quality of life (QoL) and survival
 - burden on carers
- To establish a network of clinicians, other health professionals and researchers interested in pancreatic cancer in Ireland (*All-Ireland Pancreatic Cancer Study Group*)



Subjects

Cases: newly diagnosed with pancreatic cancer; autumn 2007 onwards
Controls: individuals without pancreatic cancer; from general practices
(Carers: main family member involved in caring for patient)

Participation

Cases and controls: socio-demographic, lifestyle and dietary questionnaire
blood (serum, plasma, DNA); urine; toe-nails
Cases: EORTC quality-of-life questionnaires
Carers: Caregiver Reaction Scale questionnaire

Sample size (eventually) 500 cases; 500 controls; 250 carers

Currently, include

- Adelaide & Meath Hospital, Tallaght
- Cork University Teaching Hospitals
- Bon Secours
- St James' Hospital
- St Vincents' Healthcare Group
- Royal Victoria Hospital, Belfast
- Belfast City Hospital
- Mater Hospital, Belfast

Additional centres

- HSE South-east Hospitals (ethical approval obtained)
- Beaumont (ethical application under review)
- Mater (ethical application being prepared)
- In 2008 - if additional funding secured -
 - Limerick
 - Galway Hospitals

Conclusions: descriptive epidemiology

- increase in numbers of cases (population changes); no change in incidence rates
- projected doubling of numbers of cases by 2020
- long-term fall in mortality rates
- survival improving – mainly surgically-treated patients
- surgical resection rate stable; chemotherapy increasing

Conclusions: risk factors

Probably increase risk

- family history
- smoking
- higher BMI
- chronic pancreatitis
- diabetes

Possibly increase risk

- central adiposity
- tooth loss/peridontal disease
- higher red meat intake

Possibly decrease risk

- higher folate intake
- higher fruit intake
- more physical activity

PanCAM: further information

Please contact:

RoI

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