**Trends in incidence and survival in squamous-cell** **carcinoma of the** **anal canal in France**

**A population-based study**

**BOUVIER Anne-Marie1, BELOT Aurélien**2**, MANFREDI Sylvain**3**, JOOSTE** **Valérie1, UHRY Zoé**2**, FAIVRE Jean1, DUPORT Nicolas**4**, GRABAR Sophie5, *and the French network of cancer registries FRANCIM***

1 Registre Bourguignon des Cancers Digestifs INSERM U866, CHU Dijon, Université de Dijon, Faculté de Médecine, Dijon, France, Réseau français des registres de Cancers (FRANCIM).

2 Hospices Civils de Lyon, Service de Biostatistique, F-69003, Lyon, France ; Université de Lyon, F-69000; Université Lyon 1, F-69100 ; CNRS, UMR5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biotatistique-Santé, F-69100, Villeurbanne, France

3 Service des Maladies de l’Appareil Digestif, CHU Pontchaillou, Rennes, France

4 Département des Maladies Chroniques et Traumatismes, Institut de Veille Sanitaire (InVS), French Institute for Public Health Surveillance, 94415 Saint-Maurice Cedex, France

**5** INSERM UMRS 943 – UPMC Univ Paris 6 UMRS 943, Paris, France

**Running head**:incidence and survival of anal cancer

**Corresponding author**: **Dr Anne-Marie Bouvier**

Digestive Cancer Registry of Burgundy; University Hospital Dijon, F-21079; INSERM U866; University of Burgundy, Dijon

BP 87900, 21079 Dijon Cedex France

Tel: +33 3 80 39 33 38, Fax: +33 3 80 66 82 51

Email: anne-marie.bouvier@u-bourgogne.fr

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**Abstract**

**Objectives**: Data on anal cancer epidemiology are rare. The aim of this study was to report on trends in incidence and survival in anal cancer in France before the implementation of HPV vaccine.

**Methods**: The analysis was carried out on 1,150 squamous cell carcinomas of the anal canal diagnosed from 1989 to 2004 in a population of 5.7 million people covered by 8 population-based cancer registries. Time trends in incidence were modelled using an age-period-cohort model. Net survivals were obtained using the recently validated unbiased Pohar-Perme estimator.

**Results:** The incidence of squamous cell carcinoma of the anal canal increased from 0.2 to 0.5 per 100,000 person-years between 1982 and 2012, respectively, in men, and from 0.7 to 1.3, respectively, in women. In women, the increase peaked after 2005, with an annual percentage change of +3.4% between 2005 and 2012, as compared to +2.6% in men. Net survival was 56% (95% CI[49-64]) at 5 years and 48% [33-70] at 10 years in men. It was higher in women at 65% [61-69] and 56% [50-63], respectively. The prognosis improved between 1989-1997 and 1998-2004. This improvement was slightly greater for men than women, thus progressively reducing the gap between sexes.

**Discussion**: Squamous cell anal canal cancer incidence slightly increased for both sexes, but was more marked in women than men. The potential benefit of prophylactic female HPV vaccination against cervical cancer in France should be further evaluated.

**Key words:** anal cancer, incidence, survival, cancer registry

**Introduction**

Anal cancer is a rare tumour representing less than 5% of cancers of the lower gastrointestinal tract ([Clark](#_ENREF_9" \o "Clark, 2004 #1) *[et al.](#_ENREF_9" \o "Clark, 2004 #1)*[, 2004](#_ENREF_9" \o "Clark, 2004 #1)). It develops in the mucosa-lined anal canal or the more distal epidermis-covered anal margin. Many publications concerning the epidemiology of anal cancers confound squamous cell carcinoma and adenocarcinomas that originate from the low rectum, which causes confusion ([Faivre](#_ENREF_18" \o "Faivre, 2012 #2) *[et al.](#_ENREF_18" \o "Faivre, 2012 #2)*[, 2012](#_ENREF_18" \o "Faivre, 2012 #2)). However, most invasive anal cancers are squamous-cell carcinomas. Others are exceptional adenocarcinomas that arise in anal glandular mucosa or cancers with another histology. This study will concern only squamous-cell carcinoma of the anal canal.

The role of High-risk Human Papilloma Virus (HR-HPV) infection, immunodepression, tobacco and sexual practices (particularly men who have sex with men [MSM]) is well established in anal carcinogenesis ([Daling *et al.*, 2004](#_ENREF_14), [Durante *et al.*, 2003](#_ENREF_17), [Frisch *et al.*, 1999](#_ENREF_21)). HR-HPV infection (predominantly HPV16 and HPV18) is the most important etiological factor that facilitates HPV-induced anal dysplasia and malignant transformation. The increase in the prevalence of HR-HPV infection over time may have led to an increase in squamous-cell carcinomas. Data on the incidence of squamous-cell carcinoma are not frequent ([Brewster and Bhatti, 2006](#_ENREF_7), [Goldman *et al.*, 1989](#_ENREF_23), [Nielsen *et al.*, 2011](#_ENREF_31), [Robinson *et al.*, 2009](#_ENREF_41)). They are often provided by specialized centers and thus cannot be used as a reference because of unavoidable institutional referral bias. Population-based studies, which record all cases in a well-defined population, are the best way to assess the epidemiological characteristics of diseases. Because anal cancers are rare, there are few reports on their incidence and their prognosis. There has been a progressive implementation of HPV vaccine in France since 2007. This underlines the need to provide reference data for epidemiological indicators. The aim of this study was 1) to describe trends in the incidence of squamous-cell anal canal carcinoma in France over a 30-year period, and 2) to provide net survival estimates at 5 and 10 years using the Pohar-Perme estimator.

**Methods**

*Data sources*

The network of French population-based cancer registries FRANCIM, in collaboration with the biostatistics department of the Hospices Civils de Lyon, the French Institute for Public Health Surveillance (InVS, *Institut de veille sanitaire*), and the French National Cancer Institute (INCa, *Institut national du cancer*) manage a common database of all cancers diagnosed in well-defined administrative areas called ‘départements’. The data of eight ‘départements’ were gathered for this study (around 5.7 million inhabitants). Quality checks are carried out at both the registry level, using local controls, and at the common database level, using particularly the DepEdit software provided by the International Agency for Research on Cancer. The quality and exhaustiveness of these registries are certified every four years by an audit of the National Institute of Health and Medical Research (INSERM), the InVS and the INCa. Notification of cases comes from many sources: public and private pathology laboratories, regional databases of the National Health System, public and private hospital discharge databases. French registries do not record incident cases that are notified by death certificates only. However, death certificates are used to identify missing cases.

*Definition of anal cancer*

Only invasive tumours of the anal canalwere considered in the calculation of incidence rates. All anal canal cancers were identified according to the International Classification of Diseases for Oncology version 3 (ICD-O-3) site codes C21([Percy *et al.*, 1990](#_ENREF_37)). According to the WHO classification, anal canal cancers are mostly squamous-cell carcinomas, which represent 95% of cases. Publications often report data on squamous-cell anal cancer and adenocarcinoma arising in the low rectum, and results may therefore be confusing. All cases of microscopically confirmed invasive (behaviour code 3) squamous cell (morphology codes 8050-8084, 8123, 8124) tumours were included.

### *Time trends estimates of incidence*

To estimate incidence time trends between 1982 and 2012, cases diagnosed in eight registries between 1982 and 2010 were included. Incidence was modelled using an age-period-cohort model as described elsewhere ([Belot *et al.*, 2008](#_ENREF_5), [Binder-Foucard *et al.*, 2014](#_ENREF_6)). Briefly, data for incidence and population were tabulated by 1-year classes for age and cohort. An age-cohort model was used, with a linear-linear interaction between age and cohort (which is equivalent to an age-period-cohort model with a second-order period term p2) to estimate trends in incidence. The second-order period term p2 was introduced into the model only when it was statistically significant (likelihood ratio test, α=1%). The net cumulative risk of developing anal cancer between 0 and 74 years was calculated by birth cohort. This represents the probability of developing anal cancer between 0 and 74 years of age, in the absence of mortality.

*Survival estimates*

An active search for the vital status at 01/01/2008 was carried out for the 1150 anal cancer cases diagnosed between 1989 and 2004 using a single standardized routine procedure. The information was collected first via public services at the patient’s birthplace or an electronic request to the National directory for the identification of natural persons, which regularly updates civil status changes. Both procedures required knowledge of the patient’s birthplace. Whenever the birthplace was missing, other sources of information on the vital status were used, such as the medical records or the public services of the place of residence. The general principle was to minimize the number of patients lost to follow-up without compromising the quality of the information or introducing bias. The proportion of patients lost to follow-up was 3.6% at 10 years.

Among various survival indicators, net survival, defined as the survival that would be observed if anal canal cancer was the only possible cause of death, is of major importance in population-based studies because comparisons of net survivals are not affected by differences in other-cause mortalities. This method therefore allows comparisons between countries or periods. Net survivals were obtained using the unbiased Pohar-Perme estimator ([Perme *et al.*, 2012](#_ENREF_38)). The expected mortality rates were available by age, sex, year of diagnosis, and *Département* of residence (French administrative area). The dynamics of the excess net mortality rates over time since diagnosis was obtained by smoothing and deriving the net cumulative rate estimate. Age-standardized net survival estimates were calculated using the International Cancer Survival Standard weights ([Corazziari *et al.*, 2004](#_ENREF_11)).

Treatment strategies for anal cancer changed considerably over time with the introduction of radiotherapy ([Papillon *et al.*, 1983](#_ENREF_32)) then of concomitant chemotherapy ([Flam *et al.*, 1996](#_ENREF_19), [Party, 1996](#_ENREF_36)), which progressively replaced surgery. Accordingly, the years of diagnosis in survival analyses were divided into two periods, 1989-1997 (before radiochemotherapy) and 1998-2004 (after radiochemotherapy).

**Results**

**Time trends in incidence by period and birth cohort**

Squamous-cell anal canal cancer incidence rates increased over time in men and in women (Table 1). It increased progressively in men from 0.2 per 100,000 in 1982 to 0.5 per 100,000 in 2010. There was little variation between 1982 and 2000 in women, but this stability was followed by an increase from 0.9 to 1.3 per 100,000 in 2010. Assuming that the 1982-2010 trends would continue until 2012 led to an increasing projected age-standardized incidence rate in both sexes. In women, the increase in incidence peaked after 2005, with an annual percentage change of +3.4% between 2005 and 2012, as compared to +2.6 %.in men. The women to men incidence rate ratio decreased from 3.5 to 2.6 between 1980 and 2010. There was a marked decrease in the median age at diagnosis, in both males and females. Median age was similar in both sexes: it varied from 71 years in 1982-1984 to 63 years in 2010-2012.

The cohort’s cumulative risk of developing squamous cell carcinoma of the anal canal over the age range 0-74 years by sex is given in Figure 1. There was a slight increase in risk in the first cohorts (1920 to 1945) for men and women. The cumulative risk increased slightly between the most recent birth cohorts 1945 and 1950, rising from 0.5‰ to 0.7‰ for men and from 1.0‰ to 1.4‰ for women.

**Survival**

Global net survival was 88% (95% CI [86-90]) at 1 year, 70% [67-73] at 3 years, 63% [59-66] at 5 years and 54% [48-61] at 10 years (Figure 2). Figure 2 also presents the dynamics of the excess mortality rate over time since diagnosis. The excess rate of mortality for anal canal cancer was maximal just after diagnosis, and then seemed to stabilize between one and two years following diagnosis. It then decreased continuously up to 10 years. The gap in net survival between women and men persisted as the time since diagnosis increased. It was 5% one year after diagnosis (89% vs. 84%) and 8% ten years after diagnosis (56% vs. 48%). Table 2 presents the 1, 5- and 10-year net survivals by sex and age. Survival was higher in women than in men whatever the time since diagnosis except for the youngest 15-44 age class. Table 3 presents survival by sex and age according to the period of diagnosis. The prognosis improved between the two time periods, and was slightly better for men than for women, thus progressively reducing the gap between sexes.

**Discussion**

This study provides an unbiased picture of trends in incidence and survival in squamous cell carcinoma of the anal canal at a population level. Its strength is that it examined all cases recorded in long-standing population-based cancer registries with complete follow-up. All data were collected using a consistent procedure regardless of the time period or place of diagnosis.

This study confirmed that anal canal cancer is still a rare malignancy in France. Worldwide incidence data are available from cancers registries, in particular through the 4 volumes of Cancer Incidence in Five Continents, which covers the period analysed in this study ([Curado *et al.*, 2007](#_ENREF_13), [Forman *et al.*, 2013](#_ENREF_20), [Parkin *et al.*, 1997](#_ENREF_34), [Parkin *et al.*, 2002](#_ENREF_35)). There was no huge variation in anal cancer incidence worldwide. Its incidence increased over time for both sexes in Canada as was the case in our study, and only for women in Slovenia, the United Kingdom and New Zealand. In the United States, the increase principally concerned women, especially black and elderly women ([Johnson *et al.*, 2004](#_ENREF_27)). Incidence remained stable in Japan, Italy and Slovakia whereas it decreased slightly in both sexes in the Czech Republic, Spain and Croatia. The increase in incidence was observed since the 60’s in the United States, in Denmark and in Sweden ([Frisch *et al.*, 1993](#_ENREF_22), [Goldman *et al.*, 1989](#_ENREF_23), [Melbye *et al.*, 1994](#_ENREF_29)). In three recent European studies, the increase in incidence persisted in women ([Brewster and Bhatti, 2006](#_ENREF_7), [Nielsen *et al.*, 2011](#_ENREF_31), [Robinson *et al.*, 2009](#_ENREF_41)) and some data showed a peak in incidence for young men ([Cress and Holly, 2003](#_ENREF_12), [Jin *et al.*, 2011](#_ENREF_26)). Human papillomavirus, smoking and sexual practices are well established risk factors. Cancer registries only partially cover France. As they do not include areas more prone to high-risk sexual behaviour such as Paris, one might think that the incidence reported here could be underestimated. HPV cellular DNA is positive in around 90% of anal cancer cases ([Abramowitz *et al.*, 2011](#_ENREF_1), [Munoz *et al.*, 2003](#_ENREF_30)). In a recent population-based Danish study, the increase in incidence concerned only HPV-related squamous-cell anal cases whereas the incidence of non-HPV-related cases remained stable, especially in men ([Nielsen *et al.*, 2011](#_ENREF_31)). Similar trends in the incidence of cancers of the anus and the oropharynx, primarily caused by HPV infection, have been reported in previous studies([Chaturvedi *et al.*, 2008](#_ENREF_8), [Cole *et al.*, 2012](#_ENREF_10)), this latter location being potentially associated with ethnic variations in oncogenic HPV infection ([Shack *et al.*, 2014](#_ENREF_42)). Increasing social acceptance of premarital sex, multiple sex partners, anal sex practices and oral sex over the last several decades have likely contributed to increased oral HPV infection([Herrero *et al.*, 2003](#_ENREF_24)). In women, the incidence of cervical cancer has declined over time in countries with established screening programs ([Shack *et al.*, 2014](#_ENREF_42), [Vaccarella *et al.*, 2014](#_ENREF_44)). In France, HPV vaccination has only been proposed to young girls aged 14 years with a catch-up to young girls aged 15 to 23 years between 2007 and 2012, and, since 2013, to young girls aged 11 to 14 years with a catch-up to young girls aged 15 to 20 years. Thus, it cannot have affected the incidence rate in our study ~~and could partly explain the relatively greater increase in incidence in women~~. However, it underscores the importance of continuing the registration of incidence data at a population level.

 Different studies have pointed out that the incidence of HIV-related anal cancer is continuing to increase despite long-term combined antiretroviral treatment ([Piketty *et al.*, 2012](#_ENREF_39), [Simard *et al.*, 2011](#_ENREF_43)). A nationwide hospital-based cohort, the French Hospital Database study on HIV between 1992 and 2004, showed that the incidence of anal cancer has increased among HIV-infected patients in France since 1996, the advent of antiviral treatments. Combination antiretroviral therapy does not prevent anal cancer in these patients ([Piketty *et al.*, 2008](#_ENREF_40)). The individual HIV status was not available for the population of the present study, but one might think that changing trends in the incidence of HIV infection do not explain all of the observed trends as the regions covered by the Francim registries do not include regions of France with the highest levels of HIV-infection (Paris region and South of France)([Hleyhel *et al.*, 2013](#_ENREF_25)). The association between tobacco consumption and anal cancer has been known for a long time ([Daniell, 1985](#_ENREF_16)). This association seems to concern active smokers and premenopausal women in particular, suggesting either a possible hormonal interaction ([Frisch *et al.*, 1999](#_ENREF_21)) or the reflect of a higher sexual activity in these women. An American study suggested that tobacco could be a promoter during the last stages of carcinogenesis ([Daling *et al.*, 1992](#_ENREF_15)). The increase in tobacco consumption in women could be partly related to the observed trends in anal cancer incidence.

Population-based data on anal cancer survival are scarce ([Faivre *et al.*, 2012](#_ENREF_18), [Johnson *et al.*, 2004](#_ENREF_27), [Park *et al.*, 2013](#_ENREF_33)). They provide survival rates of the same order of magnitude taking into account differences in the studied periods. Survival was consistently poorer for men than for women and increased over time. Similar trends were reported from the SEER program, in which 5-year relative survival increased from 59% to 73% between 1973-1979 and 1994-2000([Johnson *et al.*, 2004](#_ENREF_27)). In an Australian study, 5-year relative survival increased from 59% to 68% between 1982-1988 and 1997-2004 ([Jin *et al.*, 2011](#_ENREF_26)) and in a Korean study from 58% to 75% between 1993-1995 and 2002-2010 ([Park *et al.*, 2013](#_ENREF_33)).

Prognostic factors for anal cancer are not well established. Male gender, node involvement and size over 5 cm were pejorative factors in some clinical trials ([Ajani *et al.*, 2008](#_ENREF_2), [Ajani *et al.*, 2010](#_ENREF_3), [Bartelink *et al.*, 1997](#_ENREF_4)) and cohort studies. Advanced age decreased survival in the Australian and Korean population-based studies ([Jin *et al.*, 2011](#_ENREF_26), [Park *et al.*, 2013](#_ENREF_33)). The management of anal cancers has improved over time since the introduction of radiochemotherapy rather than radical surgery ([Papillon *et al.*, 1983](#_ENREF_32)). Then, the combination regimen of radiotherapy and infused 5-fluorouracil and mitomycin showed a reduced risk of local failure and of death from anal cancer for patients receiving this combined therapy ([1996](#_ENREF_36)). Improved survival over time may be at least partly related to these progressive advances in radio and chemotherapy combinations. One limitation of our study is the absence of data on time trends for stage at diagnosis. Nevertheless, as the current study focused on invasive disease, the increase in the incidence of *in situ* disease as a result of increased surveillance, particularly in high-risk populations, probably did not contribute greatly to the observed increase in survival([Machalek *et al.*, 2012](#_ENREF_28)).

To conclude, although squamous cell carcinoma of the anal canal is rare, its frequency has increased slightly in both sexes, and more markedly in women. Exposure to HPV concerns both men and women. A substantial proportion of these cancers should be preventable by HPV vaccination as confirmed in April 2014 by the Committee for Medicinal Products for Human Use of the European Medicines Agency. This could thus cause a downturn in trends in incidence in the near future more marked for women. ~~for the general population.~~

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**Figure 1. Cumulated 0-74 years risk of anal cancer by birth cohort**

**Figure 2 – Net 10-year survival and dynamics of the excess mortality rates for squamous-cell** **anal cancer.**