

Factors associated with compliance to cervical cancer screening in France: The EDIFICE 6 survey

Thibault de La Motte Rouge, Chantal Touboul, Christine Lhomel, Morgan Rouprêt, Jean-François Morère

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- 1 Factors associated with compliance to cervical cancer screening in France: the
- 2 **EDIFICE 6 survey**
- 3 Thibault de la Motte Rouge¹, Chantal Touboul², Christine Lhomel³, Morgan Rouprêt⁴, Jean-
- 4 François Morère⁵
- 5 Short title:
- 6 Cervical cancer screening in France
- 7 Affiliations
- 8 ¹Centre Eugène-Marquis, Rennes, France
- 9 ²Kantar, Health Division, Paris, France
- 10 ³Roche, Boulogne-Billancourt, France
- 11 ⁴Sorbonne Université, GRC n°5, ONCOTYPE-URO, Assistance Publique Hôpitaux de
- 12 Paris, Hôpital Pitié-Salpêtrière, Sorbonne Université, 75 013 PARIS, France.
- 13 ⁵Hôpital Paul Brousse, Villejuif, France
- 14 Corresponding author
- 15 Thibault de la Motte Rouge, Centre Eugène-Marquis, av Bataille Flandres Dunkerque C S
- 16 44229, 35042 Rennes Cedex, France
- 17 Tel +33 2 99 25 29 69/ Fax +33 2 99 25 29 38
- 18 Email t.delamotterouge@rennes.unicancer.fr
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- 26 no conflicts of interest to declare.

- 28 Data statement
- 29 The data that support the findings of this study are available from the corresponding author
- 30 upon reasonable request.

32	Abstract
33	Introduction. A nationwide cervical cancer (CC) screening program was implemented in
34	France in 2018. Asymptomatic women are invited for a cytological test once every 3 years
35	(age, 25-29 years), and an HPV test every 5 years (age, 30-65 years). We investigated the
36	characteristics of women who are resistant to CC screening.
37	Methods. Since 2005, the EDIFICE survey program has assessed attitudes toward cancer
38	screening in France. The 6th edition (2017) included 12 046 representative women (age, 18-
39	69 years). Social vulnerability was assessed using the EPICES score. Multivariate stepwise
40	logistic regression analysis identified factors correlated with nonuptake of CC screening.
41	Results. Questionnaires from 4499 women (age, 25-65 years) with no history of cancer were
42	analyzed; 88% (N=3960) reported at least one test in their lifetime, and 73% (N=3262) did
43	the test in the previous 3 years. Compared to ever-screened women, never-screened women
44	were younger (38±11 yrs vs 44±12 yrs, P<0.05), and more likely to be single (48% vs 20%,
45	P<0.05) and/or socially vulnerable (59% vs 38%, P<0.05). In multivariate analysis, items
46	significantly (P<0.05) associated with never screening included living alone (OR=2.26, 95%
47	CI [1.85-2.75]) and social vulnerability (OR=1.95 [1.59-2.40]). Women who were not
48	compliant with recommendations were more likely to be older (mean age, 49.2 yrs vs. 43.2
49	yrs), living alone (single, widowed or divorced, 40% vs. 30%, P<0.05), and/or socially
50	vulnerable (55% vs. 35%, P<0.05; OR=1.78, 95% CI [1.49-2.12]).
51	Conclusion. This analysis identified several factors associated with never screening and
52	under-screening. Effective prevention messages should specifically target these populations.
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54	Keywords

- 55 Uterine Cervical Neoplasms
- 56 Early Detection of Cancer

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- 58 Attitude to Health
- 59 Socioeconomic factors
- 60 Risk factors

Introduction

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Cervical cancer (CC) is the most frequent human papillomavirus (HPV)-related disease worldwide with the majority of cases attributable to this group of viruses. Although most HPV infections resolve spontaneously (90% within two years), the risk of cervical cancer persists for 15 to 20 years, even in women with a normal immune system. The incidence rate of CC increases between the ages of 20 and 25 years, with a peak in the fourth decade. Median age at diagnosis is 53 years [1]. The World Health Organization recommends primary prevention based on HPV vaccination, and secondary prevention through screening and treatment of pre-cancerous lesions in women from the age of 30 [2]. The efficacy and benefit/risk ratio of organized nationwide cancer screening programs are largely contingent on the age range of eligible average-risk populations. The first guidelines for organized population-based CC screening in Europe were published in 1993 [3]. Although only nine of the 28 European member states had effective organized nationwide screening programs in place in 2016, 22 were in the process of implementing such programs [3]. Opportunistic screening for cervical cancer depends on individual initiatives or physician recommendations, and has existed in France for many years, independently of any organized population-based program. The recommendations for this approach were established following the 1990 Lille consensus conference [4], and stipulate that asymptomatic women between the ages of 25 and 65 years should be called for a Pap smear test once every 3 years following two normal initial tests at a one-year interval. Universal healthcare coverage exists in France, thus providing access to health-related examinations for all women. A notable decrease in the frequency of CC and the subsequent death-rate was observed in France between 1990 and 2018 [1]. Although the annual incidence rates dropped on average

by -1.8% between 1990 and 2018 (10.2 per 100 000 in 1990 vs. 6.1 in 2018), the trend was

88 less notable over the period 2010-2018 (-0.7% per year). Stagnation in screening coverage 89 and the limitations of individual screening likely contributed to this effect [1]. 90 The organized national program was implemented in France in 2018. It is based on a 91 cervical cytology screening test once every 3 years for women between the ages of 25 and 92 30 (following normal results on two tests at a 1-year interval) and an HPV screening test 93 once every 5 years for women between 30 and 65 years of age. Since the implementation of 94 the organized program, women now receive an invitation to the screening test. Screening 95 tests may be indicated before the age of 25, notably in immune-compromised women who 96 require more specifically targeted care. 97 Additionally, since 2007, primary prevention with prophylactic HPV vaccination has been in 98 place for girls aged 11-14 years. Vaccination coverage however remains low: in 2018, 23.7% 99 of 16-year-old girls had received the 2 doses of the vaccine [5]. 100 The EDIFICE survey program (Etude sur le Déplstage des cancers et ses Facteurs de 101 compliance [Study on cancer screening and compliance factors]) was initiated in 2005 with a 102 view to improving our understanding of the behavior of the French population with regard to 103 cancer screening. The first five editions of the survey were conducted using the same 104 methodology (computer-assisted telephone interviewing [CATI]) with populations of 105 approximately 1500 men and women. These surveys have provided robust evidence on 106 prevention and screening of breast, cervical, colorectal, prostate, and lung cancer in France 107 [6], including misconceptions relating to risk factors for cancer [7], the role of general 108 practitioners in screening programs [8], the influence of social vulnerability [9], and evolving 109 trends in prostate cancer screening [10]. 110 In 2017, the methodology was changed to online self-administered questionnaires addressed 111 to approximately 12 000 individuals for the EDIFICE 6 survey. 112 In the present analysis of the 6th edition, we sought to determine the characteristics of

women who resist CC screening, and those who have undergone at least one Pap smear

test but without returning for the repeat test after the recommended 3-year interval. We also studied off-target populations who undergo opportunistic screening for cervical cancer up to 5 years before the recommended age.

Methods

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The sixth edition of the survey was conducted with a new methodology via online selfadministered questionnaires, from 26 June to 28 July 2017 in 12 046 individuals (age, 18-69 years). The study population was selected from the Kantar LightSpeed Panel according to the following criteria: gender, age (six strata), professional categories (three strata), town size (five strata), and region of France (12 strata), according to the classification of the French National Institute for Statistics and Economic Studies (Institut National de Statistiques et d'Etudes Economiques [INSEE]), Paris, France. Representativeness of the sample population was ensured by the quota method based on statistics from the French Employment Survey, adjusted for sex, age, and profession. The quotas were based on 6 strata, with 4 for the 25-65-year age group. Social vulnerability was determined using the EPICES score [11], which is calculated from weighted scoring of responses to 11 questions, giving an overall score between 0 and 100. Questions cover health insurance, living arrangements (alone/with a partner), home ownership, financial situation, physical exercise, recreational activities, vacations, family ties, and social support. Vulnerability is defined by a mean EPICES score ≥30. The study questionnaire requires approximately 25 minutes to complete. All returned questionnaires underwent quality-control; questionnaires (1) completed in less than 15 minutes, and (2) with too many identical answers to similar question types on the Likert-scale or qualitative questions were rejected. Respondents were asked the following questions: "Have you ever had a Pap smear test

during a gynecological examination" (all women 18-65 years). If the answer to this was "yes",

the next question was: "When was your last Pap smear test?" (all women 18-65 years); if the

answer was "No", the next question was: "Why have you never had a Pap smear test" (only women 25-65 years). Compliance to the recommended period of 3 years between two successive examinations was determined according to the date of last Pap smear test; and reasons for non-compliance were collected from the question "Why did you not return for the repeat examination?". Answers to these questions were assessed according to marital status (single, living with a partner), socioprofessional category, smoking status (current, former/never smoker), and social vulnerability (EPICES score). Information on the type of residential area (urban, rural), close relatives with cancer, and personal interpretation of own cancer risk (greater, identical/lower than average) was also collected. Quantitative data were expressed as means and standard deviation (SD), and categorical data as percentages. Multivariate stepwise logistic regression analysis was used to identify factors likely to explain the non-uptake of screening and non-uptake of follow-up screening. In addition, data were analyzed using a technique of customized statistics implemented under the R software environment. This approach—hereafter referred to as the Target & Levers analysis—combines the search for a sample structure (targets) and the search for criteria (levers). Target criteria can be continuous, discrete, qualitative, or ordinal quantitative variables. The method identifies the best segmentation (according to certain performance criteria) by testing each variable and each division. Levers are obtained by regression models for the segment identified. Protection of personal data was ensured in line with European Directives and fulfilled the requirements of the French Data-Protection Watchdog (CNIL [Commission Nationale de l'Informatique et des Libertés]). The survey was carried out in accordance with the international code of ethics governing opinion polls.

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Population

Of the total survey population of 12 046 individuals (age, 18-69 years), 11 307 had no personal history of cancer, and 4499 of the latter were in the target population (age, 25-65 years) for CC screening. Of those, 88% (N=3960) reported having done at least one Pap smear test in their lifetime, and 73% (N=3262) did the test in the past 3 years. Forty-two percent (N=264) of the off-target sub-group (N=633; age, 20-24 years) had a Pap smear test up to 5 years before the recommended age.

Never-screened women

Twelve percent (N=539) of those who had not previously taken part in a screening program were in the CC screening target age group. Notable characteristics of the never-screened population (versus women who had undergone CC screening at least once in their lifetime) were: a lower mean age (38±11 yrs vs. 44±12 yrs, P<0.05), and higher proportions of single women (48% vs. 20%, P<0.05), socially vulnerable individuals (59% vs. 38%, P<0.05), and never-smokers (69% vs. 49%, P<0.05) (Table 1). Multivariate analysis showed a statistically significant association (P<0.05) between not undergoing CC screening and living alone (OR=2.26, 95% CI [1.85-2.75]); social vulnerability (OR=1.95 [1.59-2.40]); and belonging to the socioprofessional categories of unskilled workers (OR=1.89 [1.17-2.94]), skilled manual workers and supervisory or clerical workers (OR=1.80 [1.02-3.05]), and higher managerial and professional occupations (OR=1.74 [1.32-2.28]). Additionally, the status of "current smoker" was inversely associated with never-screening (OR=0.62 [0.49-0.78]). The most frequently cited reasons for not undergoing screening were "I don't feel concerned" (40%), "individual negligence/not a priority" (31%), reasons related to the examination (28%) or to the physician (25%, "I don't go to see my doctor regularly" or "my doctor didn't prescribe it". Interestingly, non-vulnerable women cited, "I don't feel concerned" (45% vs. 36%, P<0.05) and reasons related to the examination/results (36% vs. 25%, P<0.05), more frequently than

vulnerable women. One percent of never-screened women declared having had a hysterectomy ("I no longer have a uterus").

The Target & Levers analysis highlighted three profiles of women in terms of sociodemographic attributes and attitudes towards screening. Firstly, the pivotal age of 32.5 years segmented the study population into two subgroups. Younger women (<32.5 years) who had never been screened were noticeably more likely to be single and to belong to the higher socioprofessional categories (higher managerial and professional occupations). Marital status subsequently segmented the population of older women (≥32.5 years) into two further profiles: among those living with a partner, the fact of belonging to lower socioprofessional categories (unskilled workers) was significantly associated with neverscreening whereas in the group of single older women, social vulnerability was associated with never-screening (Table 2 and Figure 1). Social vulnerability was consistently associated with never screening in all subgroups of age and marital status, and in the main population.

Under-screened women

Fifteen percent (N=671) of women in the target age range for CC screening, and who had done at least one Pap smear test in their lifetime, did not return for the repeat examination within the recommended 3 years. Compared to those who were compliant with the recommendations, the population of non-compliant women was older (mean age 49.2 yrs *vs.* 43.2 yrs); there were also higher proportions of women living alone (single, widowed or divorced, 40% *vs.* 30%, P<0.05), and socially vulnerable individuals (55% *vs.* 35%, P<0.05), smokers (35% *vs.* 26%, P<0.05), and lower proportions of high socioprofessional categories (23% *vs.* 34%, P<0.05) (Table 3). In multivariate analysis, the items associated with non-compliance included: social vulnerability (OR=1.78, 95% CI [1.49-2.12]), current smoking (OR=1.54 [1.28-1.85]) and rating as "not important" the progress enabled by clinical research (OR=1.49 [1.10-1.99]).

The most frequently cited reasons for non-uptake of subsequent Pap smear tests were "I don't feel concerned" (48%), "individual negligence/not a priority" (42%), reasons related to the physician (27%) or to the examination (22%). Vulnerable women cited reasons related to the physician (30% *vs.* 23%) more frequently than non-vulnerable women. Eleven percent of under-screened women declared having had a hysterectomy ("I no longer have a uterus).

Off-target screening

Premature CC screening was more frequent among current smokers compared to non-smokers, and among women living with a partner compared to those living alone. Other characteristics such as living in urban or rural areas, or social vulnerability had no significant impact on premature screening (Figure 2).

Discussion

This analysis of the EDIFICE 6 survey shows that 73% of the CC screening target population had one Pap smear test within the past 3 years, thus complying with the recommended 3-year interval. It also brings to light certain characteristics of women who are in the target population for CC screening yet appear reluctant, either because they have never had a screening test in their lifetime or because they did not do the repeat test within the recommended timeframe.

While our analysis focuses on the population in France, large disparities in screening uptake are known to exist worldwide, with compliance rates of approximately 80% in North America [12, 13], but below 20% in China [14], and ranging from 70-75% in New Zealand and 60% in Australia to 32% in Japan and 2.6% in India [15]. Our results can legitimately be compared to European data published by the International Agency for Research on Cancer (IARC) [16], where examination coverage figures correspond to the proportion of the target population tested in the year, and include opportunistic screening. Rates ranging from 9.2% (Romania) to 86.3% (Sweden) were reported (all ages). Among other features, inter-country disparities reflect the differences in progress in terms of the implementation of cancer screening

programs. It must however be noted that these figures date back to 2013 and have likely evolved as health policies focus actively on promoting organized programs.

There is a paucity of recent data on CC screening uptake in France. In 2010, two studies reported uptake rates of 72% [17] and 83% [18]. More recently, preliminary estimations from a pilot program of organized screening showed that 62% of the target population from 13 French departments respected the recommended 3-year timeframe over the period 2010-2012 [19].

Age and marital status

The Target & Levers analysis suggests that the socioprofessional subgroup of neverscreened women may be closely correlated with age and marital status. We postulate that young women who are committed to their education and their early career likely defer healthcare issues such as screening for cervical cancer.

Our survey was conducted shortly before the organized nationwide CC screening program was implemented in France. Women of reproductive age were most frequently referred for screening during the course of a routine gynecological check-up. In France, over 90% of Pap smear tests are done by gynecologists [20], and compliance to screening is associated with a follow-up visit for contraception [21]. Younger women and those living alone were therefore likely to have never been screened. Likewise, older (post-menopausal) women or those living alone were likely to have ceased screening [20, 22]. Lower uptake of CC screening in older age groups was reported in the context of opportunistic screening [23], but also in the pilot program of organized screening in 13 French departments [19]. Interestingly, the main factor associated with CC screening for women in the 50-65-year age group was the fact of having recently been screened for breast cancer [23]. The well-established (since 2003) breast cancer screening program in France could serve as an enabling context to increase awareness in the population of peri- and post-menopausal women and encourage participation in the more recently implemented nationwide CC screening program.

Social vulnerability

In our survey, social vulnerability was seen to be correlated with lower rates of screening in a lifetime and with higher rates of drop-out from screening recommendations. There is substantial evidence for the critical impact of socioeconomic vulnerability on cancer incidence and mortality, particularly in France [18, 24]. The greater risk of infections among socially vulnerable populations [24] likely accounts for the notably higher incidence of cervical cancer among women in the most vulnerable social groups [18]. Sub-optimal CC screening uptake also affects survival of CC patients [18] and has already been reported in vulnerable populations [17, 20, 23, 25]. The current organized nationwide CC screening program is expected to reduce the inequalities between more or less vulnerable populations [20].

Tobacco status

Several suggestions have been put forward in an attempt to explain the relationship between screening uptake and different lifestyles, including tobacco consumption [17, 22, 23]. Interestingly, healthy attitudes were seen to be associated with lower screening rates, based on the assumption that people believe their healthy lifestyle is protective. This may well apply to our observations of never smokers who were found to be less likely to begin (or to anticipate undergoing) CC screening than current smokers, whereas poor self-esteem and/or fear of the results may explain the behavior of individuals who are less compliant with the recommended timeframe for repeat screening tests [17, 20]. Regular screening is however an integral feature of health prevention, and as such is more likely to be adopted by non-smokers.

Premature screening

In line with previous findings, our analysis highlights a notably high rate of screening uptake among the 20-25-year old off-target age group [26]; this rate is even higher in current smokers and women living with a partner, and concurs with our observation on ever-

screened women in the target population. Surprisingly however, social vulnerability did not significantly affect uptake of premature screening.

In certain specific epidemiological situations where there is an increased risk of cervical cancer (mainly early sexual activity), lowering the age for the first Pap test to 20 years can be considered [27]. This may partly explain the premature CC screening rate of this population.

However, evidence does not consistently favor initiating CC screening from the age of 20 [28] and the potential risk of consequences on obstetrical morbidity has been suggested [26].

Perspectives and ultimate goal of CC screening in France and developed countries

Eliminating CC in France is currently contingent on an organized nationwide screening program stratified by age (HPV and Pap smear test), and the extension of HPV vaccination coverage (notably recently extended to include boys aged 11-14 years). In 2019, the French Health Authorities recommended primary CC screening in women as from the age of 30, using HPV testing every 5 years instead of the 3-yearly Pap smear test. The 3-yearly Pap smear test is however maintained for women before the age of 30.

Interestingly, much like France, Australia implemented HPV vaccination in 2007, has used Pap smear test screening since 1991, and recently transitioned to primary screening with HPV testing every 5 years [29-31]. HPV screening was shown to still be cost effective despite high vaccination coverage [32] and reasons for under-screening and never-screening were very similar to our own findings [29]. A modelling study in 2018 anticipated the elimination of CC in Australia (<4 cases per 100 000 women) within the next 20 years, as long as vaccination coverage remains high, and screening is maintained with 5-yearly HPV primary screening for women between 25-65 years [30]. Another study has however suggested that this novel approach may actually increase the incidence of CC in Australia [31]. It would be interesting to determine whether our findings on different populations who are resistant to cervical cancer screening are also observed in other developed countries. Should that be the case, the development of appropriate targeted measures could be

facilitated, resulting in a more favorable cost/benefit ratio for screening. Conducted concurrently with vaccination strategies, this approach has the potential to enable preventive strategies to achieve the ultimate goal of virtually eliminating cervical cancer mortality.

An additional approach to improving cervical cancer screening could be based on self-testing. Self-testing is not yet available in France. The National Cancer Institute (INCa) is funding research projects and medico-economic studies on this test to assess the usefulness in the current national setting. Preliminary results show that it is indeed a potentially useful method, particularly for women who are not compliant with conventional screening [33]. We believe that this may be an additional means to improve the overall cervical cancer screening rate, and we hope that self-testing will become available in the near future.

Limitations of the study

The findings of the EDIFICE 6 survey may be affected by the inherent bias of declarative surveys. The proportion of women who reported having undergone screening at least once may therefore be over-estimated and a memory bias may have impacted the under-screened rate. However, the large sample size confirms the statistical power.

Conclusion

Targeted awareness campaigns are currently needed to specifically reach certain populations, namely socially vulnerable women—who are known to have a greater risk of cervical cancer—and those who do not undergo regular gynecological check-ups. The latter are more likely to be single and either peri-/post-menopausal (under-screened), or young women with no children (never screened). Effective prevention messages should specifically target the most common reasons for under-screening and never-screening.

342	Contributions of authors
343	Thibault de la Motte Rouge, Chantal Touboul, Christine Lhomel, Morgan Rouprêt and Jean-
344	François Morère were involved in the conception and design of the study. Thibault de La
345	Motte Rouge and Chantal Touboul wrote the manuscript.
346	Chantal Touboul provided study material and collected the data. Thibault de la Motte Rouge
347	Chantal Touboul, Christine Lhomel, Morgan Rouprêt and Jean-François Morère analyzed
348	and interpreted the data. All authors validated the report.
349	
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Figure 1

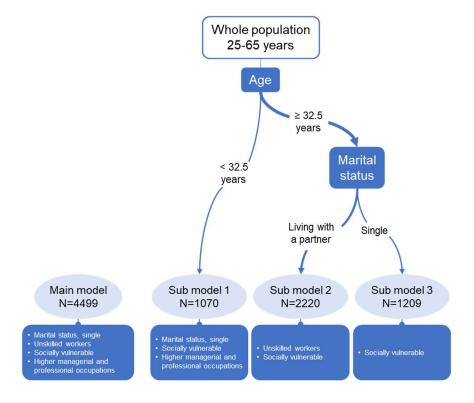


Figure 1 Main factors associated with never-screening. Main model and Target & Lever analysis showing the segmentation of the study population.

Figure

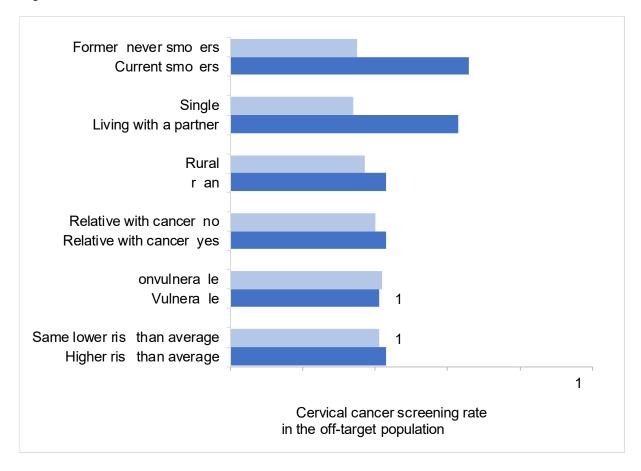


Figure Indicators of premature cervical cancer screening amongst off-target su - populations who underwent opportunistic screening for cervical cancer y prior to the recommended age.

Table 1. Characteristics of the study population. Comparison (Z-Test) of women who had at least one smear test in their lifetime (N=3960) and never screened women (N=539). † assessed by the EPICES score

Characteristics	Screened at least once (N=3960)	Never screened (N=539)	P Value (Z-Test)
Mean age (SD), years	44.2 (11.6)	38.0 (11.0)	<0.05
Marital status Living with a partner Single	68%	46%	<0.05
	32%	54%	<0.05
Socially vulnerable † Not socially vulnerable †	38%	59%	<0.05
	62%	41%	<0.05
Socioprofessional category (SPC) High SPC Low SPC Retired Unemployed	32%	33%	NS
	45%	43%	NS
	10%	4%	<0.05
	13%	20%	<0.05
Tobacco status Current smokers Former smokers Never smokers	27%	21%	<0.05
	24%	10%	<0.05
	49%	69%	<0.05

Table 2. Target & Levers analysis. Significant odd ratios (p<0.05) provided in the main model based on the whole population (4499 women, 25-65 years) and on the sub populations (sub model 1 : 1070 women, < 32.5 years; submodel 2 : 2220 women, \geq 32.5 years and living with a partner; submodel 3 : women \geq 32.5 years and single). NS : not significant.

	Sample populations			
			≥ 32.5 years	
	All women	< 32.5 years	Living with a	
			partner	Single
	Main model	Sub model 1	Sub model 2	Sub model 3
	(N=4499)	(N=1070)	(N=2220)	(1209)
Marital status, single	2.31	2.58	-	-
SPC, unskilled workers	1.95	NS	2.81	NS
Socially vulnerable	1.83	1.76	2.15	1.77
SPC, higher managerial				
and professional	4.69	2.42	NS	NS
occupations				

Table 3. Characteristics of the study population. Comparison (Z-Test) between compliant women who returned after the recommended 3-year interval (N=3262) and non-compliant women (N=678). † assessed by the EPICES score

Characteristics	Compliant (N=3262)	Not compliant (N=671)	P Value (Z-Test)
Mean age (SD), years	43.2 (11.4)	49.2 (11.4)	<0.05
Marital status Living with a partner Single	70% 30%	60% 40%	<0.05 <0.05
Socially vulnerable † Not socially vulnerable †	35% 65%	55% 45%	<0.05 <0.05
Socioprofessional category (SP High SPC Low SPC Retired Unemployed	9 °C) 34% 45% 8% 13%	23% 42% 17% 18%	<0.05 NS <0.05 NS
Tobacco status Current smokers Former smokers Never smokers	26% 24% 50%	35% 23% 42%	<0.05 NS <0.05