Cervical morbidity in Alsace, France: results from a regional organized cervical cancer screening program

Jean-Jacques Baldauf[a], Muriel Fender[c], Christine Bergeron[d], Emilie Marrer[e], Michel Velten[b], Pierre Pradat[f] and Marc Arbyn[g]

In 1994, a pilot program of cervical cancer screening was introduced in the Alsace region, France. Women aged 25–65 years were proposed to have one Pap smear every 3 years. The objective was to assess cervical morbidity in Alsace before the human papillomavirus vaccinated population reaches the age of screening. Data on cervical lesions and cancers were collected by EVE for the period September 2008 to August 2011 from existing medical services and cytopathology laboratories in Alsace. Cytological and histological data were completed with data from the two cancer registries covering the region (Bas-Rhin and Haut-Rhin). Cancer incidence rates were computed for the target population (truncated to 25–64 years) and were age standardized according to the world reference population. World standardized incidence rates for the whole female population were obtained from the two cancer registries. During 2008–2011, 565 153 smears were performed in 498 913 women aged 25–64 years, representing an average of 1.13 smears/woman and 1.62 smears/screened woman. The overall screening coverage was 70.1% over the 3-year period. Histologically confirmed high-grade lesions were found in 2303 women (0.5%). Moreover, 215 cervical cancers were reported among women aged 25–64 years (crude and standardized truncated incidence rate of 10.6 and 10.0/100 000 women-years, respectively). The overall screening coverage of 70% at 3 years is higher than the national rate (57%), and the overall cancer incidence of 5.5/100 000 is below the national French level. The EVE database will be useful to assess trends in cervical morbidity over time and to further assess the effect of screening as well as of human papillomavirus vaccination. ***European Journal of Cancer Prevention*** **28:33–39 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

European Journal of Cancer Prevention 2019, **28**:33–39

Keywords: cervical cancer, incidence, morbidity, screening

[a]Department of Obstetrics and Gynecology, CHU Hautepierre, [b]Department of Epidemiology and Public Health, Bas-Rhin Cancer Registry, University of Strasbourg, Strasbourg, [c]Association EVE, Illkirch Graffenstaden, [d]Cerba Laboratory, Cergy Pontoise, [e]Haut-Rhin Cancer Registry, Mulhouse Hospital, Mulhouse, [f]Department of Hepatology, Centre for Clinical Research, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon, France and [g]Belgian Cancer Centre/Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium

Correspondence to Jean-Jacques Baldauf, MD, PhD, Department of Obstetrics and Gynecology, CHU Hautepierre, Avenue Molière, 67098 Strasbourg Cedex, France
Tel: +33 388 127 472; fax: +33 388 127 457;
e-mail: jean-jacques.baldauf@chru-strasbourg.fr

Received 12 December 2016 **Accepted** 5 July 2017

Introduction

Cervical cancer is one of the most common cancers occurring in women worldwide with 485 000 cases diagnosed in 2013 and 236 000 deaths (Fitzmaurice *et al.*, 2015). Its association with human papillomavirus (HPV) is now well established (Tommasino, 2014), and effective HPV vaccines are today available and recommended as a primary prevention measure (Bosch *et al.*, 2013). However, cervical cancer screening still remains necessary. In spite of European guidelines (Arbyn *et al.*, 2010), cervical cancer prevention differs between countries or regions and screening may be either organized or opportunistic (Elfström *et al.*, 2015a, 2015b). In France, smears are recommended in women aged 25–65 years once every 3 years following two negative smear results performed at 1-year interval (Anon, 1990). However, it is estimated that 40% of French women have never had a cervical smear test, and this rate increases up to 80% in women older than 60 years (Eisinger *et al.*, 1994).

In Alsace, a French region of ~1.8 million inhabitants, a pilot program of cervical cancer screening was introduced in 1994 in the Bas-Rhin Department and extended to the whole Alsace region in 2001 (Fender *et al.*, 1998). The objectives of this program are to increase screening coverage and to ensure high quality at every step of the screening process using existing health services. Organized screening programs may also help to better estimate the burden of cervical lesions within a given well-defined geographical area (Arbyn *et al.*, 2009).

The objective of this study was to assess, within the context of an organized cervical cancer screening program, cervical morbidity in Alsace before the vaccinated population reaches the age of screening.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, *www.eurjcancerprev.com*.

Materials and methods

Study period and geographical scope

Data on cervical lesions and cancers were collected for the period September 2008 to August 2011. The data collection covered the Alsace region including the two departments of Bas-Rhin and Haut-Rhin. In 2011, 498 913 women aged 25–65 years, resident of Alsace, belonged to the target population eligible for a screening Pap smear. The burden of cervical lesions in the study period was only slightly influenced by HPV vaccination. HPV vaccination was recommended in France since 2007 for 14-year-old girls and for 15–23-year-old women (as part of 'catch-up' vaccination), and since 2013 for 11–14-year-old girls with a catch-up for 15–19-year-old women. A recent HPV vaccination coverage study conducted by EVE, based on reimbursement data, showed that ~4% of women in the target screening population may have been vaccinated (Baldauf JJ, unpublished data).

Organized cervical cancer screening in Alsace

Cervical cancer screening is offered by existing medical services. Data were obtained from all cytopathology laboratories in Alsace. Cytological data were collected since 1994 (Bas-Rhin) and 2001 (Haut-Rhin), whereas histological data were available from the laboratories of both departments since 2007. Before 2007, histological data were obtained from physicians who provided the follow-up of abnormal Pap smear results. Data were centralized and managed by the EVE association sponsored by National Educational and Health Information Funds (FNPEIS) and by the local councils (Anon, 2016a). The Alsace screening program checks records from the French National Health Services and invites women who do not have a Pap smear recorded within the previous 3 years. The central database allows tracking the follow-up of women with abnormal smears. Cytological lesions are classified according to the 2001 Bethesda classification (Solomon *et al.*, 2002) and histological lesions according to the WHO classification (Anon, 2017). Screening in Alsace is organized taking the European guidelines for Quality Assurance of Cervical Cancer Screening into account (Arbyn *et al.*, 2010).

Cancer registries

Cytological and histological data are completed with data from two population-based cancer registries of Bas-Rhin and Haut-Rhin. These registries allow the identification of cancer cases diagnosed inside and outside the screening program hereby contributing to more complete data.

Statistical analysis

Population data used for calculations of the burden of disease were extracted from the National Institute of Statistics and Economic Studies (INSEE) (Anon, 2011). Five-year age groups were constructed on women's age in 2011. Screening coverage was defined as the proportion of 25–64-year-old women residing in Alsace in 2011 with at least one Pap smear in the 3 or the 5 previous years.

The burden of lesions was described by absolute numbers and as proportions. For cytology, the percentage of abnormal Pap smears was computed, whereas prevalence of histological lesions was calculated as number of women with cervical intraepithelial neoplasia detected during the study period (selecting highest degree of lesion occurring in the 3-year period/population screened × 1000). The truncated incidence of cancer is expressed as new cases of invasive cancer per 100 000 women-years in the target study population. Age-standardized incidence rates were computed as proposed by Jenssen *et al.* (1991), using the World standard population as reference [world standardized incidence rate (WSIR)]. The truncated WSIR was computed from the database, whereas the WISRs including all age groups were obtained from the Cancer Registries of Bas-Rhin and Haut-Rhin (Anon, 2016b).

Cytopathology classifications

CIN2+ (cervical intraepithelial neoplasia of grade 2 or worse) was defined as CIN2, CIN3, or adenocarcinoma *in situ* (Richart, 1973), whereas ASC-US+ was defined as ASC-US (atypical squamous cells of undetermined significance) + ASC-H (atypical squamous cells cannot exclude HSIL) + AGC (atypical glandular cells) + LSIL (low-grade squamous intraepithelial lesion) + HSIL (high-grade squamous intraepithelial lesion) + cytological findings compatible with adenocarcinoma in-situ or cancer. Finally, ASC-H+ was defined as ASC-H + HSIL + cytological findings compatible with adenocarcinoma in-situ or cancer (Solomon *et al.*, 2002).

Ethical considerations

In accordance with the French legislation, the Alsace screening program received approval from the Commission Nationale de l'Informatique et des Libertés (CNIL) (Anon, 2016c) (agreement no. 289520 received on 23 January 1993, modified on 16 March 2005, 17 November 2010, and 9 February 2011). All screened women received information on collection and linkage of relevant screening data and on their right to refuse the use of their personal data.

Results

Target population

In 2011, 498 913 women aged 25–64 were living in the Alsace region. The age distribution is given in Supplementary Table 1 (Supplemental digital content 1, *http:///links.lww.com/EJCP/A179*).

Number of Pap smears and screening coverage

The total number of smears per age category is given in Supplementary Table 1 (Supplemental digital content 1, *http:///links.lww.com/EJCP/A179*). For the whole Alsace region, 565 153 smears were performed during the 2008–2011 period in 498 913 women, representing an average of 1.13 smears/woman living in Alsace and 1.62 smears/screened woman. This latter ratio varied by age

decreasing from about 2.05 in women aged less than 30 to 1.33 in women over 60 years.

The overall screening coverage was 70.1% over the 3-year period and varied by age. It increased from 63.4% in women aged 25–29 to 83.4% in women aged 30–34 and then decreased regularly to 56.7% in 60–64-year-old women (Fig. 1). The overall screening coverage rate considered over a 5-year period was 81.3%.

Cytological lesions

During the 2008–2011 period, 8180 smears were classified as low-grade lesions (LSIL) representing a prevalence of 1.45/100 smears (Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/EJCP/A180*). This prevalence was 3.04% in the 25–29 age group and decreased to 0.41% in women aged 60–64 years (Fig. 2).

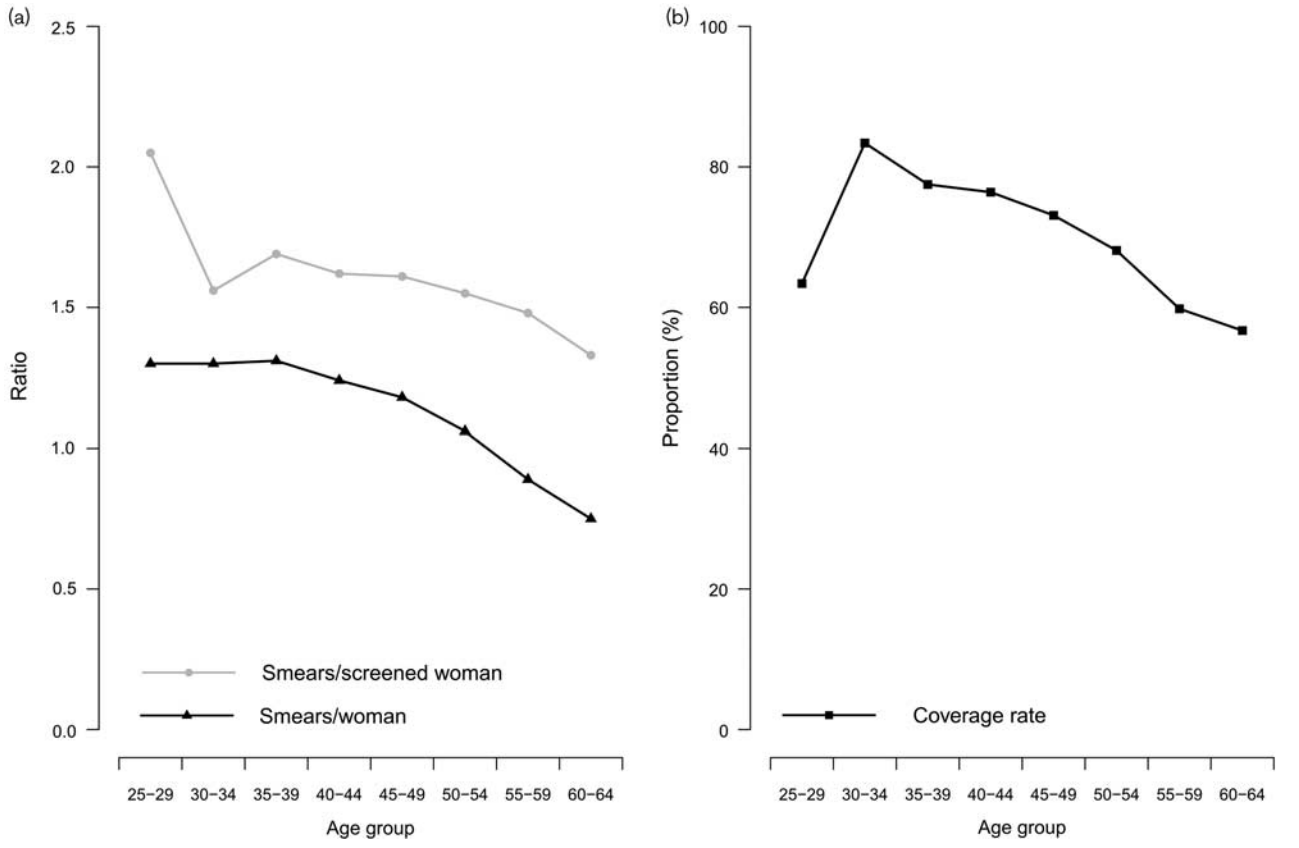
In the same period, 1690 smears were classified as high-grade lesions (HSIL) with an overall prevalence of 0.30/100 smears, decreasing from 0.51% in 25–29-year-old women to 0.08% in women 60–64 years old. Five smears were suggestive of adenocarcinoma *in situ* and 73 smears were suggestive of invasive cervical cancer. Among them, 24 were suggestive of squamous carcinoma, 13 of adenocarcinoma, and 36 of unspecified cervical cancer. Overall, 535 378 smears (94.7%) were considered as within normal limits.

Histologically confirmed cervical intraepithelial neoplasia

Over the 3-year period, 2664 cases of CIN1, 962 CIN2, and 1283 CIN3 were reported, representing a prevalence of 5.34/1000, 1.93/1000 and 2.57/1000 screened women, respectively. The world standardized prevalence of CIN1, CIN2, and CIN3 was 6.11/1000 (95% confidence interval: 5.87–6.34/1000), 2.19/1000 (2.05–2.33/1000), and 2.92/1000 (2.76–3.09/1000), respectively. The prevalence of these lesions was highest in younger women (25–29 years) and lowest in women aged 60–64 years (Table 1). Fifty-eight cases of adenocarcinoma in-situ (AIS) were reported giving a prevalence of 0.12/1000.

Table 2 gives the proportion of CIN2+ lesions among all cytological lesions (ASC-US+) and among ASC-H+ (ASC-H, HSIL, or adenocarcinoma in-situ or cancer). Approximately 8.4% of all smears with cytological lesion (ASC-US+) turned to be CIN2+ whereas 88.6% of

Fig. 1



Average number of smears per woman and per screened woman (a) and variation of the 3-year screening coverage rate in Alsace in 2008–2011 according to 5-year age category (b).

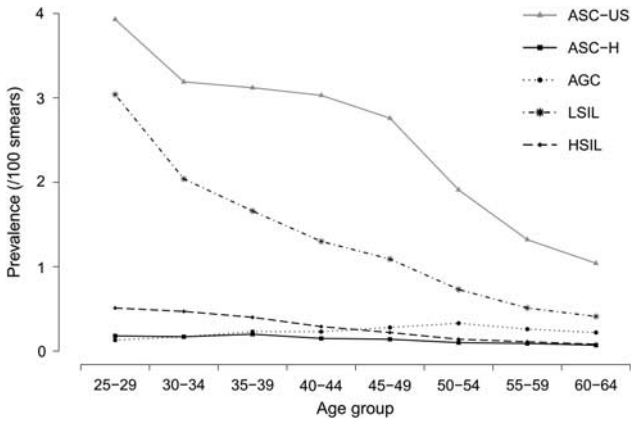
smears evocating a high-grade lesion (ASC-H+) turned to be CIN2+.

Cancer cases

For the whole Alsace region, 215 cervical cancers were reported during the 2008–2011 period, giving a crude incidence rate of 10.6/100 000 women-years in the target age group (25–64 years) (Table 3). The world standardized incidence, restricted to the study target population, was 10.0/100 000 women-years (8.6–11.3/100 000). The incidence increased from 3.2/100 000 in women aged 25 to 29 years, to ~15.0/100 000 in women between 40 and 54 years, and decreased after 55 years reaching 8.3/100 000 in 60–64-year-old women. These cancers were mainly squamous carcinomas (78%). Among 204 cases of squamous carcinoma or adenocarcinoma, 30% were detected in women who had a smear during the past 3 years.

The world age-standardized incidence rates of cervical cancer for all age groups reported by the cancer registries of Bas-Rhin and Haut-Rhin for the period 2008–11 were 5.3 and 5.6/100 000 women-years, respectively (Anon, 2016b).

Fig. 2



Prevalence (/100 smears) of cytological lesions according to 5-year age category (ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude HSIL; AGC, atypical glandular cells; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

For cytological and histological lesions as well as for cancers, no difference was observed in terms of prevalence/incidence between the Bas-Rhin and Haut-Rhin departments (data not shown), and data were thus pooled together, representing the whole Alsace region.

Discussion

Based on an organized and long-lasting cervical cancer screening program, our study gives an overview of cervical morbidity in Alsace between 2008 and 2011. The overall screening coverage of 70% at 3 years is higher than the national screening coverage rate (57% during 2006–2008) (Anon, 2016d) but remains below the recommended European coverage of 85% (Coleman *et al.*, 1993). Such a high rate is only achieved among 30–34-year-old women (84.7%) whereas rates of ~60% are observed in younger women (25–29 years) and in women older than 55 years. Even if a general trend toward lower coverage in young women has been reported in other developed countries (Lancucki *et al.*, 2010), the coverage in younger women in our study (25–29 years) is underestimated as not all women had the opportunity to contribute over the whole study period. For example, women who were 25 years old in 2011 only contributed over 1 year of the study period (2011). It is noteworthy that the overall screening coverage rate increases from 70 to 83% when considering a 5-year interval. This underlines the benefit of an organized screening program with systematic reminding for women with no smear during the past 3 years (Heranney *et al.*, 2011).

The average number of smears of 1.62/screened woman is excessive to cover the whole population suggesting a substantial amount of over screening. The average ratio of 1.62 varies according to age, with highest values in the younger and lowest values in the older target age groups. The higher ratio of 2.05 observed in the 25–29 age group is explained by the French guidelines which specify that the first screening smear must be repeated at 1 year before spacing at 3 years.

The overall screening coverage rate of 70% reflects the strength of this organized screening program which

Table 1 Total number of CIN1, CIN2, CIN3, or AIS cases in Alsace in 2008–2011 by age category and average crude prevalence per 1000 women (between brackets)[a]

	Age group								
Nb (rate) by lesion severity	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	Total
CIN1[a]	743 (12.6)	483 (8.26)	447 (6.99)	386 (5.74)	304 (4.44)	160 (2.44)	95 (1.51)	46 (0.86)	2664 (5.34)
CIN2[a]	247 (4.17)	176 (3.01)	195 (3.05)	141 (2.1)	99 (1.45)	53 (0.81)	34 (0.54)	17 (0.32)	962 (1.93)
CIN3[a]	305 (5.15)	283 (4.84)	258 (4.04)	191 (2.84)	141 (2.06)	60 (0.92)	24 (0.38)	21 (0.39)	1283 (2.57)
AIS[a]	11 (0.19)	10 (0.17)	6 (0.09)	5 (0.07)	8 (0.12)	7 (0.11)	5 (0.08)	6 (0.11)	58 (0.12)
CIN2, CIN3, or AIS[a]	563 (9.51)	469 (8.02)	459 (7.18)	337 (5.01)	248 (3.62)	120 (1.83)	63 (1)	44 (0.82)	2303 (4.62)
CIN2, CIN3, or AIS/1000 screened	563 (15.0)	469 (9.62)	459 (9.26)	337 (6.56)	248 (4.96)	120 (2.69)	63 (1.68)	44 (1.45)	2303 (6.58)

AIS, adenocarcinoma *in situ*; CIN, cervical intraepithelial neoplasia; NB, Number of cases (rate).
[a]Prevalence computed as number of women with the highest degree of lesion occurring in the 3-year period/target population × 1000.

Table 2 Number of CIN2+ lesions (CIN2, CIN3, or adenocarcinoma *in situ*) and proportion of CIN2+ among all cytological lesions (ASC-US+) and among severe cytological lesions (ASC-H+)

	Age group								
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	Total
CIN2+	563	469	459	337	248	120	63	44	2303
Total cytological lesions ASC-US+[a]	5994	4585	4703	4150	3628	2244	1296	737	27337
Total cytological lesions ASC-H+[b]	534	497	510	376	306	181	125	71	2600
CIN2+/total cytological lesions ASC-US+ (/100)	9.4	10.2	9.8	8.1	6.8	5.3	4.9	6.0	8.4
CIN2+/total cytological lesions ASC-H+ (/100)	100.0	94.4	90.0	89.6	81.0	66.3	50.4	62.0	88.6

ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion.
[a]Total cytological lesions ASC-US+ = ASC-US + ASC-H + AGC + LSIL + HSIL + adenocarcinoma in-situ or cancer.
[b]Total cytological lesions ASC-H+ = ASC-H + HSIL + adenocarcinoma in-situ or cancer.

Table 3 Total number and crude incidence rates of cervical invasive cancers by histology and age category in Alsace, 2008–2011

	Age group								
n (/100 000/year)	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	25–64
Squamous carcinoma									
N	6	10	18	29	35	31	23	15	167
I	2.4	4.2	6.7	10.4	12.6	11.7	9.3	7.4	8.2
Adenocarcinoma									
N	0	2	4	8	8	7	6	2	37
I	0.0	0.8	1.5	2.9	2.9	2.6	2.4	1.0	1.8
Other invasive neoplasms									
N	2	1	2	3	2	0	1	0	11
I	0.8	0.4	0.7	1.1	0.7	0.0	0.4	0.0	0.5
All cancers									
N	8	13	24	40	45	38	30	17	215
I	3.2	5.4	8.9	14.4	16.2	14.3	12.1	8.3	10.6

N = total number of cervical cancers over the period 2008–2011/age category.
I = age specific incidence (Nb of cervical cancers/average population/3).

should be extended to other regions in France. However, the amount of over screening merits attention as this activity involves substantial resources without proven benefit but with associated adverse effects (Thiery *et al.*, 2017). Restriction of reimbursement of screening according to recommended screening intervals implemented in Belgium was successful in reducing excessive Pap smear use (Arbyn *et al.*, 2014). In France, a first step was taken by changing the coding system for reimbursements of acts, now allowing the distinction between screening smears and follow-up smears. However, the new national screening guidelines are still not mentioning that over screening is not reimbursed.

HPV vaccination is recommended in France since 2007 for 14-year-old girls and for 15–23-year-old women (as part of 'catch-up' vaccination), and since 2013 for 11–14-year-old girls with a catch-up for 15–19-year-old women. Therefore, no influence was expected during this study which covered the 2008–2011 period as almost all women vaccinated since 2007 could not be included because of their age. These results of the 'prevaccination' period will be a reference to assess the effect of routine HPV vaccination on the burden of cervical lesions in France when vaccinated cohorts reach the target age for screening.

Since the first historical histological study on cervical lesions in France (Sastre-Garau *et al.*, 1996), a recent study conducted by the FRANCIM network (France Cancer Incidence et Mortalité) reported data on the burden of cervical lesions in nine different departments of France (20% of the French population) between 2000 and 2009 (Woronoff *et al.*, 2017), but using limited data regarding the classification of CIN (Richart, 1990). Indeed since the recommended use of the CIN classification for cervical lesions in France, some registries merged the different classes of CIN, more particularly CIN2 and CIN3. To face this discrepancy, the authors revised all the registries and decided to take only CIN3 into account. They found 10 879 cervical lesions (CIN3) and 3562 related cancers between 2000 and 2009, with a mean yearly incidence rate of CIN3 ranging from 0.26/1000 in 2000 to 0.30/1000 in 2009, with a significant increase of 2% every year. They also showed that the incidence rate during 2007–2009 varied between the different departments covered by the study, from 0.17 to 0.42/1000/year. These variations may reflect geographical differences regarding the prevalence of risk factors but also differential participation of risk groups, and variation in exhaustivity of registration and sensitivity of screening and diagnosis of cervical precancer (Murthy and Mathew, 2000). Such geographic variations have also been

observed between the different states of the USA (Anon, 2016e). The incidence data presented by Woronoff *et al.* (2017) including the total female population cannot be compared with the prevalence data restricted to women aged 25–64 years in the current report, given the differences in definition and computation of the indicators. The incidence rates presented by Woronoff *et al.* (2017) showed that the incidence of CIN3+ for Bas-Rhin (0.39/1000) and Haut-Rhin (0.26/1000) were, respectively, higher and lower than the overall average for all French registries (0.30/1000).

Interestingly, we observed that 8% of abnormal smears (ASC-US+) and 89% of smears evocating high-grade cytological lesion (ASC-H+) turned to be CIN2+ lesion representing positive predictive values of 8 and 89%, respectively.

National (Anon, 2016f) and international (Arbyn *et al.*, 2011) estimates of the age-standardized rates (ASIR) of cervical cancer incidence in France around 2008 are similar (7–8/100 000 women-years) when using the world standard population as reference. With this burden, France ranks in the lower quarter of countries in Europe (ranked by increasing burden), where the ASIR varies between 3.7 (Finland) and 23.9/100 000/year (Romania) (Arbyn *et al.*, 2011). The cervical cancer incidence rate in our study (10.6/100 000 women) is computed for women aged 25–64 years. The WSIRs of cervical cancer for the whole female population of Bas-Rhin and Haut-Rhin for the study period (5.3 and 5.6/100 000 women-years, respectively) were lower than the incidence estimated from nine French registries, which was 6.2/100 000 (Woronoff *et al.*, 2014), and lower than the national incidence of 6.8/100 000 estimated in 2010 (Binder-Foucard *et al.*, 2014). As screening coverage in Alsace is higher, and as primary risk of cervical cancer probably is not substantially different in Alsace, lower cancer rates may reflect higher program effectiveness compared with other French regions.

In the present study, 30% of invasive squamous carcinomas or adenocarcinomas were detected in women with regular screening, that is, in women who had at least one smear during the past 3 years. Such cases may represent interval cancer cases, that is, cancers following a normal smear performed within the past 3 years. They may also represent cancer cases associated with an abnormal smear. In this latter situation, it is possible that women with abnormal smear had no follow-up biopsy or that a diagnosis or therapeutic failure occurred (Andrae *et al.*, 2008). It is noteworthy that an increased screening coverage is expected to result in an overall decreased number of cancer cases in women with suboptimal screening which is paralleled with an increased proportion of interval cancer cases. However, these latter cases are known to be less severe than noninterval cases (Andrae *et al.*, 2008; Gök *et al.*, 2011).

The Alsace has pioneered organized cervical cancer screening in France, which has led to high population coverage and lower burden of cervical cancer compared with other regions. The Alsace screening and pathology databases demonstrate how trends evolved in relation to screening parameters. These databases – if linked to vaccination registries – will also allow monitoring the effect of HPV vaccination in the future (Pollock *et al.*, 2014; Arbyn *et al.*, 2016).

Acknowledgements

Conflicts of interest

The work of J-J.B., M.F., C.B., and P.P. was supported in part by a non-conditional grant from Sanofi-Pasteur MSD France (Lyon). M.A. was supported by the Seventh Framework Program of the Directorate-General for Research and Innovation of the European Commission through the COHEAHR network (grant 603019) and by the Joint Action on Comprehensive Cancer Control, which has received funding from the European Union within the framework of the Health Program (2008–2013).

References

Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, *et al.* (2008). Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst* **100**:622–629.

Anon (1990). Fédération des gynécologues et obstétriciens de langue française. Conférence de consensus sur le dépistage du cancer du col utérin [Federation of French Gynecologists and Obstetricians. Consensus Conference on Cervical Cancer Screening]. Lille 5–8 September 1990. (1990). *J Gynecol Obstet Biol Reprod* **19**:1–16.

Anon. (2011) French National Institute of Statistics and Economic studies (INSEE). (n.d.). Available at: *http://www.insee.fr/en/*. [Accessed 18 April 2017].

Anon. (2016a) Association pour la prévention du cancer du col de l'utérus (EVE) [Association for the prevention of cervical cancer (EVE)]. (n.d.). Available at: *http://www.eve.asso.fr/*. [Accessed 18 April 2017].

Anon. (2016b) Registre des Cancers. Laboratoire d'Epidemiologie et de Santé Publique [Cancers Registry. Department of Epidemiology and Public Health. Strasbourg University]. Université de Strasbourg. (n.d.). Available at: *http://epidemio.unistra.fr/index.php?option=com_content&view=article&id=17&Itemid=29*. [Accessed 18 April 2017].

Anon. (2016c) Commission Nationale de l'Informatique et des Libertés (CNIL) [French Data Protection Authority (CNIL)]. (n.d.). Available at: *http://www.cnil.fr*. [Accessed 18 April 2017].

Anon. (2016d) Taux de couverture pour le dépistage du cancer du col de l'utérus. Institut National du Cancer [Coverage rate for cervical cancer screening. National Cancer Institute]. (n.d.). Available at: *http://www.e-cancer.fr/Professionnels-de-sante/Depistage-et-detection-precoce/Depistage-du-cancer-du-col-de-l-uterus/Le-depistage-par-frottis-cervico-uterin*. [Accessed 18 April 2017].

Anon. (2016e) National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer of the cervix uteri. (n.d.). Available at: *http://seer.cancer.gov/archive/csr/1975_2010/browse_csr.php?sectionSEL=5&pageSEL=sect_05_table.12.html*. [Accessed 18 April 2017].

Anon. (2016f) Le cancer du col de l'utérus en France. Institut National du Cancer [Cervical cancer in france. National Cancer Institute]. (n.d.). Available at: *http://www.e-cancer.fr/content/download/63375/570309/file/ETACOLUTE10.pdf*. [Accessed 18 April 2017].

Anon 2017. Tumours of the uterine cervix. Chapter 5. International Agency for Research on Cancer. (n.d.). Available at: *https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb4/bb4-chap5.pdf*. [Accessed 18 April 2017].

Arbyn M, Rebolj M, De Kok IMCM, Fender M, Becker N, O'Reilly M, *et al.* (2009). The challenges of organising cervical screening programmes in the 15 old member states of the European Union. *Eur J Cancer 1990* **45**: pp. 2671–2678.

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, *et al.* (2010). European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition–summary document. *Ann Oncol* **21**:448–458.

Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, *et al.* (2011). Worldwide burden of cervical cancer in 2008. *Ann Oncol* **22**:2675–2686.

Arbyn M, Fabri V, Temmerman M, Simoens C (2014). Attendance at cervical cancer screening and use of diagnostic and therapeutic procedures on the uterine cervix assessed from individual health insurance data (Belgium, 2002-2006). *PLoS One* **9**:e92615.

Arbyn M, Broeck DV, Benoy I, Bogers J, Depuydt C, Praet M, *et al.* (2016). Surveillance of effects of HPV vaccination in Belgium. *Cancer Epidemiol* **41**:152–158.

Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff AS, Remontet L, French network of cancer registries (Francim) (2014). Cancer incidence and mortality in France over the 1980–2012 period: solid tumors. *Rev Épidémiologie Santé Publique* **62**:95–108.

Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, *et al.* authors of ICO Monograph Comprehensive Control of HPV Infections and Related Diseases Vaccine Volume 30, Supplement 5, 2012 (2013). Comprehensive control of human papillomavirus infections and related diseases. *Vaccine* **31** (**Suppl 7**):H1–H31.

Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, *et al.* (1993). European Guidelines for Quality Assurance in Cervical Cancer Screening. Europe against cancer programme. *Eur J Cancer* **29A** (**Suppl 4**):S1–S38.

Eisinger F, Moatti JP, Béja V, Obadia Y, Alias F, Dressen C (1994). Attitude of the French female population to cancer screening. *Bull Cancer* **81**:683–690.

Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J (2015a). Cervical cancer screening in Europe: Quality assurance and organisation of programmes. *Eur J Cancer* **51**:950–968.

Elfström KM, Dillner J, Arnheim-Dahlström L (2015b). Organization and quality of HPV vaccination programs in Europe. *Vaccine* **33**:1673–1681.

Fender M, Schaffer P, Dellenbach P (1998). Can we and must we organize cervical cancer screening in France? Results of the pilot project 'EVE' in the department of Bas-Rhin. *J Gynécol Obstet Biol Reprod (Paris)* **27**:683–691.

Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, *et al.* (2015). The global burden of cancer 2013. *JAMA Oncol* **1**:505–527.

Gök M, Rozendaal L, Berkhof J, Visser O, Meijer CJLM, van Kemenade FJ (2011). Cytology history preceding cervical cancer diagnosis: a regional analysis of 286 cases. *Br J Cancer* **104**:685–692.

Heranney D, Fender M, Velten M, Baldauf JJ (2011). A prospective randomized study of two reminding strategies: telephone versus mail in the screening of cervical cancer in women who did not initially respond. *Acta Cytol* **55**:334–340.

Jenssen O, Parkin D, MacLennan R, Muir C, Skeet R (1991). *Cancer Registration Principles and Methods*, 95th ed. Lyon: International Agency for Research on Cancer. pp. 1–288.

Lancucki L, Fender M, Koukari A, Lynge E, Mai V, Mancini E, *et al.* (2010). A fall-off in cervical screening coverage of younger women in developed countries. *J Med Screen* **17**:91–96.

Murthy NS, Mathew A (2000). Risk factors for pre-cancerous lesions of the cervix. *Eur J Cancer Prev* **9**:5–14.

Pollock KGJ, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, *et al.* (2014). Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer* **111**:1824–1830.

Richart RM (1973). Cervical intraepithelial neoplasia. *Pathol Annu* **8**:301–328.

Richart RM (1990). A modified terminology for cervical intraepithelial neoplasia. *Obstet Gynecol* **75**:131–133.

Sastre-Garau X, Asselain B, Bergeron C, Cartier I, Souques M (1996). Precancerous and cancerous involvement of the uterine cervix. Results of a survey conducted by the 'Genital Cancers' group of Ile-de-France, May 1990-May 1992, based on 8,805 biopsies. *Bull Cancer* **83**:400–406.

Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, *et al.* Forum Group Members, and Bethesda 2001 Workshop (2002). The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* **287**:2114–2119.

Thiery A, Akladios C, Fender M, Severac F, Baldauf JJ (2017). Excess cervical cancer screening smears: Any benefit? A retrospective cohort in Alsace, France. *J Med Screen* **24**:92–97.

Tommasino M (2014). The human papillomavirus family and its role in carcinogenesis. *Semin Cancer Biol* **26**:13–21.

Woronoff A, Trétarre B, Champenois V (2017) (n.d.) Monitoring of precancerous and cancerous lesions of the cervix by the FRANCIM Network Cancer Registries. Available at: *http://www.invs.sante.fr/beh/2014/13-14-15/index.html*. [Accessed 18 April 2017].

Woronoff A, Trétarre B, Champenois V, Duport N, Bara S, Lapotre-Ledoux B, *et al.* (2014). Surveillance des lésions précancéreuses et cancéreuses du col del'utérus par les registres descancers du réseau Francim/Monitoring of precancerous and cancerous lesions of the cervix by the FRANCIM Network. *Bull Epidem Hebd* **13-15**:234–240.