Short Communication

Early Onset Pancreatic Cancer: Evidence of a Major Role for Smoking and Genetic Factors

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Abstract

Pancreatic cancer ranks 4th as a cause of cancer mortality and in ~5% to 10% of patients, this lethal tumor develops before age 50. We used age-, sex-, and country-specific cancer incidence and mortality data to describe the burden of early onset pancreatic cancer (EOPC) worldwide. We also reviewed the current published evidence on smoking and genetic factors associated with EOPC. We found an excess of EOPC resulting in a substantial number of years-of-life-lost in countries from Central and Eastern Europe. Worldwide, the proportion of EOPC is strongly correlated with lung cancer mortality (R^2 = 0.53), suggesting that approximately half of the variation in the proportion of EOPC could be explained by smoking. The unusual pattern of the incidence of pancreatic cancer by gender and race supports the primary role of smoking in the etiology of EOPC: the excess male-to-female rate ratio, attributable mainly to smoking, gradually approaches unity with increasing age. Moreover, male-to-female rate ratios are greater in blacks than in whites only in younger patients. Published studies also identified genetic alterations involved either alone or in association with smoking in the development of EOPC. In conclusion, EOPC constitutes only 1% to 5% of the total deaths from pancreatic cancer worldwide, but is responsible for 20% to 30% of the total number of years-of-life-lost caused by the disease. Smoking and genetic mutations are the major identified risk factors and seem to be even more important for EOPC than for PC in older age groups. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1894–7)

Introduction

Pancreatic cancer (PC) ranks 4th as a cause of cancer mortality (1) and its prognosis still remains poor (2). As the mortality from major cancers such as cancer of the breast and colon decreases, an increasing proportion of cancer deaths will be due to PC. The average age at onset of PC is ~66 years, and ~5% to 10% of patients develop this tumor before age 50 (3). Several risk factors are known to cause PC, among which smoking seems to play the major role (3, 4), but it is not known whether risk factors for PC are the same for all age groups. Identifying factors leading to early onset pancreatic cancer (EOPC) could potentially yield strategies to postpone the onset of this tumor, or help formulate new therapeutic approaches. The aim of this report is to provide a descriptive analysis of the burden of EOPC in different populations and to highlight the possible role of smoking and genetic factors in EOPC development.

Materials and Methods

Data Sources. We retrieved mortality data from the WHO mortality database for the most recent period with complete data available (1995-1999). We used code C25 of the 10th International Classification of Disease to identify PC (5). Unfortunately, no information on morphologic subtypes was available. We extracted the numbers of PC deaths and calculated Age-Standardized Mortality Rates (ASMR) on the basis of the world standard population (6). Sex-specific ASMR were obtained separately for EOPC (individuals ages 0-49) and for late onset PC. In order to ensure stable and reliable rates, we restricted our analysis to countries for which >20 deaths were reported in the EOPC group over the 5-year period.

We also evaluated racial difference in the incidence pattern of PC in the U.S. population using data from the Surveillance, Epidemiology, and End Results (SEER) registries (6).

In addition, we reviewed published articles hinting at smoking and genetic factors leading to EOPC. The articles were identified through a Medline search, using different combinations of the keywords ''early onset'', ''young

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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patients'', ''pancreatic cancer'', and ''pancreas cancer.'' The computer search was supplemented by consulting the references of the articles. Twenty-seven articles reporting data on EOPC were included in this review.

Statistical Analysis. We estimated the ratio of early onset to late onset PC. Because the rate of EOPC was small, relative to the rate of late onset PC, the results approximate the percentage of patients with EOPC in the entire population. We also calculated, for each country, the number of years-of-potential-life-lost (YPLL) for PC before age 75 years based on 5-year age group data.

In order to assess whether high mortality from EOPC could be associated with smoking, we examined the correlation between PC rate ratio and early lung cancer mortality (deaths before age 50), weighting for the total number of PC in each country.

Results

Sex-specific pancreatic rate ratios, and the percentage of YPLL due to EOPC for 36 countries with available data are presented in Table 1, grouped by geographic area. The highest pancreatic rate ratios for both genders were found in Central/Eastern European countries: the ratios ranged from 2.4 to 4.5 for males and from 1.6 to 4.3 for females. The country with the highest pancreatic rate ratio for males was Bulgaria (4.5), followed by the Republic of Moldova (4.2) and Romania (4.0). The same three countries also presented the highest pancreatic rate ratios for females. The overall percentage of YPLL due to EOPC was 23% and 20% for males and females, respectively. High percentages of YPLL due to EOPC were observed in Asia (up to 37%) and in Central/Eastern Europe (up to 40%), whereas low percentages were observed in Western Europe (Table 1).

Table 1. ASMR and pancreatic cancer rate ratio in selected countries, calculated per 100,000 (world standard population), 1995-1999

Registry	Males				Females			
	ASMR (<50 y)	ASMR (>50 y)	Pancreatic cancer rate ratio*	YPLL (%)†	ASMR (<50 y)	ASMR (>50 y)	Pancreatic cancer rate ratio*	YPLL (%)†
America	0.5-0.7	32.9-34.0	1.5-2.1	21-25	0.4	24.4-24.9	1.6	22
Canada	0.5	32.9	1.5	21	0.4	24.4	1.6	22
U.S.	0.7	34.0	2.1	25	0.4	24.9	1.6	22
Asia	0.4-0.8	18.7-40.0	2.0-2.3	20-37	0.2-0.4	11.8-24.0	0.8-1.8	18-33
China, Hong Kong	0.4	18.7	2.1	35	0.2	11.8	1.7	33
Israel	0.7	34.0	2.1	27	0.2	24.0	0.8	18
Japan	0.8	40.0	2.0	20	0.4	22.6	1.8	18
Republic of Korea	0.7	32.7	2.1	31	0.3	16.9	1.8	24
Singapore	0.5	22.0	2.3	37	—	—	—	—
Europe	0.4-1.6	25.8-49.4	1.3-4.5	15-40	0.3-0.7	14.7-31.7	1.2-4.3	15-35
Central and Eastern Europe	0.6-1.6	27.4-49.4	2.4-4.5	24-40	0.4-0.7	15.6-31.7	1.6-4.3	18-35
Bulgaria	1.3	29.1	4.5	32	0.5	15.6	3.2	25
Croatia	1.1	38.9	2.8	25	0.5	22.7	2.2	18
Czech Republic	1.2	49.3	2.4	24	0.6	31.7	1.9	21
Estonia	1.6	47.1	3.4	27	—	—	—	—
Hungary	1.6	49.4	3.2	30	0.6	30.3	2	20
Lithuania	1.6	44.5	3.6	29	0.4	20.8	1.9	18
Macedonia	1.0	27.4	3.6	33	0.5	16.6	3.0	29
Republic of Moldova	1.3	31.0	4.2	40	0.7	16.4	4.3	35
Romania	1.3	32.2	4.0	32	0.5	16.7	3.0	25
Slovakia	1.3	42.2	3.1	32	0.4	22.8	1.8	22
Slovenia	0.6	35.9	2.5	27	0.4	24.7	1.6	19
Western Europe	0.4-0.8	25.8-41.4	1.3-2.7	15-26	0.3-0.5	14.7-30.2	1.2-2.0	15-22
Austria	0.7	41.4	1.7	20	0.4	28.3	1.4	16
Denmark	0.7	36.1	1.9	21	0.5	30.2	1.7	15
Finland	0.7	40.3	1.7	21	0.5	27.8	1.8	21
France	0.8	34.2	2.3	24	0.3	19.3	1.6	22
Germany	0.8	37.9	2.1	20	0.4	25.3	1.6	17
Greece	0.6	28.8	2.1	20	0.3	17.7	1.7	18
Ireland	0.5	35.1	1.4	20	0.3	25.8	1.2	15
Italy	0.7	34.1	2.1	19	0.3	22.3	1.3	16
Netherlands	0.6	32.5	1.8	23	0.4	25.5	1.6	21
Norway	0.5	33.6	1.5	19	0.4	26.4	1.5	17
Portugal	0.7	25.8	2.7	26	0.3	14.7	2.0	21
Spain	0.7	27.4	2.6	24	0.3	15.8	1.9	22
Sweden	0.5	35.4	1.4	16	0.5	30.1	1.7	16
Switzerland	0.6	31.8	1.9	22	0.4	23.3	1.7	18
UK, England and Wales	0.5	29.7	1.7	20	0.3	22.1	1.4	17
UK, Scotland	0.4	31.2	1.3	15	0.4	23.1	1.7	16
Oceania	0.5	17.0-28.3	1.8-1.9	23-25	0.3	21.5-22.4	1.3-1.4	19-22
Australia	0.5	28.3	1.8	23	0.3	21.5	1.4	22
New Zealand	0.5	27.0	1.9	25	0.3	22.4	1.3	19

NOTE: The countries included in this table are those presenting at least 20 deaths for EOPC in the 5-yr period.
*Pancreatic cancer rate ratio = (ASMR PC 0-49 years / ASMR PC >50 y) × 100.
†Percentage of YPLL due to early onset PC.

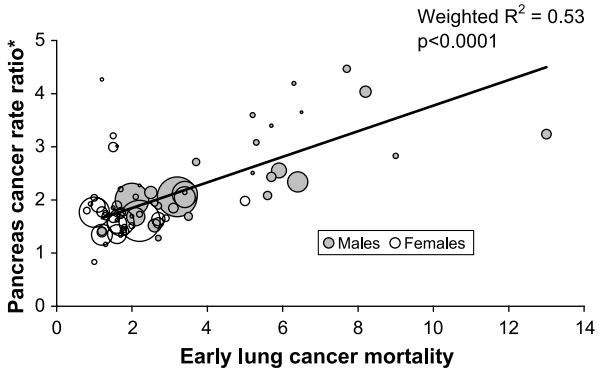

Figure 1. Worldwide correlation between ASMR for early onset lung cancer (ages 0-49) and pancreatic cancer rate ratio in males and females, 1995 to 1999. ASMR are calculated per 100,000 (world standard population).

In order to assess whether smoking was responsible for the excess of EOPC in some countries, we examined the association between PC rate ratio and early lung cancer mortality and found a significant positive correlation for males and females taken together (R^2 = 0.53, P < 0.0001; Fig. 1). When analyzed separately, males showed a persistent correlation (R^2 = 0.58, P < 0.0001), but there was no significant correlation for females, probably due to a lower smoking prevalence.

Figure 2 presents age- and race-specific male-to-female (M/F) rate ratios for PC patients using SEER incidence data for the period 1993 to 1997 (6). We observed that the excess M/F rate ratio, attributable mainly to smoking, gradually approaches unity with increasing age. The M/F ratio presented a larger range in blacks (0.9-2.0) than in whites (1.1-1.5). Moreover, the M/F ratios are greater in blacks than in whites only in the younger age classes (ages 0-59).

Discussion

We combined WHO cancer mortality data, SEER cancer incidence data, and reviewed published literature reports to study EOPC with a particular focus on the role of tobacco smoking.

Incidence rates of PC increase rapidly with age and early onset cancer is uncommon. However, as shown in Table 1, the ratio of early-to-late onset PC varies widely across countries. An excess of EOPC is seen in Central/Eastern European countries—an area with high smoking prevalence rates (7). In this region, the proportion of YPLL from EOPC could represent as much as one-third of the total mortality burden from PC. We found that rates for EOPC are consistently higher in males than in females, which is consistent with known gender-specific smoking prevalence rates.

We showed that approximately half of the variation in the proportion of EOPC could be explained by smoking (Fig. 1; R^2 = 0.53). Because pancreas and lung cancer rates were obtained from the same age range (ages 0-49), we believe that the results are not affected by potential temporal variation in smoking prevalence. Unfortunately, in this analysis, we could not take into account the histopathologic changes in the prevalence of lung cancer which occurred over the last three decades because information on histologic subtypes were not available from the WHO database.

Cigarette smoking is a well-established risk factor for PC, but whether the risk is similar in all age groups has not been studied thus far. In both blacks and whites, males consistently smoke more than females, allowing us to use the M/F rate ratio as a surrogate measure of smoking prevalence. We found that the M/F ratio gradually approaches unity with increasing patient age. One interpretation is that individuals more susceptible to pancreatic damage caused by tobacco-derived carcinogens would tend to develop PC early. Unlike lung cancer, no more than 30% of PC is caused by tobacco smoking (4), suggesting that other causative factors are associated with later onset of the disease. Previous reports support our findings: Zisman et al. (8) observed that smoking accelerated the onset of PC development in sporadic patients, whereas Olson et al. (9) reported a higher smoking frequency in patients diagnosed with PC before the age of 60 compared with those diagnosed at an older age.

We believe that interaction between genetic factors and smoking is another reasonable explanation for EOPC. In previous studies, EOPC has been reported in patients who smoke and carry mutations that increase the risk of PC: among individuals with a family history of PC, Schenk et al. (10) observed a significant higher risk of PC for smokers only if their proband had PC before age 60, suggesting an interaction between the age of the case-proband and smoking status. In family members with pancreatic cancer, Rulyak et al. (11) found that smokers developed cancer one decade earlier than nonsmokers. In patients with hereditary pancreatitis, which is caused by a mutation in the trypsinogen gene and is associated with an elevated risk of PC, Lowenfels et al. (12) found that smokers developed PC, on average, 20 years prior to nonsmokers. Hemminki and Li (13) found a strong association between family history of lung cancer and EOPC. This could be due to an interaction between shared familial smoking habits and genetic susceptibility for cancer development. Finally, beyond finding a significantly greater proportion of EOPC in familial PC than in sporadic PC, James et al. (14) observed that smoking was more commonly associated with familial PC and concluded that smoking may play a significant role in the risk or promotion of pancreatic cancer in patients

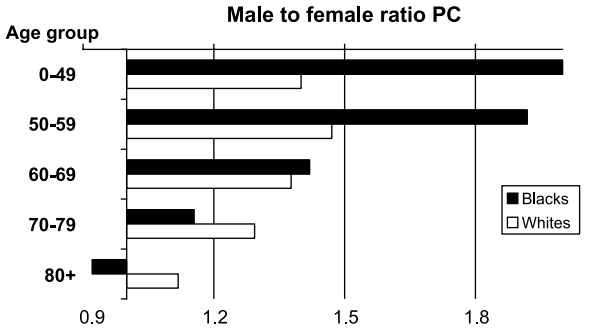

Figure 2. Male to female rate ratio for PC by age and ethnicity in the U.S. SEER registry (6).

with an inherited predisposition. In fact, a continuum of gene-environment interactions have been described in pancreatic cancer (15) and special attention has been made to EOPC in a few reports (Supplementary Table S1). EOPC has often been diagnosed in individuals carrying mutations in various tumor suppressor genes such as *TP53* (Li-Fraumeni syndrome), *CDKN2A/P16* (FAMM), *FA* (Fanconi Anemia), or *LKB1/STK11* (Peutz-Jeghers syndrome), in genes related to familial PC or cystic fibrosis, or in genes possibly related to other cancer syndromes, such as the breast cancer genes *BRCA1* and *BRCA2*. The role of these genetic alterations in the development of EOPC is very likely because the multistage theory of carcinogenesis predicts that early development of cancer is likely to have a genetic component (16).

In this report, we have summarized available information on EOPC. In further studies, it would be important to include pathologic information because EOPC could be associated with unusual histologic types (17). More detailed genetic information about patients with EOPC may help define pathways leading to more effective screening, or to the development of more effective therapeutic strategies than are currently available.

In summary, international data reveals that deaths from EOPC constitute ~1% to 5% of the deaths from PC, but in certain regions, such as Eastern Europe, years-of-life-lost from EOPC could represent as much as one-third of the total burden. Smoking seems to play a major role, but there are also many genetic mutations which seem to be responsible, either alone or in association with smoking, for the early onset of cancer. Smoking cessation reduces the frequency of PC at all ages, but is particularly important for the prevention of EOPC.

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